Safeguarding public health

MHRA

# Public Assessment Report

# Mutual Recognition Procedure

**Prexige 100mg Tablets**
**Frexocel 100mg Tablets**
**Stellige 100mg Tablets**
**Hirzia 100mg Tablets**

**MRP no: UK/H/887-890/01/MR**
**UK licence no: PL 00101/0677, 0692, 0695, 0698**

**Applicant: Novartis Pharmaceuticals UK Limited**

# Prexige 100mg Tablets
# Frexocel 100mg Tablets
# Stellige 100mg Tablets
# Hirzia 100mg Tablets

## LAY SUMMARY

Austria, Belgium, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Iceland, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia and Slovak Republic have approved Marketing Authorisations (licences) to Novartis Pharmaceuticals UK Limited for the medicinal product Prexige 100mg Tablets following acceptance of the UK marketing authorisation. Identical duplicate products Frexocel (in Austria, Germany, Greece, Italy, Portugal, Slovenia), Stellige 100mg Tablets (in Belgium, Germany, Spain, Ireland, Italy, Poland, Portugal) and Hirzia (in Germany, Italy, Portugal) were also approved in the member states indicated.

These are prescription-only medicines (POM) used in the treatment of osteoarthritis of the knee and hip.

These products contain the active ingredient lumaricoxib, which is non-steroidal anti-inflammatory product.

All issues regarding the safety of the products have been assessed by the RMS and appropriate action taken, where necessary. All safety matters are discussed within the public assessment report.

**Note:** Following consultation with the MHRA and other European regulators, the manufacturer of lumiracoxib (Prexige, and duplicates), is writing to health professionals to inform them of new restrictions on the prescribing of lumiracoxib according to agreement with national health authorities. The updated information can be found at: http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2032098&ssTargetNodeId=221

Additional prescribing advice and any updates to the SPC and product literature will be issued following further assessment.

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# Module 1

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| **Product Name** | Prexige 100mg Tablets<br>Frexocel 100mg Tablets<br>Stellige 100mg Tablets<br>Hirzia 100mg Tablets |
| **Type of Application** | New active substance<br>Initial application<br>Full dossier, Article 8.3<br>Chemical substance<br>Prescription only |
| **Active Substance** | Lumaricoxib |
| **Form** | Film-coated tablets |
| **Strength** | 100mg |
| **MA Holder** | Novartis Pharmaceuticals UK Limited |
| **RMS** | United Kingdom |
| **CMS** | **Prexige Tablets (UK/H/887/01/MR):** Austria, Belgium, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Iceland, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, Slovak Republic<br>**Frexocel Tablets (UK/H/888/01/MR):** Austria, Germany, Greece, Italy, Portugal, Slovenia<br>**Stellige Tablets (UK/H/889/01/MR):** Belgium, Germany, Spain, Ireland, Italy, Poland, Portugal<br>**Hirzia Tablets (UK/H/890/01/MR):** Germany, Italy, Portugal |
| **Procedure Number** | UK/H/887-90/01/MR |
| **Timetable** | Final Day 60 position following CMD(h) referral: 27th October 2006 |

# Module 2

## SUMMARY OF PRODUCT CHARACTERISTICS

**Note: The attached SPC was approved at Day 60 of the CMD(h) referral. However, following consultation with the MHRA and other European regulators, the manufacturer of lumiracoxib (Prexige, and duplicates), is writing to health professionals to inform them of new restrictions on the prescribing of lumiracoxib. The updated information can be found at:**
**http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2032098&ssTargetNodeId=221**

**Additional prescribing advice and any updates to the SPC and product literature will be issued following further assessment.**

### 1. NAME OF THE MEDICINAL PRODUCT

PREXIGE 100 mg film-coated tablets
FREXOCEL 100 mg film-coated tablets
STELLIGE 100 mg film-coated tablets
HIRZIA 100 mg film-coated tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg lumiracoxib.
Excipients: Each tablet contains 23.3 mg lactose.
For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
Ovaloid, red, film-coated tablets with "NVR" debossed on one side and "OB" on the other side.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Symptomatic relief in the treatment of osteoarthritis of the knee and hip.
The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see sections 4.3 and 4.4).

#### 4.2 Posology and method of administration

PREXIGE tablets are administered orally and may be taken with or without food.
As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
The recommended dose is 100 mg once daily. Patients should not exceed this dose. Clinical safety data are only available up to 12 months.

*Ethnic differences:* Dosing recommendations are the same for Asians, Blacks and Caucasians. (see section 5.2).

*Elderly:* As with other medicinal products, caution should be exercised in elderly patients. (see sections 4.3, 4.4 and 5.2).

*Hepatic impairment:* No dose adjustment is necessary for patients with mild (Child-Pugh 5-6) to moderate (Child-Pugh 7-8) hepatic impairment. Severe hepatic impairment is contraindicated (see sections 4.3, 4.4, 4.8 and 5.2).

*Renal insufficiency:* No dose adjustment is necessary for patients with creatinine clearance ≥50 ml/min. Lumiracoxib is contraindicated in patients with moderate to severe renal impairment (estimated creatinine clearance ≤50 ml/min) (see sections 4.3, 4.4 and 5.2).

*Paediatric use:* There is no experience in patients under 18 years of age. PREXIGE is contraindicated in patients under 18 years of age (see section 4.3).

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Patients who have experienced asthma, acute rhinitis, nasal polyps, angioedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs).
- Patients with active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients with inflammatory bowel disease.
- Patients with congestive heart failure (NYHA II-IV).
- Patients with established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Patients with moderate to severe renal dysfunction (estimated creatinine clearance <50 ml/min).
- Patients with severe hepatic disease (Child-Pugh ≥9).
- Third trimester of pregnancy (see sections 4.6 and 5.3).
- Patients under 18 years of age.

## 4.4 Special warnings and precautions for use

*GI effects*

Upper GI complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in a fatal outcome, have occurred in patients treated with lumiracoxib. In clinical studies, few patients (<0.4%) treated with lumiracoxib developed perforations, obstruction or bleeds (POBs) (see section 5.1).

Caution is advised with treatment of patients most at risk of developing a GI complication with NSAIDs: the elderly, patients using any other NSAID or ASA concomitantly, or patients with a prior history of GI disease, such as ulceration and GI bleeding.

There is a further increase in the risk of GI adverse events (GI ulceration or other GI complications) when lumiracoxib is taken concomitantly with ASA (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + ASA versus NSAIDs + ASA has not been demonstrated in long-term clinical trials (see section 5.1).

*Renal effects*

Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of lumiracoxib may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function.

Patients at greatest risk of this response are those with pre-existing renal dysfunction, uncompensated heart failure, or cirrhosis and those receiving diuretics or angiotensin converting enzyme (ACE) inhibitors. Monitoring of renal function in such patients should be considered. Caution should be used when initiating treatment with lumiracoxib in patients

with dehydration. It is advisable to rehydrate patients prior to starting therapy with lumiracoxib.

*Hypertension and oedema*
As with other substances known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in patients taking lumiracoxib in clinical trials. Therefore, lumiracoxib should be used with caution in patients with history of cardiac failure, left ventricular dysfunction or hypertension, and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of lumiracoxib should be taken.
Medically appropriate supervision should be maintained when using lumiracoxib in the elderly and in patients with mild renal, hepatic or cardiac dysfunction.

*Hepatic effects*
Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) greater than three times the upper limit of normal (>3xULN) have been reported in placebo/active-controlled clinical studies up to one year in approximately 1.0% of patients with lumiracoxib 100 mg daily. Marked elevations (>8xULN) have been observed in 0.2% of patients with 100 mg daily in one year studies. As with other NSAIDs, it is recommended to monitor hepatic function as well as the hemogram regularly during prolonged administration.

Rare cases of hepatitis have been reported (see section 4.8).

Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored. If signs of hepatic insufficiency occur, or if abnormal liver function tests (ALT or AST>3xULN) persist, lumiracoxib should be discontinued.

*Cardiovascular effects*
COX-2 selective inhibitors are not a substitute for ASA for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued (see sections 4.5 and 5.1).

Clinical trials suggest that the selective COX-2 inhibitor class of medicinal products may be associated with a risk of thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (see sections 4.2, 4.3, 4.8 and 5.1).

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with lumiracoxib after careful consideration (see section 5.1).

*Skin reactions*
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance. Patients appear to be at highest risk for these reactions early in the course of therapy, with the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving lumiracoxib. Some selective COX-2 inhibitors have been associated

with an increased risk of skin reactions in patients with a history of any medicinal product allergy. Lumiracoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

*General*
If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of lumiracoxib therapy should be considered.

Use of lumiracoxib, as with any substance known to inhibit COX-2, is not recommended in women attempting to conceive (see section 4.6).

As with other NSAIDs, lumiracoxib may mask fever and other signs of inflammation or infection.

The film-coated tablets contain 23.3 mg of lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

## 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

**Pharmacodynamic Interactions**
*Oral anticoagulants:* In a medicinal product interaction study in healthy subjects stabilised on warfarin therapy, the administration of lumiracoxib 400 mg once daily for five days was associated with an approximate 15% increase in prothrombin time. Therefore, anticoagulant activity should be monitored in patients taking warfarin or similar agents, particularly in the first few days after initiating or changing the dose of lumiracoxib.

*Diuretics, ACE inhibitors and Angiotensin II Antagonists:* NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal functions), the co-administration of an ACE inhibitor or angiotensin II antagonist and agents that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be given consideration in patients taking lumiracoxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

*Other NSAIDs:* Lumiracoxib can be used with low-dose ASA. However, concomitant administration of lumiracoxib with high doses of ASA, other NSAIDs or COX-2 inhibitors should be avoided.

*Ciclosporin or tacrolimus:* Although this interaction has not been studied with lumiracoxib, co-administration of ciclosporin or tacrolimus and any NSAID may increase the nephrotoxic effect of ciclosporin or tacrolimus. Renal function should be monitored when lumiracoxib and either of these medicinal products is used in combination.

**Pharmacokinetic Interactions**
Based on *in vitro* studies, interactions involving plasma protein binding are not expected to have any clinically relevant effects on lumiracoxib or co-administered medicinal products.

*Effects of lumiracoxib on the pharmacokinetics of other medicinal products*
*Warfarin:* In a study with warfarin, which is considered to be a CYP2C9 substrate sensitive to medicinal product interactions, co-administration with lumiracoxib 400 mg had no effect on plasma AUC, Cmax or Tmax of R-warfarin or S-warfarin. Compared to placebo treatment, recovery of the S-7-OH warfarin metabolite in urine was about 25% lower in subjects treated with lumiracoxib. (See also Pharmacodynamic interactions for the interactions with oral anticoagulant medicinal products.)

*Methotrexate:* Co-administration of lumiracoxib at doses of 400 mg once daily and methotrexate at rheumatological doses had no clinically significant effects on the plasma pharmacokinetics, plasma protein binding or urinary excretion of methotrexate and of the 7-hydroxy methotrexate metabolite. However, adequate monitoring of methotrexate-related toxicity should be considered when the medicinal products are used concomitantly.

*Oral contraceptives:* Co-administration of lumiracoxib did not affect the steady-state pharmacokinetics or the efficacy of ethinylestradiol and of levonorgestrel. Thus no alteration in oral contraceptive medication is necessary when lumiracoxib is co-administered.

*Lithium:* NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus when lumiracoxib and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

*Digoxin:* NSAIDs can reduce the renal clearance of digoxin. Monitoring of the digoxin plasma concentrations is advised when initiating or ending concomitant treatment with NSAIDs in patients treated with digoxin.
In vivo studies suggest that lumiracoxib has low potential for interactions with CYP2C9 substrates. However, care should be exercised when lumiracoxib is co-administered with substrates of CYP2C9 that have very narrow therapeutic index, such as phenytoin and warfarin. In vitro studies indicate that lumiracoxib is not a significant inhibitor of other cytochrome P450 isoforms, including CYP1A2, CYP2C8, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

*Effects of other medicinal products on the pharmacokinetics of lumiracoxib*
Several pathways appear to be involved in the metabolism of lumiracoxib, including glucuronidation and oxidation. The main oxidative pathway is mediated by CYP2C9. However, this is apparently not the major pathway, as fluconazole, a potent inhibitor of CYP2C9, had only a small effect on lumiracoxib pharmacokinetics. Omeprazole, an inhibitor of CYP2C19, also had no effect on lumiracoxib pharmacokinetics.

*Fluconazole:* Co-administration of lumiracoxib with the potent CYP2C9 inhibitor fluconazole had no clinically relevant effect on the pharmacokinetics or the COX-2 selectivity of lumiracoxib.

*Omeprazole:* Omeprazole had no effect on the pharmacokinetics of lumiracoxib.

*Antacids:* (aluminium hydroxide/magnesium hydroxide) had no clinically relevant effect on the pharmacokinetics of lumiracoxib.

## 4.6 Pregnancy and lactation
The use of lumiracoxib, as with any other medicinal products that inhibit COX-2, is not recommended in women attempting to conceive (see sections 4.4 and 5.1).

*Pregnancy:*

There are no adequate data from the use of lumiracoxib in pregnant women. However, based on human experience with other medicinal products known to inhibit prostaglandin synthesis, lumiracoxib may cause uterine inertia resulting in delayed or prolonged labour, and premature closure of the ductus arteriosus. Lumiracoxib is contraindicated during the last trimester of pregnancy (see section 4.3).

Animal studies have shown reproductive effects (see section 5.3). The potential risk for humans is unknown. Lumiracoxib should not be used during the first two trimesters of pregnancy unless unless the clinical condition of the woman requires treatment with lumiracoxib..

*Lactation:*
It is unknown whether lumiracoxib is excreted in human breast milk. Animal studies have shown excretion of lumiracoxib in breast milk.

A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Lumiracoxib should be made taking into account the benefit of breast-feeding to the child and the benefit of lumiracoxib therapy to the woman.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, patients who experience dizziness, vertigo or somnolence while taking lumiracoxib should refrain from driving or operating machinery.

## 4.8 Undesirable effects

In clinical trials, lumiracoxib was evaluated for safety in approximately 18,500 patients, including approximately 15,850 patients with osteoarthritis (OA) (approximately 13,500 patients were treated for 3 months, 9,640 patients for 6 months, and 6,650 patients were treated for 1 year). Of those, approximately 1,850 OA patients were treated with lumiracoxib 100 mg od for 3 months, and 750 patients were treated with lumiracoxib 100 mg od for 1 year.

In clinical studies the following undesirable effects were reported at an incidence greater than placebo in patients treated with lumiracoxib for up to one year.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. *[Common (>1/100, <1/10) Uncommon (>1/1,000, <1/100) Rare (>1/10,000, <1/1,000) Very rare (<1/10,000)]*

***Infections***
Common: Influenza like symptoms, Respiratory tract infection (e.g bronchitis), Urinary tract infection
Uncommon: Candidiasis, Ear infection, Herpes simplex, Tooth infection

***Blood and lymphatic system disorders***
Uncommon: Anaemia
Rare: Pancytopenia, Neutropenia, Leucopenia

***Psychiatric disorders***
Uncommon: Depression, Insomnia, Anxiety

***Nervous system disorders***
Common: Dizziness, Headache

Uncommon: Syncope, Hypoaesthesia, Migraine, Paraesthesia, Dysgeusia, Vertigo, Tinnitus

***Eye disorders***
Uncommon: Conjunctivitis, Dry eye, Visual disturbance (e.g. blurred vision)
Rare: Keratitis

***Cardiac disorders***
Uncommon: Palpitations, Myocardial infarction*
Rare: Cardiac failure, Atrioventricular block of first degree

***Vascular disorders***
Uncommon: Venous insufficiency, Hypotension, Cerebrovascular accident*
Very rare: hypertensive crisis

***Respiratory disorders***
Common: Cough, Pharyngitis
Uncommon: Dyspnoea, Epistaxis, Rhinitis, Sinus congestion, Asthma

***Gastrointestinal disorders***
Common: Abdominal pain, Constipation, Diarrhoea, Dyspepsia, Nausea, Vomiting, Flatulence
Uncommon: Gastroduodenal ulcer, Gastroduodenitis, Oesophagitis, Abdominal distension, Aphthous stomatitis, Dry mouth, Dysphagia, Epigastric discomfort, Eructation, Gastrooesophageal reflux disease, Gingivitis, Hyperacidity, Toothache
Rare: Gastrointestinal haemorrhage

***Hepatobiliary disorders***
Rare: Cholecystitis, Cholelithiasis, (Acute) hepatitis with and without jaundice

***Skin and subcutaneous tissue disorders***
Uncommon: Contusion, Exanthema, Pruritus, Rash, Urticaria
Rare: Angioedema

***Musculoskeletal disorders***
Uncommon: Joint swelling, Muscle cramps, Arthralgia

***Renal and urinary disorders***
Uncommon: Dysuria, Urinary frequency, Cystitis
Rare: Chromaturia, Renal failure

***Reproductive system disorders***
Rare: Erectile dysfunction

***General disorders***
Common: Fatigue, Oedema (e.g. lower limb)
Uncommon: Appetite increased or decreased, Chest pain, Rigors, Thirst
Rare: Anaphylaxis

***Investigations***
Uncommon: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatinine increased, Blood urea increased, Gamma-glutamyltransferase increased, Weight increased.
Rare: Blood bilirubin increased, Blood glucose increased

* Based on analyses of long-term placebo and active controlled clinical trials, some selective COX-2 inhibitors have been associated with an increased risk of serious thrombotic arterial events, including MI and stroke. The absolute risk increase for such events is unlikely to exceed 1% per year based on existing data (uncommon).

The following rare serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for lumiracoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and jaundice; cutaneo-mucosal adverse events and severe skin reactions.

### 4.9 Overdose
No case of overdose has been reported.

In the event of suspected overdose, appropriate supportive medical care should be provided, e.g. by eliminating the gastric contents, clinical supervision and, if necessary, the institution of symptomatic treatment.

Haemodialysis is unlikely to be an efficient method of lumiracoxib removal due to high protein binding.

## 5. PHARMACOLOGICAL PROPERTIES
### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs
ATC code: M01 AH 06

***Mechanism of action***
Lumiracoxib is an orally active, selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range.

Cyclooxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thromboembolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. Across clinical pharmacology studies, lumiracoxib produced dose-dependent inhibition of COX-2 in plasma without inhibition of COX-1.

***Efficacy***
In patients with OA of the knee, lumiracoxib 100 mg once daily provided significant improvements in pain, stiffness, function and patient assessments of disease status up to 13 weeks in placebo-controlled studies and efficacy was maintained up to 52 weeks in one comparative study. Increasing the dose to 200 mg daily is not recommended, as this does not provide any additional benefit. The efficacy of lumiracoxib 100 mg daily in OA of joints

other than the knee has not been confirmed, except in one 4-week study in a small number of patients with hip OA.

***Safety***
The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)a 12-month, double-blind, phase III study included 18,325 OA patients randomized to lumiracoxib 400 mg once daily (four times the recommended OA dose), naproxen 500 mg twice daily or ibuprofen 800 mg three times daily TARGET included patients taking low-dose ASA (75-100 mg daily) for primary or secondary prevention of coronary heart disease. Randomization was stratified by low-dose ASA use (24 % of patients in the overall study population) and age.

The primary endpoint was time to event distribution of definite or probable upper gastrointestinal tract ulcer (UGIT) complications (POBs). In the population not using low-dose ASA, the incidence of POBs was 14/6,950 patients (0.2%) for lumiracoxib versus 64/6,968 patients (0.92%) for NSAIDs, with a hazard ratio (HR) of 0.21 [95% CI 0.12-0.37] ($p<0{\cdot}0001$). In the population using low-dose aspirin, there was no significant difference between lumiracoxib and NSAIDs.

The primary cardiovascular (CV) endpoint studied was the Antiplatelet Trialists' Collaboration (APTC) endpoint: confirmed or probable MI (clinical or silent), stroke (ischaemic or haemorrhagic) and CV death. There were no significant differences between lumiracoxib and NSAIDs. There was no statistically significant difference between lumiracoxib and NSAIDs for incidence of MI (clinical MI and silent MI).

## 5.2 Pharmacokinetic properties

***Absorption***
Lumiracoxib is rapidly absorbed following oral administration. Median tmax is about 2 hours post dose. Over the range of 25 to 800 mg, extent of exposure (AUC) increases in a dose-proportional manner and the peak plasma concentration ($C_{max}$) was roughly dose-proportional.

The absolute bioavailability of lumiracoxib is approximately 74%.

Food had no significant effect on either $C_{max}$ or AUC of lumiracoxib when 200 mg tablets of PREXIGE were taken with a high-fat meal. PREXIGE tablets can be administered without regard to timing of meals.

***Distribution***
Lumiracoxib is highly bound to plasma proteins, (≥98%), and binding is independent of concentration over a range of 0.1 to 100 µg/ml.

The volume of distribution (Vss) is 9 l.

By about 5 hours post dose, concentrations of lumiracoxib in human synovial fluid of RA patients were higher than plasma and remained substantially higher for the remainder of the dose interval (AUC12-24 in synovial fluid was 2.6 times higher than that for plasma). No difference was observed in the extent of lumiracoxib protein binding in synovial fluid compared to plasma.

***Biotransformation***
In humans, lumiracoxib undergoes extensive hepatic metabolism. Several enzymes have been identified which participate in the metabolism of lumiracoxib, including glucuronosyl transferase and cytochrome P450 enzymes. Of the P450 enzymes, CYP2C9 was found to

have the highest activity, with lesser activity shown for CYP1A2 and CYP2C19. However, CYP2C9 metabolism appears not to be the major elimination pathway in vivo, based on the minimal increase in lumiracoxib exposure observed when a CYP2C9 inhibitor (fluconazole) was co-administered. Of the total active substance-related material in plasma, unchanged lumiracoxib is the major component. Three major metabolites were identified in plasma: 4'-hydroxy-lumiracoxib, 5-carboxy-lumiracoxib and 4'-hydroxy-5-carboxy-lumiracoxib. In addition various conjugates (glucuronides and sulfates) of these metabolites are formed. The 4'-hydroxy metabolite has potency and COX-2 selectivity that is one third of lumiracoxib.

***Elimination***
Lumiracoxib is eliminated predominantly via hepatic metabolism. After administration of a single dose of lumiracoxib 400 mg to healthy subjects, 54% of active substance-related material was excreted in urine and 43% in faeces. Only about 5% of the administered dose was recovered in excreta as unchanged lumiracoxib.

Plasma clearance is 7.7 l/h.

The mean plasma half-life of lumiracoxib is approximately 4 hours. Lumiracoxib does not accumulate in plasma under once or twice daily administration and steady state is achieved on the first day of administration with no increase in $C_{max}$ or AUC after extended dosing.

***Characteristics in patients***
*Gender:*
There is no difference in exposure of lumiracoxib in men and women.

*Elderly:*
In elderly subjects (over 65 years old), a 15% increase in AUC was observed as compared to younger subjects. Dosage adjustment in the elderly is not necessary.

*Race:*
The pharmacokinetics of lumiracoxib are similar in Asians, Blacks and Caucasians.

*Hepatic insufficiency:*
Compared to healthy subjects, exposure to lumiracoxib was not changed in patients with moderate hepatic impairment (Child-Pugh score 7-8). No difference was observed in the plasma protein binding between the two groups. The pharmacokinetics of lumiracoxib have not been studied in patients with severe hepatic impairment (Child-Pugh ≥9). (See also sections 4.2, 4.3, 4.4 and 4.8).

*Renal insufficiency:*
When lumiracoxib was administered to patients with end-stage renal disease, a 33% decrease in lumiracoxib $C_{max}$ and a 27% decrease in AUC were observed compared to healthy subjects. Mean exposure to the active 4'-hydroxy-lumiracoxib metabolite was largely unaffected.

Plasma protein binding of lumiracoxib was similar in healthy subjects and in patients with end-stage renal disease. Dialysis has no effect on the exposure of patients to lumiracoxib or its active metabolite. (See also sections 4.2, 4.3, 4.4 and 4.8).

*Paediatric patients:*
The pharmacokinetics of lumiracoxib in paediatric patients have not been studied.

## 5.3 Preclinical safety data
In preclinical studies, lumiracoxib did not reveal mutagenic or carcinogenic potential.

In repeat-dose toxicity studies in rats and monkeys, target organs were the GI tract and kidney. Systemic exposure levels with no adverse effect (NOAEL) for these targets in rat (26-week study) and monkey (39-week study) were 3.6 and 12 times that in man following a 400 mg therapeutic dose, respectively. In two-year carcinogenicity studies in rats and mice, the systemic exposures at the NOAEL for GI ulceration were 0.9 times and 0.1 times that in man following a 400 mg therapeutic dose, respectively.

In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and postimplantation loss and embryo-foetal lethality. In rats, lumiracoxib increased the incidence of pre-implantation loss at a dose of ≥30 mg/kg/day (4.7 times the clinical exposure following a 400 mg dose, based on AUC values), which did not cause maternal toxicity. In a pre- and post-natal development study in rats, dystocia was evident and an increase in stillborn pups and in pup mortality postpartum day 0-4 was seen at maternally toxic doses ≥3 mg/kg/day (0.8 times clinical exposure following a 400 mg dose based on AUC values). In rabbits, increased early and late resorptions, a decrease in viable foetuses and delayed ossification of the sternebrae and phalanges in the presence of moderate maternal toxicity was seen at a dose of 60 mg/kg/day (4.9 times clinical exposure following a dose of 400 mg based on AUC values).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Core:
Cellulose microcrystalline
Croscarmellose sodium
Lactose monohydrate
Povidone K30
Titanium dioxide (E171)
Magnesium stearate

Coating:
Hypromellose
Macrogol 4000
Talc
Iron oxide red (E 172)
Iron oxide black (E 172)
Titanium dioxide (E 171)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Clear or opaque PVC/aluminium blisters in packs containing 2, 4, 5, 6, 10, 20, 30, 50, 100, or 600 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7. MARKETING AUTHORISATION HOLDER
To be completed nationally.

## 8. MARKETING AUTHORISATION NUMBER(S)
To be completed nationally.

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
To be completed nationally.

## 10. DATE OF REVISION OF THE TEXT
To be completed nationally.

# Module 3

# Product Information Leaflet & Technical Leaflet

NOVARTIS

Prexige®

## Prexige® 100 mg, Film Coated Tablets (lumiracoxib)

**Read all of this leaflet carefully before you start taking this medicine**

Keep this leaflet. You may need to read it again.

If you have further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### In this leaflet



### 1. What Prexige is and what it is used for

Lumiracoxib is a non steroidal anti-inflammatory product (NSAID). It belongs to a group of medicines called cyclo-oxygenase-2 (COX-2) inhibitors. This group of medicines prevents the body from producing substances called prostaglandins. Some prostaglandins are responsible for causing pain and inflammation in the body, while others protect the stomach lining. Prexige reduces the amount of those prostaglandins which cause pain and inflammation but does not lower the amount of those which protect the stomach.

Prexige is used to treat painful symptoms of osteoarthritis of the knee and hip.

### 2. Before you take Prexige

**Do not take Prexige**

- if you are allergic (hypersensitive) to lumiracoxib or to any of the other ingredients of Prexige
- if you have an ulcer in your stomach or upper bowel
- if you have gastrointestinal bleeding, symptoms of which may include blood in vomit or when emptying bowels, or black, tarry stools
- if you suffer from any inflammatory bowel disorders (e.g. ulcerative colitis or Crohn's disease)
- if you have ever experienced any breathing problems including asthma, a runny nose, nasal polyps, skin rash, swelling of the face, lip or tongue or any other allergic-type reactions after taking medicines to treat arthritis or pain (e.g. aspirin or ibuprofen)
- if you have had heart problems including heart failure, angina (chest pain), if you have had a heart attack, stroke or if you have poor circulation in your legs or feet
- if you have serious kidney or liver problems
- if you are in the last three months of pregnancy
- if you are less than 18 years of age.

If any of these apply to you, tell your doctor before taking Prexige.

**Take special care with Prexige**

- if you have, or have ever had, a heart condition, or any vascular obstruction
- if you have a condition which increases your risk of heart disease, such as high blood pressure, diabetes, high cholesterol, or if you smoke
- if you have any swelling due to fluid retention
- if you have ever had gastrointestinal problems such as bleeding or ulcers in your gullet (oesophagus), stomach or upper bowel
- if you have kidney or liver disease
- if you might be dehydrated – this may happen if you have had diarrhoea or have been vomiting or unable to drink fluids.

If any of these apply to you, tell your doctor before you take Prexige.

Prexige may reduce the symptoms of an infection (e.g. headache, high temperature) and may therefore make it more difficult to detect. If you feel unwell and need to see a doctor, remember to mention that you are taking Prexige.

Prexige may cause serious allergic reactions. Therefore, stop taking Prexige and inform your doctor immediately if you experience symptoms such as skin rash or mucosal injuries.

**Taking other medicines**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those without prescription. It is particularly important to tell your doctor if you are taking any of the following medicines:

- medicines to prevent blood clots and blood thinning tablets such as warfarin
- methotrexate (a medicine also used to treat rheumatoid arthritis)
- diuretics (medicines used to increase the amount of urine)
- ciclosporin or tacrolimus (medicines used to suppress the immune system)
- lithium (a medicine used to treat some types of depression)
- phenytoin (a medicine used in epilepsy)
- medicines used to treat high blood pressure and heart failure (e.g. ACE inhibitors)
- digoxin (a medicine used to treat heart problems)
- other COX-2 inhibitors or related medicines (e.g. ibuprofen, high-dose aspirin or other aspirin -like medicines).

Prexige can be taken with low-dose aspirin. If your doctor has recommended that you take low-dose aspirin for the prevention of stroke or heart attack, you should not stop taking this without consulting the doctor first.

**Pregnancy and breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine.

Do not take Prexige if you are in the last three months of pregnancy. In the first and second trimesters of pregnancy, you should take Prexige only after consulting your doctor. If you are trying to become pregnant, you must discuss with your doctor before taking Prexige.

If you are breast-feeding tell your doctor. He or she will discuss with you the possible risks of taking Prexige during breast-feeding.

**Driving and using machines**

If you feel dizzy or have sight disturbances when you take Prexige, do not drive or use machines until these effects wear off.

**Important information about some of the ingredients of Prexige**

Prexige tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

### 3. How to take Prexige

Always take Prexige exactly as your doctor has told you even if different from this leaflet and check with your doctor or pharmacist if you are not sure.

Swallow Prexige tablets whole with a small amount of water. Do not chew or crush the tablets. Prexige tablets may be taken with or without food.

Your doctor will want to discuss your treatment from time to time. You should not take Prexige for longer than necessary.

Do not take a higher daily dose than recommended as daily doses higher than those recommended do not provide an additional benefit.

**Osteoarthritis**

The recommended dose is one tablet of 100 mg once daily.

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### If you take more Prexige than you should

If you take too many tablets, tell your doctor or pharmacist or go to the nearest hospital emergency unit at once. You may require medical attention. Take your medicine with you.

### If you forget to take Prexige

If you forget to take a dose, take one as soon as you remember. If it is nearly time for your next dose, you should simply take the next dose at the usual time. Do not double the next dose to make up for the one you missed.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, Prexige can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If you get any of the following, STOP taking the tablets immediately and tell your doctor:

- Severe or persistent stomach pain
- Shortness of breath, chest pains or ankle swelling
- Any sign of bleeding in your stomach or intestine, for example when emptying your bowels, blood in vomit or black, tarry stools
- Allergic reactions such as skin rash, wheezing, swelling of the face, tongue or pharynx, difficulty to swallow or shortness of breath
- Jaundice, yellowing of your skin or the whites of your eyes.

The following side effects were reported with Prexige.

Common side effects *(these are likely to affect between 1 and 10 in every 100 people):*

- Flu-like symptoms, urinary infection, respiratory infection (e.g. bronchitis)
- Headache, dizziness
- Diarrhoea, constipation, stomach pain, flatulence or wind, indigestion, nausea (feeling sick) or vomiting
- Cough, pharyngitis (inflammation of part of the throat)
- Tiredness, oedema (swelling of the legs and /or feet due to fluid retention).

Uncommon side-effects *(these are likely to affect between 1 and 10 in every 1,000 people):*

- Candidiasis (a yeast infection commonly known as thrush), ear infection, herpes simplex, tooth infection
- Sleep problems, anxiety, depression
- Fainting, changes in touch sensation, pins and needles, migraine, changes in the way things taste
- Conjunctivitis (itching and redness of the eyes), dry eye, visual disturbance (e.g. blurred vision)
- Imbalance, hissing or ringing in ears
- Palpitations (fast or irregular heartbeat), heart attack
- Hypotension (low blood pressure), numbness, inability or difficulty to speak, paralysis of one side of the body (cerebral attack)
- Asthma, breathlessness, nosebleeds, blocked or runny nose
- Ulcers in the digestive system, gastritis (inflamed stomach), oesophagitis (inflamed gullet), abdominal bloating or discomfort, mouth ulcers, dry mouth, difficulty in swallowing, burping, gastro-oesophageal reflux disease (reflux of stomach contents into the gullet), gingivitis (inflammation of the gums), increase in stomach acid secretions, toothache
- Bruising, rash, redness or itching of the skin
- Swollen joints, muscle cramps, bone pain
- Difficulty urinating or pain when passing urine, or urinating more often
- Chest pain, rigors (shivering with a fever), thirst
- Increase or loss of appetite, weight gain
- Changes in blood or urine tests relating to the liver or the kidney
- Anaemia (low number of red blood cells)

Rare side effects *(these are likely to affect between 1 and 10 in every 10,000 people):*

- Changes in the number of blood platelets (responsible for clotting blood) and white blood cells, changes in blood sugar levels
- Watery, painful eyes
- Bleeding of the digestive system
- Inflammation of the gall bladder, gallstones
- Discolouration of urine
- Impotence
- Hepatitis or changes in liver function
- Abnormalities of the heart rhythm
- Renal failure (severely decreased urine output)
- Cardiac failure (breathlessness, difficulty breathing when lying down, swelling of the feet or legs).

Very Rare side effects *(these are likely to affect less than 1 in every 10,000 people):*

- Crisis of hypertension (high blood pressure).

Other rare side-effects have been reported with the use of anti-inflammatory drugs and cannot be ruled out for Prexige: kidney damage or failure, liver damage or failure, severe skin reactions.

If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. How to store Prexige

- Keep out of the reach and sight of children
- Do not use after the expiry date shown on the carton and blister
- This medicinal product does not require any special storage conditions
- Do not use if the pack is damaged or shows signs of tampering.

## 6. Further information

### What Prexige contains

The active substance is lumiracoxib. Each film-coated tablet contains 100 mg lumiracoxib. The other ingredients are:

Core: cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, povidone, titanium dioxide (E171), magnesium stearate.

Coat: hypromellose, macrogol, talc, iron oxide red (E172), iron oxide black (E172) and titanium dioxide (E171).

### What Prexige looks like and contents of the pack

Prexige 100 mg film-coated tablets are ovaloid, red with "NVR" on one side and "OB" on the other. They are available in blister packs containing 2, 4, 5, 6, 10, 20, 30, 50, 100 or 600 tablets. Not all pack sizes may be marketed.

### Marketing Authorisation Holder

Novartis Pharmaceuticals UK Ltd

Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR

### Manufacturer

Novartis Pharmaceuticals UK Ltd

Wimblehurst Road, Horsham, West Sussex RH12 5AB

### This medicinal product is authorised in the Member States of the EEA under the following names

AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IC, IE, IT, LI, LU, LA, MT, NL, NO, PL, PT, SW, SL, SK: Prexige

AT, DE, EL, IT, PT, SL: Frexocel

BE, DE, ES, IE, IT, PL, PT: Stellige

DE, IT, PT: Hirzia

### Date of Last Revision

February 2007

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NOVARTIS

Frexocel® 100 mg, Film Coated Tablets

Lumiracoxib

**Read all of this leaflet carefully before you start taking this medicine**

Keep this leaflet. You may need to read it again.

If you have further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet



## 1. What Frexocel is and what it is used for

Lumiracoxib is a non steroidal anti-inflammatory product (NSAID). It belongs to a group of medicines called cyclo-oxygenase-2 (COX-2) inhibitors. This group of medicines prevents the body from producing substances called prostaglandins. Some prostaglandins are responsible for causing pain and inflammation in the body, while others protect the stomach lining. Frexocel reduces the amount of those prostaglandins which cause pain and inflammation but does not lower the amount of those which protect the stomach.

Frexocel is used to treat painful symptoms of osteoarthritis of the knee and hip.

## 2. Before you take Frexocel

Do not take Frexocel

- if you are allergic (hypersensitive) to lumiracoxib or to any of the other ingredients of Frexocel
- if you have an ulcer in your stomach or upper bowel
- if you have gastrointestinal bleeding, symptoms of which may include blood in vomit or when emptying bowels, or black, tarry stools
- if you suffer from any inflammatory bowel disorders (e.g. ulcerative colitis or Crohn's disease)
- if you have ever experienced any breathing problems including asthma, a runny nose, nasal polyps, skin rash, swelling of the face, lip or tongue or any other allergic-type reactions after taking medicines to treat arthritis or pain (e.g. acetylsalicylic acid or ibuprofen)
- if you have had heart problems including heart failure, angina (chest pain), if you have had a heart attack, stroke or if you have poor circulation in your legs or feet
- if you have serious kidney or liver problems
- if you are in the last three months of pregnancy
- if you are less than 18 years of age.

If any of these apply to you, tell your doctor before taking Frexocel.

Take special care with Frexocel

- if you have, or have ever had, a heart condition, or any vascular obstruction
- if you have a condition which increases your risk of heart disease, such as high blood pressure, diabetes, high cholesterol, or if you smoke
- if you have any swelling due to fluid retention
- if you have ever had gastrointestinal problems such as bleeding or ulcers in your gullet (oesophagus), stomach or upper bowel
- if you have kidney or liver disease
- if you might be dehydrated – this may happen if you have had diarrhoea or have been vomiting or unable to drink fluids.

If any of these apply to you, tell your doctor before you take Frexocel.

Frexocel may reduce the symptoms of an infection (e.g. headache, high temperature) and may therefore make it more difficult to detect. If you feel unwell and need to see a doctor, remember to mention that you are taking Frexocel.

Frexocel may cause serious allergic reactions. Therefore, stop taking Frexocel and inform your doctor immediately if you experience symptoms such as skin rash or mucosal injuries.

Taking other medicines

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those without prescription. It is particularly important to tell your doctor if you are taking any of the following medicines:

- medicines to prevent blood clots and blood thinning tablets such as warfarin
- methotrexate (a medicine also used to treat rheumatoid arthritis)
- diuretics (medicines used to increase the amount of urine)
- ciclosporin or tacrolimus (medicines used to suppress the immune system)
- lithium (a medicine used to treat some types of depression)
- phenytoin (a medicine used in epilepsy)
- medicines used to treat high blood pressure and heart failure (e.g. ACE inhibitors)
- digoxin (a medicine used to treat heart problems)
- other COX-2 inhibitors or related medicines (e.g. ibuprofen, high-dose acetylsalicylic acid or other acetylsalicylic acid -like medicines).

Frexocel can be taken with low-dose acetylsalicylic acid. If your doctor has recommended that you take low-dose acetylsalicylic acid for the prevention of stroke or heart attack, you should not stop taking this without consulting the doctor first.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Do not take Frexocel if you are in the last three months of pregnancy. In the first and second trimesters of pregnancy, you should take Frexocel only after consulting your doctor. If you are trying to become pregnant, you must discuss with your doctor before taking Frexocel.

If you are breast-feeding tell your doctor. He or she will discuss with you the possible risks of taking Frexocel during breast-feeding.

Driving and using machines

If you feel dizzy or have sight disturbances when you take Frexocel, do not drive or use machines until these effects wear off.

Important information about some of the ingredients of Frexocel

Frexocel tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Frexocel

Always take Frexocel exactly as your doctor has told you even if different from this leaflet and check with your doctor or pharmacist if you are not sure.

Swallow Frexocel tablets whole with a small amount of water. Do not chew or crush the tablets. Frexocel tablets may be taken with or without food.

Your doctor will want to discuss your treatment from time to time. You should not take Frexocel for longer than necessary.

Do not take a higher daily dose than recommended as daily doses higher than those recommended do not provide an additional benefit.

Osteoarthritis

The recommended dose is one tablet of 100 mg once daily.

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If you take more Frexocel than you should

If you take too many tablets, tell your doctor or pharmacist or go to the nearest hospital emergency unit at once. You may require medical attention. Take your medicine with you.

If you forget to take Frexocel

If you forget to take a dose, take one as soon as you remember. If it is nearly time for your next dose, you should simply take the next dose at the usual time. Do not double the next dose to make up for the one you missed.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, Frexocel can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If you get any of the following, STOP taking the tablets immediately and tell your doctor:

- Severe or persistent stomach pain
- Shortness of breath, chest pains or ankle swelling
- Any sign of bleeding in your stomach or intestine, for example when emptying your bowels, blood in vomit or black, tarry stools
- Allergic reactions such as skin rash, wheezing, swelling of the face, tongue or pharynx, difficulty to swallow or shortness of breath
- Jaundice, yellowing of your skin or the whites of your eyes.

The following side effects were reported with Frexocel.

Common side effects *(these are likely to affect between 1 and 10 in every 100 people)*:

- Flu-like symptoms, urinary infection, respiratory infection (e.g. bronchitis)
- Headache, dizziness
- Diarrhoea, constipation, stomach pain, flatulence or wind, indigestion, nausea (feeling sick) or vomiting
- Cough, pharyngitis (inflammation of part of the throat)
- Tiredness, oedema (swelling of the legs and / or feet due to fluid retention).

Uncommon side-effects *(these are likely to affect between 1 and 10 in every 1,000 people)*:

- Candidiasis (a yeast infection commonly known as thrush), ear infection, herpes simplex, tooth infection
- Sleep problems, anxiety, depression
- Fainting, changes in touch sensation, pins and needles, migraine, changes in the way things taste
- Conjunctivitis (itching and redness of the eyes), dry eye, visual disturbance (e.g. blurred vision)
- Imbalance, hissing or ringing in ears
- Palpitations (fast or irregular heartbeat), heart attack
- Hypotension (low blood pressure), numbness, inability or difficulty to speak, paralysis of one side of the body (cerebral attack)
- Asthma, breathlessness, nosebleeds, blocked or runny nose
- Ulcers in the digestive system, gastritis (inflamed stomach), oesophagitis (inflamed gullet), abdominal bloating or discomfort, mouth ulcers, dry mouth, difficulty in swallowing, burping, gastro-oesophageal reflux disease (reflux of stomach contents into the gullet), gingivitis (inflammation of the gums), increase in stomach acid secretions, toothache
- Bruising, rash, redness or itching of the skin
- Swollen joints, muscle cramps, bone pain
- Difficulty urinating or pain when passing urine, or urinating more often
- Chest pain, rigors (shivering with a fever), thirst
- Increase or loss of appetite, weight gain
- Changes in blood or urine tests relating to the liver or the kidney
- Anaemia (low number of red blood cells)

Rare side effects *(these are likely to affect between 1 and 10 in every 10,000 people)*:

- Changes in the number of blood platelets (responsible for clotting blood) and white blood cells, changes in blood sugar levels
- Watery, painful eyes
- Bleeding of the digestive system
- Inflammation of the gall bladder, gallstones
- Discolouration of urine
- Impotence
- Hepatitis or changes in liver function
- Abnormalities of the heart rhythm
- Renal failure (severely decreased urine output)
- Cardiac failure (breathlessness, difficulty breathing when lying down, swelling of the feet or legs).

Very Rare side effects *(these are likely to affect less than 1 in every 10,000 people)*:

- Crisis of hypertension (high blood pressure).

Other rare side-effects have been reported with the use of anti-inflammatory drugs and cannot be ruled out for Frexocel: kidney damage or failure, liver damage or failure, severe skin reactions.

If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. How to store Frexocel

- Keep out of the reach and sight of children
- Do not use after the expiry date shown on the carton and blister
- This medicinal product does not require any special storage conditions
- Do not use if the pack is damaged or shows signs of tampering.

## 6. Further information

What Frexocel contains

The active substance is lumiracoxib. Each film-coated tablet contains 100 mg lumiracoxib. The other ingredients are:

Core: cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, povidone, titanium dioxide (E171), magnesium stearate.

Coat: hypromellose, macrogol, talc, iron oxide red (E172), iron oxide black (E172) and titanium dioxide (E171).

What Frexocel looks like and contents of the pack

Frexocel 100 mg film-coated tablets are ovaloid, red with "NVR" on one side and "OB" on the other. They are available in blister packs containing 2, 4, 5, 6, 10, 20, 30, 50, 100 or 600 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Novartis Pharmaceuticals UK Ltd

Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR

Manufacturer

Novartis Pharmaceuticals UK Ltd

Wimblehurst Road, Horsham, West Sussex RH12 5AB

This medicinal product is authorised in the Member States of the EEA under the following names

AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IC, IE, IT, LI, LU, LA, MT, NL, NO, PL, PT, SW, SL, SK: Prexige

AT, DE, EL, IT, PT, SL: Frexocel

BE, DE, ES, IE, IT, PL, PT: Stellige

DE, IT, PT: Hirzia

Date of Last Revision

DD/MM/YYYY

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NOVARTIS

Stellige®
LUMIRACOXIB

# Stellige® 100 mg, Film Coated Tablets

Lumiracoxib

**Read all of this leaflet carefully before you start taking this medicine**

Keep this leaflet. You may need to read it again.

If you have further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet



## 1. What Stellige is and what it is used for

Lumiracoxib is a non steroidal anti-inflammatory product (NSAID). It belongs to a group of medicines called cyclo-oxygenase-2 (COX-2) inhibitors. This group of medicines prevents the body from producing substances called prostaglandins. Some prostaglandins are responsible for causing pain and inflammation in the body, while others protect the stomach lining. Stellige reduces the amount of those prostaglandins which cause pain and inflammation but does not lower the amount of those which protect the stomach.

Stellige is used to treat painful symptoms of osteoarthritis of the knee and hip.

## 2. Before you take Stellige

Do not take Stellige

- if you are allergic (hypersensitive) to lumiracoxib or to any of the other ingredients of Stellige
- if you have an ulcer in your stomach or upper bowel
- if you have gastrointestinal bleeding, symptoms of which may include blood in vomit or when emptying bowels, or black, tarry stools
- if you suffer from any inflammatory bowel disorders (e.g. ulcerative colitis or Crohn's disease)
- if you have ever experienced any breathing problems including asthma, a runny nose, nasal polyps, skin rash, swelling of the face, lip or tongue or any other allergic-type reactions after taking medicines to treat arthritis or pain (e.g. acetylsalicylic acid or ibuprofen)
- if you have had heart problems including heart failure, angina (chest pain), if you have had a heart attack, stroke or if you have poor circulation in your legs or feet
- if you have serious kidney or liver problems
- if you are in the last three months of pregnancy
- if you are less than 18 years of age.

If any of these apply to you, tell your doctor before taking Stellige.

Take special care with Stellige

- if you have, or have ever had, a heart condition, or any vascular obstruction
- if you have a condition which increases your risk of heart disease, such as high blood pressure, diabetes, high cholesterol, or if you smoke
- if you have any swelling due to fluid retention
- if you have ever had gastrointestinal problems such as bleeding or ulcers in your gullet (oesophagus), stomach or upper bowel
- if you have kidney or liver disease
- if you might be dehydrated – this may happen if you have had diarrhoea or have been vomiting or unable to drink fluids.

If any of these apply to you, tell your doctor before you take Stellige.

Stellige may reduce the symptoms of an infection (e.g. headache, high temperature) and may therefore make it more difficult to detect. If you feel unwell and need to see a doctor, remember to mention that you are taking Stellige.

Stellige may cause serious allergic reactions. Therefore, stop taking Stellige and inform your doctor immediately if you experience symptoms such as skin rash or mucosal injuries.

Taking other medicines

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those without prescription. It is particularly important to tell your doctor if you are taking any of the following medicines:

- medicines to prevent blood clots and blood thinning tablets such as warfarin
- methotrexate (a medicine also used to treat rheumatoid arthritis)
- diuretics (medicines used to increase the amount of urine)
- ciclosporin or tacrolimus (medicines used to suppress the immune system)
- lithium (a medicine used to treat some types of depression)
- phenytoin (a medicine used in epilepsy)
- medicines used to treat high blood pressure and heart failure (e.g. ACE inhibitors)
- digoxin (a medicine used to treat heart problems)
- other COX-2 inhibitors or related medicines (e.g. ibuprofen, high-dose acetylsalicylic acid or other acetylsalicylic acid -like medicines).

Stellige can be taken with low-dose acetylsalicylic acid. If your doctor has recommended that you take low-dose acetylsalicylic acid for the prevention of stroke or heart attack, you should not stop taking this without consulting the doctor first.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Do not take Stellige if you are in the last three months of pregnancy. In the first and second trimesters of pregnancy, you should take Stellige only after consulting your doctor. If you are trying to become pregnant, you must discuss with your doctor before taking Stellige.

If you are breast-feeding tell your doctor. He or she will discuss with you the possible risks of taking Stellige during breast-feeding.

Driving and using machines

If you feel dizzy or have sight disturbances when you take Stellige, do not drive or use machines until these effects wear off.

Important information about some of the ingredients of Stellige

Stellige tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Stellige

Always take Stellige exactly as your doctor has told you even if different from this leaflet and check with your doctor or pharmacist if you are not sure.

Swallow Stellige tablets whole with a small amount of water. Do not chew or crush the tablets. Stellige tablets may be taken with or without food.

Your doctor will want to discuss your treatment from time to time. You should not take Stellige for longer than necessary.

Do not take a higher daily dose than recommended as daily doses higher than those recommended do not provide an additional benefit.

Osteoarthritis

The recommended dose is one tablet of 100 mg once daily.

XXXXXX GB

If you take more Stellige than you should

If you take too many tablets, tell your doctor or pharmacist or go to the nearest hospital emergency unit at once. You may require medical attention. Take your medicine with you.

If you forget to take Stellige

If you forget to take a dose, take one as soon as you remember. If it is nearly time for your next dose, you should simply take the next dose at the usual time. Do not double the next dose to make up for the one you missed.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, Stellige can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If you get any of the following, STOP taking the tablets immediately and tell your doctor:

- Severe or persistent stomach pain
- Shortness of breath, chest pains or ankle swelling
- Any sign of bleeding in your stomach or intestine, for example when emptying your bowels, blood in vomit or black, tarry stools
- Allergic reactions such as skin rash, wheezing, swelling of the face, tongue or pharynx, difficulty to swallow or shortness of breath
- Jaundice, yellowing of your skin or the whites of your eyes.

The following side effects were reported with Stellige.

Common side effects *(these are likely to affect between 1 and 10 in every 100 people)*:

- Flu-like symptoms, urinary infection, respiratory infection (e.g. bronchitis)
- Headache, dizziness
- Diarrhoea, constipation, stomach pain, flatulence or wind, indigestion, nausea (feeling sick) or vomiting
- Cough, pharyngitis (inflammation of part of the throat)
- Tiredness, oedema (swelling of the legs and / or feet due to fluid retention).

Uncommon side-effects *(these are likely to affect between 1 and 10 in every 1,000 people)*:

- Candidiasis (a yeast infection commonly known as thrush), ear infection, herpes simplex, tooth infection
- Sleep problems, anxiety, depression
- Fainting, changes in touch sensation, pins and needles, migraine, changes in the way things taste
- Conjunctivitis (itching and redness of the eyes), dry eye, visual disturbance (e.g. blurred vision)
- Imbalance, hissing or ringing in ears
- Palpitations (fast or irregular heartbeat), heart attack
- Hypotension (low blood pressure), numbness, inability or difficulty to speak, paralysis of one side of the body (cerebral attack)
- Asthma, breathlessness, nosebleeds, blocked or runny nose
- Ulcers in the digestive system, gastritis (inflamed stomach), oesophagitis (inflamed gullet), abdominal bloating or discomfort, mouth ulcers, dry mouth, difficulty in swallowing, burping, gastro-oesophageal reflux disease (reflux of stomach contents into the gullet), gingivitis (inflammation of the gums), increase in stomach acid secretions, toothache
- Bruising, rash, redness or itching of the skin
- Swollen joints, muscle cramps, bone pain
- Difficulty urinating or pain when passing urine, or urinating more often
- Chest pain, rigors (shivering with a fever), thirst
- Increase or loss of appetite, weight gain
- Changes in blood or urine tests relating to the liver or the kidney
- Anaemia (low number of red blood cells)

Rare side effects *(these are likely to affect between 1 and 10 in every 10,000 people)*:

- Changes in the number of blood platelets (responsible for clotting blood) and white blood cells, changes in blood sugar levels
- Watery, painful eyes
- Bleeding of the digestive system
- Inflammation of the gall bladder, gallstones
- Discolouration of urine
- Impotence
- Hepatitis or changes in liver function
- Abnormalities of the heart rhythm
- Renal failure (severely decreased urine output)
- Cardiac failure (breathlessness, difficulty breathing when lying down, swelling of the feet or legs).

Very Rare side effects *(these are likely to affect less than 1 in every 10,000 people)*:

- Crisis of hypertension (high blood pressure).

Other rare side-effects have been reported with the use of anti-inflammatory drugs and cannot be ruled out for Stellige: kidney damage or failure, liver damage or failure, severe skin reactions.

If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. How to store Stellige

- Keep out of the reach and sight of children
- Do not use after the expiry date shown on the carton and blister
- This medicinal product does not require any special storage conditions
- Do not use if the pack is damaged or shows signs of tampering.

## 6. Further information

What Stellige contains

The active substance is lumiracoxib. Each film-coated tablet contains 100 mg lumiracoxib. The other ingredients are:

Core: cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, povidone, titanium dioxide (E171), magnesium stearate.

Coat: hypromellose, macrogol, talc, iron oxide red (E172), iron oxide black (E172) and titanium dioxide (E171).

What Stellige looks like and contents of the pack

Stellige 100 mg film-coated tablets are ovaloid, red with "NVR" on one side and "OB" on the other. They are available in blister packs containing 2, 4, 5, 6, 10, 20, 30, 50, 100 or 600 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Novartis Pharmaceuticals UK Ltd

Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR

Manufacturer

Novartis Pharmaceuticals UK Ltd

Wimblehurst Road, Horsham, West Sussex RH12 5AB

This medicinal product is authorised in the Member States of the EEA under the following names

AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IC, IE, IT, LI, LU, LA, MT, NL, NO, PL, PT, SW, SL, SK: Prexige

AT, DE, EL, IT, PT, SL: Frexocel

BE, DE, ES, IE, IT, PL, PT: Stellige

DE, IT, PT: Hirzia

Date of Last Revision

DD/MM/YYYY

XXXXXX GB

NOVARTIS

# Hirzia® 100 mg, Film Coated Tablets

Lumiracoxib

**Read all of this leaflet carefully before you start taking this medicine**

Keep this leaflet. You may need to read it again.

If you have further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet



## 1. What Hirzia is and what it is used for

Lumiracoxib is a non steroidal anti-inflammatory product (NSAID). It belongs to a group of medicines called cyclo-oxygenase-2 (COX-2) inhibitors. This group of medicines prevents the body from producing substances called prostaglandins. Some prostaglandins are responsible for causing pain and inflammation in the body, while others protect the stomach lining. Hirzia reduces the amount of those prostaglandins which cause pain and inflammation but does not lower the amount of those which protect the stomach.

Hirzia is used to treat painful symptoms of osteoarthritis of the knee and hip.

## 2. Before you take Hirzia

Do not take Hirzia

- if you are allergic (hypersensitive) to lumiracoxib or to any of the other ingredients of Hirzia
- if you have an ulcer in your stomach or upper bowel
- if you have gastrointestinal bleeding, symptoms of which may include blood in vomit or when emptying bowels, or black, tarry stools
- if you suffer from any inflammatory bowel disorders (e.g. ulcerative colitis or Crohn's disease)
- if you have ever experienced any breathing problems including asthma, a runny nose, nasal polyps, skin rash, swelling of the face, lip or tongue or any other allergic-type reactions after taking medicines to treat arthritis or pain (e.g. acetylsalicylic acid or ibuprofen)
- if you have had heart problems including heart failure, angina (chest pain), if you have had a heart attack, stroke or if you have poor circulation in your legs or feet
- if you have serious kidney or liver problems
- if you are in the last three months of pregnancy
- if you are less than 18 years of age.

If any of these apply to you, tell your doctor before taking Hirzia.

Take special care with Hirzia

- if you have, or have ever had, a heart condition, or any vascular obstruction
- if you have a condition which increases your risk of heart disease, such as high blood pressure, diabetes, high cholesterol, or if you smoke
- if you have any swelling due to fluid retention
- if you have ever had gastrointestinal problems such as bleeding or ulcers in your gullet (oesophagus), stomach or upper bowel
- if you have kidney or liver disease
- if you might be dehydrated – this may happen if you have had diarrhoea or have been vomiting or unable to drink fluids.

If any of these apply to you, tell your doctor before you take Hirzia.

Hirzia may reduce the symptoms of an infection (e.g. headache, high temperature) and may therefore make it more difficult to detect. If you feel unwell and need to see a doctor, remember to mention that you are taking Hirzia.

Hirzia may cause serious allergic reactions. Therefore, stop taking Hirzia and inform your doctor immediately if you experience symptoms such as skin rash or mucosal injuries.

Taking other medicines

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those without prescription. It is particularly important to tell your doctor if you are taking any of the following medicines:

- medicines to prevent blood clots and blood thinning tablets such as warfarin
- methotrexate (a medicine also used to treat rheumatoid arthritis)
- diuretics (medicines used to increase the amount of urine)
- ciclosporin or tacrolimus (medicines used to suppress the immune system)
- lithium (a medicine used to treat some types of depression)
- phenytoin (a medicine used in epilepsy)
- medicines used to treat high blood pressure and heart failure (e.g. ACE inhibitors)
- digoxin (a medicine used to treat heart problems)
- other COX-2 inhibitors or related medicines (e.g. ibuprofen, high-dose acetylsalicylic acid or other acetylsalicylic acid -like medicines).

Hirzia can be taken with low-dose acetylsalicylic acid. If your doctor has recommended that you take low-dose acetylsalicylic acid for the prevention of stroke or heart attack, you should not stop taking this without consulting the doctor first.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Do not take Hirzia if you are in the last three months of pregnancy. In the first and second trimesters of pregnancy, you should take Hirzia only after consulting your doctor. If you are trying to become pregnant, you must discuss with your doctor before taking Hirzia.

If you are breast-feeding tell your doctor. He or she will discuss with you the possible risks of taking Hirzia during breast-feeding.

Driving and using machines

If you feel dizzy or have sight disturbances when you take Hirzia, do not drive or use machines until these effects wear off.

Important information about some of the ingredients of Hirzia

Hirzia tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

## 3. How to take Hirzia

Always take Hirzia exactly as your doctor has told you even if different from this leaflet and check with your doctor or pharmacist if you are not sure.

Swallow Hirzia tablets whole with a small amount of water. Do not chew or crush the tablets. Hirzia tablets may be taken with or without food.

Your doctor will want to discuss your treatment from time to time. You should not take Hirzia for longer than necessary.

Do not take a higher daily dose than recommended as daily doses higher than those recommended do not provide an additional benefit.

Osteoarthritis

The recommended dose is one tablet of 100 mg once daily.

XXXXXX GB

### If you take more Hirzia than you should

If you take too many tablets, tell your doctor or pharmacist or go to the nearest hospital emergency unit at once. You may require medical attention. Take your medicine with you.

### If you forget to take Hirzia

If you forget to take a dose, take one as soon as you remember. If it is nearly time for your next dose, you should simply take the next dose at the usual time. Do not double the next dose to make up for the one you missed.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, Hirzia can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

If you get any of the following, STOP taking the tablets immediately and tell your doctor:

- Severe or persistent stomach pain
- Shortness of breath, chest pains or ankle swelling
- Any sign of bleeding in your stomach or intestine, for example when emptying your bowels, blood in vomit or black, tarry stools
- Allergic reactions such as skin rash, wheezing, swelling of the face, tongue or pharynx, difficulty to swallow or shortness of breath
- Jaundice, yellowing of your skin or the whites of your eyes.

The following side effects were reported with Hirzia.

Common side effects *(these are likely to affect between 1 and 10 in every 100 people)*:

- Flu-like symptoms, urinary infection, respiratory infection (e.g. bronchitis)
- Headache, dizziness
- Diarrhoea, constipation, stomach pain, flatulence or wind, indigestion, nausea (feeling sick) or vomiting
- Cough, pharyngitis (inflammation of part of the throat)
- Tiredness, oedema (swelling of the legs and / or feet due to fluid retention).

Uncommon side-effects *(these are likely to affect between 1 and 10 in every 1,000 people)*:

- Candidiasis (a yeast infection commonly known as thrush), ear infection, herpes simplex, tooth infection
- Sleep problems, anxiety, depression
- Fainting, changes in touch sensation, pins and needles, migraine, changes in the way things taste
- Conjunctivitis (itching and redness of the eyes), dry eye, visual disturbance (e.g. blurred vision)
- Imbalance, hissing or ringing in ears
- Palpitations (fast or irregular heartbeat), heart attack
- Hypotension (low blood pressure), numbness, inability or difficulty to speak, paralysis of one side of the body (cerebral attack)
- Asthma, breathlessness, nosebleeds, blocked or runny nose
- Ulcers in the digestive system, gastritis (inflamed stomach), oesophagitis (inflamed gullet), abdominal bloating or discomfort, mouth ulcers, dry mouth, difficulty in swallowing, burping, gastro-oesophageal reflux disease (reflux of stomach contents into the gullet), gingivitis (inflammation of the gums), increase in stomach acid secretions, toothache
- Bruising, rash, redness or itching of the skin
- Swollen joints, muscle cramps, bone pain
- Difficulty urinating or pain when passing urine, or urinating more often
- Chest pain, rigors (shivering with a fever), thirst
- Increase or loss of appetite, weight gain
- Changes in blood or urine tests relating to the liver or the kidney
- Anaemia (low number of red blood cells)

Rare side effects *(these are likely to affect between 1 and 10 in every 10,000 people)*:

- Changes in the number of blood platelets (responsible for clotting blood) and white blood cells, changes in blood sugar levels
- Watery, painful eyes
- Bleeding of the digestive system
- Inflammation of the gall bladder, gallstones
- Discolouration of urine
- Impotence
- Hepatitis or changes in liver function
- Abnormalities of the heart rhythm
- Renal failure (severely decreased urine output)
- Cardiac failure (breathlessness, difficulty breathing when lying down, swelling of the feet or legs).

Very Rare side effects *(these are likely to affect less than 1 in every 10,000 people)*:

- Crisis of hypertension (high blood pressure).

Other rare side-effects have been reported with the use of anti-inflammatory drugs and cannot be ruled out for Hirzia: kidney damage or failure, liver damage or failure, severe skin reactions.

If any of the side effects get serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. How to store Hirzia

- Keep out of the reach and sight of children
- Do not use after the expiry date shown on the carton and blister
- This medicinal product does not require any special storage conditions
- Do not use if the pack is damaged or shows signs of tampering.

## 6. Further information

### What Hirzia contains

The active substance is lumiracoxib. Each film-coated tablet contains 100 mg lumiracoxib. The other ingredients are:

Core: cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, povidone, titanium dioxide (E171), magnesium stearate.

Coat: hypromellose, macrogol, talc, iron oxide red (E172), iron oxide black (E172) and titanium dioxide (E171).

### What Hirzia looks like and contents of the pack

Hirzia 100 mg film-coated tablets are ovaloid, red with "NVR" on one side and "OB" on the other. They are available in blister packs containing 2, 4, 5, 6, 10, 20, 30, 50, 100 or 600 tablets. Not all pack sizes may be marketed.

### Marketing Authorisation Holder

Novartis Pharmaceuticals UK Ltd

Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR

### Manufacturer

Novartis Pharmaceuticals UK Ltd

Wimblehurst Road, Horsham, West Sussex RH12 5AB

This medicinal product is authorised in the Member States of the EEA under the following names

AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IC, IE, IT, LI, LU, LA, MT, NL, NO, PL, PT, SW, SL, SK: Prexige

AT, DE, EL, IT, PT, SL: Frexocel

BE, DE, ES, IE, IT, PL, PT: Stellige

DE, IT, PT: Hirzia

### Date of Last Revision

DD/MM/YYYY

XXXXXX GB

# Module 4

# Labelling


103.0 mm
98.0 mm
72.0 mm
Laufrichtung Folie
NOVARTIS
Prexige®
100 mg Tablets
Lumiracoxib


Braille reads:
Frexocel
100 mg
NOVARTIS
30 film-coated tablets
Frexocel®100 mg film-coated tablets
LUMIRACOXIB
NOVARTIS
30 film-coated tablets
Frexocel®100 mg film-coated tablets
LUMIRACOXIB
30 film-coated tablets
NOVARTIS
Frexocel®100 mg film-coated tablets
XXXXXXX
GB
NOVARTIS
30 film-coated tablets
Frexocel®100 mg film-coated tablets
LUMIRACOXIB
EXP/LOT
NOVARTIS
For oral use only.
Keep out of the reach and sight of children.
Take as directed by your doctor.
Each film-coated tablet contains 100 mg lumiracoxib as the active.
The tablet also contains lactose monohydrate.
Read the package leaflet before use.
Marketing Authorisation Holder:
Novartis Pharmaceuticals UK Limited
Frimley Business Park, Frimley,
Camberley,
Surrey GU16 7SR
PL 00101/0692
Medicinal product subject to medical prescription.
POM
X XXXXXX XXXXXX


Braille reads:
Stellige
100 mg
NOVARTIS
30 film-coated tablets
Stellige® 100 mg film-coated tablets
LUMIRACOXIB
30 film-coated tablets
Stellige® 100 mg film-coated tablets
XXXXXX
GB
EXP/LOT
NOVARTIS
For oral use only.
Keep out of the reach and sight of children.
Take as directed by your doctor.
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Frimley Business Park, Frimley,
Camberley,
Surrey GU16 7SR
PL 00101/0692
Medicinal product subject to medical prescription.
POM
X XXXXXX XXXXXX


Braille reads:
Hirzia
100 mg
NOVARTIS
30 film-coated tablets
Hirzia® 100 mg film-coated tablets
LUMIRACOXIB
NOVARTIS
30 film-coated tablets
Hirzia® 100 mg film-coated tablets
LUMIRACOXIB
30 film-coated tablets
NOVARTIS
Hirzia® 100 mg film-coated tablets
XXXXXXX
NOVARTIS
30 film-coated tablets
Hirzia® 100 mg film-coated tablets
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The tablet also contains lactose monohydrate.
Read the package leaflet before use.
Marketing Authorisation Holder:
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Frimley Business Park, Frimley,
Camberley,
Surrey GU16 7SR
PL 00101/0698
POM
X XXXXXX XXXXXX

# Module 5
# Scientific discussion during initial procedure

## 1. INTRODUCTION

**Background**

These applications were submitted via the Mutual Recognition Procedure by Novartis Pharmaceuticals UK Ltd. Please note that in the original Mutual Recognition Procedures, applications were made for three strengths of product containing 100mg, 200mg and 400mg lumaricoxib. In addition, the therapeutic indications in the original applications were as follows:

1. Symptomatic relief in the treatment of osteoarthritis (100mg and 200mg).
2. For the short-term relief of moderate to severe acute pain associated with (100mg, 200mg and 400mg):
   - primary dysmenorrhoea,
   - dental surgery,
   - orthopaedic surgery.

These were all new active substance applications, submitted as full dossiers under Article 8.3 of Directive 2001/83/EC, as amended. These were based on national marketing authorisation granted by the UK on the 12th September 2003 (Prexige) and 9th July 2004 (Frexocel, Stellige, Hirzia). Please note that Hirzia 100, 200 and 400mg Tablets were initially called Exforge 100, 200 and 400mg Tablets during the UK national assessment. However, this product name was subsequently changed to Hirzia by variation.

Originally, the national applications for Marketing Authorisation were submitted for Prexige 200mg and 400mg tablets only. During the assessment process, the UK regulatory body proposed changes, including removing an indication for symptomatic relief in the treatment of rheumatoid arthritis and decreasing the dosage in the treatment of osteoarthritis.

The UK Advisory Committee considered the licence application on 27th March 2003 and advised that Marketing Authorisations should be conditionally granted as long as the recommended changes were incorporated.

In order to comply with the reduced dosage in the treatment of osteoarthritis, a new application was submitted for Prexige 100mg tablets (no additional clinical data were supplied) and Marketing Authorisations were granted for all three strengths on 12th September 2003.

Duplicate applications, identical to those approved for Prexige tablets, were submitted by Novartis under the product names Exforge, Frexocel and Stellige and licences were granted for these on 9th July 2004.

The tablets underwent an Outgoing Mutual Recognition Procedure in 2004 at which time new clinical data was supplied and assessed. The Outgoing Mutual Recognition Procedure was withdrawn in deference to the outcome of the Article 31 CHMP referral and other concerns from CMSs (which are all now considered addressed). Following the Europe-wide Article-31 referral for the Cox-2 class, two variations were granted to update the relevant sections of the SPC. A further variation was granted on 2nd December 2005, reducing the dosage in the treatment of osteoarthritis and primary dysmenorrhoea.

During this current MRP procedure, several member states referred the products to CMD(h) on the grounds of potential serious risk to public health. These CMS's considered that the safety and efficacy of lumaricoxib was not established in all indications sought and debated the duration of treatment in osteoarthritis. The majority opinion at CMD(h) was that the indication for treatment of osteoarthritis of the knee and hip would be acceptable with the provision that the treatment would be for the shortest duration and with the lowest dose. Thus, in order to reach agreement in all Member States, only the 100mg strengths were approved and for the indication of "symptomatic relief in the treatment of osteoarthritis of the knee and hip" only.

Marketing Authorisations were approved for Prexige 100mg Tablets in Austria, Belgium, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Hungary, Iceland, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, Slovak Republic.

Marketing Authorisations were approved for Frexocel 100mg Tablets in Austria, Germany, Greece, Italy, Portugal, Slovenia.

Marketing Authorisations were approved for Stellige 100mg Tablets in Belgium, Germany, Spain, Ireland, Italy, Poland, Portugal.

Marketing Authorisations were approved for Hirzia 100mg Tablets in Germany, Italy, Portugal.

**Overall Benefit/Risk Assessment**

Preclinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognised guidelines. The main target organs of toxicity were the gastrointestinal tract and the kidney.

Clinical studies on Prexige, Frexocel, Stellige and Hirzia 100mg, 200mg and 400mg Tablets were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

# 3. QUALITY ASPECTS

## 3.2.S DRUG SUBSTANCE

**Nomenclature**

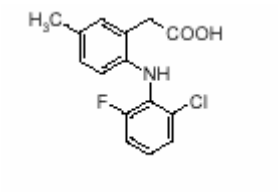
INN Lumiracoxib

Chemical name: 2-[(2-chloro-6-fluorophenyl)amino]-5-methyl benzeneacetic acid

or

[2-(2-chloro-6-fluorophenylamino)-5-methyl phenyl] acetic acid

**Structure**




$C_{15}H_{13}ClFNO_2$ RMM 293.72

**General properties**

Lumaricoxib is a white, yellowish or beige powder, which is insoluble in most aqueous solutions (e.g. water 0.01mg/ml) and only sparingly soluble in some organic solvents (e.g. methanol 20.6mg/ml) and slightly soluble in others (e.g. toluene 1.13mg/ml). The pKa in water (determined by linear extrapolation of water/acetonitrile pKa results) is 4.7. The estimated melting point is 167°C, although it decomposes on heating.

**Manufacture**

The synthetic pathway is described in detail with the reaction conditions specified where crucial for the process. The conditions used and the purification procedures are described. The quantities of raw materials and the expected yields of the isolated intermediate and the final drug substance are stated. The proposed control specifications are acceptable.

**Control of Materials**

Adequate specifications for the principal materials used in the synthesis and the other raw materials / solvents are provided. A suitable identity test is employed for each compound and other crucial tests for ensuring the quality of the material (e.g. assay, purity) are included where appropriate. The three compounds defined as starting materials are all commercially available.

**Controls of Critical Steps and Intermediates**

Appropriate in-process controls are applied, and suitable specifications and test methods are applied to the intermediate products.

**Elucidation of Structure and other Characteristics**

The structure of lumiracoxib has been adequately characterised and satisfactory confirmation of the proposed structure is provided.

**Impurities**

Potential related substances seen in batches of drug substance come from traces of starting materials, reagents and intermediates or may be formed by degradation.

All impurities observed are appropriately qualified. Residual solvents and heavy metals are also controlled.

**Drug Substance Specification**
An appropriate specification is provided for lumiracoxib bulk active pharmaceutical ingredient (API).

**Analytical Procedures**
Full details of all the analytical testing methods for lumiracoxib are provided. Data are provided to support the validity of the analytical methods. The analytical methods are appropriate for verifying compliance with the relevant specifications.

**Batch Analyses**
Batch analysis data are provided on development and production batches of API. All production batches made by the current manufacturing process comply with the proposed specification.

**Justification of Specification**
The applicant has provided justification for each of the selected tests and the proposed limits and these are satisfactory.

**Reference Standards or Materials**
A certificate of analysis is supplied for the current reference standard. The batch utilised has been rigorously evaluated with additional tests to those required in the drug substance specifications.

**Container Closure System**
Lumiracoxib is stored in a double polyethylene bag, in an outer metal container. A declaration is provided to confirm that the plastic is suitable for contact with foodstuffs.

**Stability**
A comprehensive stability testing programme has been implemented. Stress testing of lumiracoxib has also been performed. Overall lumiracoxib is a stable drug when stored protected from light under real-time conditions in the proposed packaging. An 18 month re-test date is supported by the data. Over this time period there is no evidence that there are changes to the physical characteristics of the drug; and, in addition the levels of the known degradants remain easily within the proposed limits.

## 3.2.P DRUG PRODUCT

**GMP Statement**
Acceptable standards of GMP are in place for the manufacture of these tablets. The manufacturing site is already accepted as the site of manufacture for a number of granted Marketing Authorisations, including some for film-coated tablets.

The tablets are batch released within the EU at authorised sites by a qualified person.

**Description and Composition of the Drug Product**
The drug product proposed for marketing is a film-coated tablet, containing 100 mg of the API, Lumiracoxib. The excipients present include cellulose microcrystalline, croscarmellose sodium, lactose monohydrate, povidone, titanium dioxide, magnesium stearate, hypromellose, Macrogol, talc, iron oxide red (E 172) and iron oxide black (E

172). All the excipients in the tablet cores comply with their Ph. Eur. / USP monographs. Representative Certificates of Analysis provided confirms this. The magnesium stearate is from a vegetable source and relevant information is provided in relation to lactose. Therefore there are no concerns with respect to TSE.

The coating agents are purchased commercially. Declarations are given that the components all comply with the Ph. Eur. monograph or alternative monographs where applicable. The testing specifications on the coating agents include identification test for the colouring agents and comparisons with reference samples. These are appropriate.

Tablets are ovaloid red film-coated with NVR debossed on one side and 'OB' on the other site.

**Manufacturing Process Development**
A number of processing parameters were evaluated during the optimisation of the tablet formulations but these data are not presented.

**Description of Manufacturing Process and Process Controls**
Flow diagrams are provided for the manufacturing process. Adequately detailed descriptions of the processes are provided.

**Control of Critical Steps and Intermediates**
The in-process controls are provided and the frequency of the checks is documented. These are appropriate for a product of this type.

**Process Validation and/or Evaluation**
Validation data for production scale batches, made at the proposed site of manufacture were provided. Each stage of the process has been defined as critical or non-critical with fixed or varied parameters. It is indicated that during optimisation of the process, ranges for some of the parameters were evaluated and therefore at validation of the production scale batches such parameters were fixed. Consequently only data on the compression stage of the process and the film-coating has been provided. Data are presented to demonstrate the homogeneity of the product prior to compression.

The tablet cores have been compressed at different speeds and compaction force to give different hardness. The range of the selected forces of compression and speeds of compression did not have an adverse affect on the final tablet core with all the core tablets satisfying the in-process control requirements. Film-coating the cores showed no change to the overall rate of drug release from the tablets and the film-coated tablets continued to satisfy the proposed finished product specifications.

The data provided confirm that the process is well controlled and reproducible.

**Finished Product Specifications**
Suitable tests and limits are proposed for the control of preparations of this type.

**Analytical Procedures**
A comprehensive validation package has been submitted for the analytical methods.

**Batch Analyses**
Appropriate data have been provided on batches of product manufactured at a production scale in the designated facility. These demonstrate compliance with the proposed specification.

**Characterisation of Impurities**
The potential impurities in the tablets are the same as those for the active substance. The three major degradation products have been named and limits applied. These have all been detected and quantified during storage. The other known degradants are included as 'other degradation products'. It is reported that these have been detected close to the limit of quantification during storage.

**Reference Standards or Materials**
A certificate of analysis is provided for the current system suitability standard used in the method for identification, assay and purity.

**Container Closure System**
The tablets are packed into blisters composed of transparent PVC attached to aluminium foil via a heat seal lacquer. Specifications for these components are provided with representative certificates of conformity. Declarations from the suppliers of the packaging are provided to confirm compliance with Directive 90/128/EEC in relation to the suitability of the packaging in contact with food-stuffs.

**Stability**
Stability data were generated on full scale production size batches of product manufactured at the intended site and stored in the intended packaging and on small scale development batches.

The data presented demonstrate that the drug is stable in the proposed formulation under both real-time and accelerated storage. There is minimal variation to the assayed content up to 18 months of storage at real time and the impurity profile also confirms the stable nature of the drug. The appearance of the tablets is reported to be unchanged. These data are supportive of a 36-month shelf life with no additional storage precautions required.

A photostability study has also been performed, consistent with 'Note for guidance on the photostability testing of new active substances and medicinal products (ICH) 279/9'. There was no change observed to the appearance of the tablets, their dissolution, characteristics, assay content or impurity levels. Based on these data no storage warning is necessary in relation to protecting the tablets from light.

**Post-approval Stability Protocol and Stability Commitment**
A suitable commitment is provided.

**SPC**
The pharmaceutical aspects of the SPCs are acceptable.

**Labelling**
Colour mock-ups of labelling are provided both for blister strips and cartons for both strengths. These are acceptable.

**Package Leaflet**
This is considered pharmaceutically satisfactory.

**Biopharmaceutics**
Validation reports for the methods used to analyse lumiracoxib in biological samples (plasma, urine and synovial fluid) for the purposes of the bioequivalence and PK studies

were developed. Data are provided to demonstrate the methods were specific for lumiracoxib and the internal standard with satisfactory accuracy, precision, intermediate precision and linearity over an appropriate range.

From the studies performed, it was concluded that the tablet strengths proposed for marketing are bioequivalent.

**CONCLUSION**

The data presented in relation to this new chemical entity are comprehensive and satisfactory. The development of the finished product is adequately described and the manufacturing method has been suitably validated. Appropriate specifications are applied to ensure the quality of the tablets at release and through shelf life. Stability data are supportive of a 3-year shelf life at this time. The pharmaceutical expert report has been written by a qualified pharmacist with relevant experience to write this report and is a comprehensive review of the quality aspects of the dossier. It is considered that there are no outstanding quality issues to prevent a grant of a Marketing Authorisation for the100mg tablets containing lumiracoxib.

# 4. NON-CLINICAL ASPECTS

## GLP ASPECTS

All of the pivotal toxicity studies were performed in accordance with the principles of Good Laboratory Practices (GLP) and with the appropriate guidelines.

## PHARMACODYNAMICS

### Pharmacodynamics for the Proposed Indications

The *in vitro* inhibition of COX-1 and COX-2 by lumiracoxib (also referred to as CGS 35189 or COX189) was studied in comparison to celecoxib and diclofenac. Lumiracoxib and celecoxib rapidly and reversibly inhibited COX-1, but their inhibition of COX-2 was time-dependent and only slowly reversible. In contrast, the non-selective inhibitor diclofenac demonstrated a time-dependent and slowly reversible inhibition for both isoforms. Lumiracoxib and celecoxib showed a 50-fold or 75-fold greater affinity for COX-2 than COX-1. The kinetic parameters are shown in the table (Table 1) below.

**Table 1. Kinetic parameters for inhibition of COX-1 and COX-2 enzymatic activities.**

| | COX-1 | | | COX-2 | | |
|---|---|---|---|---|---|---|
| | $K_i\infty$ [μM] | $k_{on}$ ($sec^{-1}.\mu M^{-1}$) | $t_{1/2}$ (min) | $K_i\infty$ [μM] | $k_{on}$ ($sec^{-1}.\mu M^{-1}$) | $t_{1/2}$ (min) |
| **Diclofenac** | 0.01 | 0.1 | 6 | 0.01 | 0.006 | 150 |
| **Celecoxib** | 15 | $>10^5$ | <<1 | 0.2 | 0.01 | 5 |
| **CGS 35189** | 3 | $>10^5$ | <<1 | 0.06 | 0.005 | 42 |

The results are the average of two experiments.

The metabolite CGS 37645 (hydroxylated at the 4-position of aniline ring) was found to inhibit both COX-1 and COX-2, although it was 10 to 30 times less potent than the parent drug.

In a human whole blood assay, lumiracoxib (CGS 35189), celecoxib, rofecoxib and diclofenac inhibited both COX-1 ($TXB_2$ production) and COX-2 ($PGE_2$ production) in a concentration-dependent manner, with lumiracoxib showing the greatest selectivity for COX-2. The $IC_{50}$'s and $IC_{80}$'s are shown in the table (Table 2) below.

**Table 2**

**Table 3.1-1 Summary of inhibitory potencies on thromboxane $B_2$ and prostaglandin $E_2$ production**

| | $IC_{50}$ (μM) | | | $IC_{80}$ (μM) | | |
|---|---|---|---|---|---|---|
| | $TxB_2$ | $PGE_2$ | Ratio | $TxB_2$ | $PGE_2$ | Ratio |
| **CGS 35189** | 70 (±20) (12) | 0.1 (±0.04) (12) | 700 | 200 (±40) (12) | 0.4 (±0.1) (12) | 500 |
| **Rofecoxib** | 20 (±3) (6) | 0.2 (±0.04) (6) | 100 | 60 (±6) (6) | 0.4 (±0.07) (6) | 150 |
| **Celecoxib** | 5 (±2) (6) | 0.1 (±0.08) (6) | 50 | 20 (±5) (6) | 0.7 (±0.1) (6) | 30 |
| **Diclofenac** | 0.07 (±0.01) (8) | 0.01 (±0.003) (8) | 7 | 0.2 (±0.04) (8) | 0.03 (±0.007) (8) | 7 |

The results are the mean (±sem)(number of donors) values determined from the corresponding $IC_{50}$ and $IC_{80}$ results for each donor. The ratio for COX-2 selectivity is the IC value for prostaglandin $E_2$ divided by the corresponding IC value for thromboxane $B_2$.

Three metabolites of lumiracoxib were also studied in the human whole blood assay. The 4'-hydroxy metabolite NVP-LBG677 (CGS 37645, M23) showed similar potency and selectivity as the parent compound in this assay. The other metabolites, NVP-

LBH019 (5-carboxy, M11) and NVP-LBK286 (4'-hydroxy, 5-carboxy, M5)) did not show concentration-dependent inhibition of either isoform.

The comparable potency of lumiracoxib and its 4'-hydroxy metabolite in this assay is in contrast to the *in vitro* assay and *in vivo* assays, where the metabolite was 10 to 30 times less potent than lumiracoxib.

The COX-2 selectivity of both lumiracoxib and celecoxib was demonstrated in an *in vitro* cell-based assay using cloned 293 human kidney epithelial cells transfected with human recombinant COX-1 and human dermal fibroblasts induced to produce COX-2 ($IC_{50}$'s of 140nM and 306 nM, respectively, compared to > 30 μM for COX-1). The $IC_{50}$'s for diclofenac against COX-1 and COX-2 were 132 and 11 nM, respectively.

The lipopolysaccharide (LPS)-stimulated production of $PGE_2$ in rat dorsal air pouch was dose-dependently inhibited by lumiracoxib when given orally 1 hour before LPS challenge, with an $ED_{50}$ of 0.2 mg/kg. The $ED_{50}$'s for celecoxib and diclofenac in this model were 0.4 and 0.1 mg/kg respectively.

Lumiracoxib, celecoxib and diclofenac demonstrated similar anti-inflammatory activity against carrageenan-induced rat paw oedema, with $ED_{30}$'s of 0.35, 0.58 and 0.53 mg/kg, respectively, 4 hours after an oral dose. Their effects were also comparable 7 hours after the dose. The hydroxylated metabolite CGS 37645 (NVP-LBG677-NX-1) also showed activity in this assay, but with <2% of the potency of lumiracoxib.

Diclofenac, celecoxib and lumiracoxib dose-dependently decreased the severity of acute adjuvant-induced arthritis in rats. The $ED_{50}$ for celecoxib was 1.5 mg/kg and that for lumiracoxib was 4.9 mg/kg. In two separate assays, the $ED_{50}$ for diclofenac was 1.8 and 3.6 mg/kg. Similar results were obtained in chronic adjuvant-induced arthritis in rats.

Diclofenac, celecoxib and lumiracoxib administered at 10 mg/kg orally increased the pain threshold in the Randall-Selitto paw pressure hyperalgesia assay in rats.

Lumiracoxib also produced analgesic effects in complete Freund's adjuvant (CFA)-induced hyperalgesia in rat, CFA- and carrageenan-induced hyperalgesia in guinea pigs and in acetic acid-induced writhing in mice.

Diclofenac, celecoxib and lumiracoxib all showed anti-pyretic activity, producing dose-related inhibition in the LPS-induced rat fever model, with $ED_{50}$'s of 1.01, 0.34 and 0.13 mg/kg respectively.

The $ED_{50}$ of lumiracoxib on the inhibition of production of $TXB_2$ *ex vivo* was 33.5 mg/kg, compared with 5.1 mg/kg for diclofenac. The higher $ED_{50}$ of lumiracoxib for COX-1 inhibition may suggest a lower potential than diclofenac for producing gastrointestinal lesions.

The pharmacokinetics of lumiracoxib, celecoxib and rofecoxib were investigated in a rat tissue chamber model. This is similar to the air pouch, but provides a chamber from which repeated samples may be taken. Inflammation is induced by injecting carrageenan into the chamber. The fluid forming in the lumen of the tissue chamber is considered to be a surrogate for deeper compartments such as synovial fluid in joints. A similar technique, reported in the literature, has been used to investigate the pharmacokinetic properties of NSAID's in horses.

Following injection of carrageenan, the drugs were administered orally and their concentrations measured in plasma and in exudate from the chamber for 24 hours. Lumiracoxib was rapidly absorbed and distributed into the exudate, from which it was eliminated more slowly than from plasma. At 12 hours post-dose, concentrations were higher in exudate than in plasma. Rofecoxib and celecoxib were distributed into the exudate more slowly than lumiracoxib. Rofecoxib concentrations in plasma and exudate equilibrated at 16 hours post-dose, whilst celecoxib concentrations in exudate remained lower than those in plasma even after 24 hours. Therefore using this model, lumiracoxib distributes most rapidly to sites of inflammation, where it reaches therapeutically relevant concentrations more rapidly. If this model reflects the situation in man, lumiracoxib may have a more rapid onset of action than the other COX-2 inhibitors tested.

**Secondary Pharmacology**

In a fasted rat ulcer model, lumiracoxib did not produce any ulcers 4 hours after an oral dose of 100 mg/kg. Celecoxib produced minor lesions in 2/24 animals at the same dose. Diclofenac caused extensive ulceration in all 42 animals tested. The lumiracoxib metabolite CGS 36745 produced no ulcers when dosed at 100 mg/kg.

Neither lumiracoxib nor celecoxib significantly increased the intestinal permeability in rats following an acute oral dose of 30 mg/kg, as measured by the excretion of $^{51}$Cr-EDTA.

Similarly, doses of 10 mg/kg given orally on four consecutive days did not show statistically significant increases in intestinal permeability in this model. In contrast, diclofenac significantly increased intestinal permeability at 3 mg/kg. In this subchronic study, lumiracoxib significantly increased intestinal permeability at doses of 30 and 100 mg/kg. Celecoxib did not produce significant increases in permeability compared to control animals even at 100 mg/kg and therefore would appear to be better tolerated than lumiracoxib in this model.

**Safety pharmacology**

The effects of lumiracoxib on renal function have been investigated in water-loaded rats. Lumiracoxib (30 mg/kg po) did not change urine volume, urinary or serum creatinine or GFR significantly, but reduced urinary $PGE_2$ by 49%. Celecoxib had similar effects. Diclofenac decreased urine volume and caused a greater reduction in urinary $PGE_2$ (92%).

There were no significant effects on behaviour of mice given oral doses of lumiracoxib of up to 1 mg/kg. At higher doses there were indications of CNS effects, with increased pain response, grooming and spontaneous activity 1 hour after a dose of 10 mg/kg, and increased touch response at 10 and 100 mg/kg.

Lumiracoxib had no antagonistic or synergistic effects on convulsions induced by electroshock or pentylenetetrazol and did not inhibit acetic acid-induced stretching in mice up to the highest dose tested (30 mg/kg).

Lumiracoxib had no effect on cardiovascular or respiratory parameters in anaesthetised rats at doses up to 1 mg/kg i.v. Systolic blood pressure (SDP), diastolic blood pressure (DPB) and mean blood pressure (MBP) were reduced immediately after administration of 10 mg/kg but then increased; DPB and MPB were significantly higher than controls at 2 min and 2 to 5 min post-dose, respectively. Heart rate decreased (2 to 15 minutes

post-dose) and there were transient reductions in respiratory rate (5 minutes post-dose) at 10 mg/kg.

Cardiovascular effects of lumiracoxib were investigated in telemetered cynomolgus monkeys (Study 0270019). Based on the results of a 39-week study in which a dose of 150 mg/kg caused moribundity and severe anaemia, doses of 20, 40, and 100 mg/kg were selected for safety pharmacology evaluations. An additional dose of 500 mg/kg was included, in consideration of the ICH Draft Guidance on Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization by Human Pharmaceuticals (S7B).

There were no lumiracoxib-related changes observed in clinical signs, body weight or food consumption at any dose, nor were there any effects on body temperature, heart rate, blood pressure or the electrocardiogram at doses up to 100 mg/kg. An increase in mean arterial, diastolic and systolic blood pressure was observed at 500 mg/kg. Toxicokinetic analysis of plasma samples from the 100 and 500 mg/kg groups showed exposure to lumiracoxib was proportional to dose, with $AUC_{(0-24)}$ of 771 and 3350 µg.h/ml, respectively.

An apparent increase in QT interval of 30 msecs, independent of heart rate, occurred in one animal in the 500 mg/kg group at 4 hours post-dose. The applicant compared the QT values obtained at this dose with historical baseline data for these same animals at similar heart rates. The comparison revealed that the QT interval duration for each animal when compared to its own baseline remained within normal physiological limits. The applicant's historical database values also indicated that at any given heart rate, a variation of 30 msecs in QT interval is a frequent occurrence in untreated animals. Therefore the applicant considered it unlikely that an increase of 30 msecs in one animal at only one time point could be attributed to treatment with lumiracoxib. This would seem to be a reasonable argument. Therefore the only treatment-related finding in this study was an increase in blood pressure following a single oral dose of 500 mg/kg.

The effect of lumiracoxib on cloned hERG channels was investigated *in vitro*. Concentration-response curves, use-dependence and temperature –dependence of the blocking effect on hERG channels were measured. The highest concentration tested (1000 µM) inhibited hERG current by about 36%, giving an extrapolated $IC_{50}$ of 1560 µM (458 µg/ml). This is 51-times the $C_{max}$ (8.9 µg/ml) in man following a dose of 400 mg. Use-dependence of lumiracoxib at 500 µM was independent of depolarisation frequency over the range 0.3 to 3 Hz. There was no apparent temperature –dependence of the blocking effect of 500 µM lumiracoxib on hERG channels.

Lumiracoxib at concentrations of 0.3 and 1 µg/ml had no effect *in vitro* on action potential parameters in sheep Purkinje fibres paced at a frequency of 1 Hz. At 10 µg/ml, lumiracoxib produced significant decreases in $APD_{60}$ and $APD_{90}$ (-22.0% and –16.4%, respectively). Further decreases occurred at 30 µg/ml (-45.2% and –36.2%, respectively). The maximum rate of depolarisation (MRD) was also decreased (-13.4%) at this concentration. Upstroke amplitude (UA) and resting membrane potential (RMP) were not affected at any dose. Sotalol hydrochloride induced (non-significant) increases in $APD_{60}$ and $APD_{90}$ when fibres were stimulated at 1 Hz.

The effects of lumiracoxib at 200 µg/ml on maximum rate of depolarization were investigated at a stimulation frequency of 3 Hz. The action potential ceased to fire after approximately 15 minutes and therefore MRD was not recorded, but resting membrane potential was significantly depolarised.

Plasma concentrations of lumiracoxib up to 1 μg/ml are considered unlikely to affect the QRS complex or QT interval.

The effects of lumiracoxib on spontaneous locomotor activity, anaesthetic action, body temperature, gastrointestinal transit and water and electrolyte excretion were investigated in male mice or rats at oral doses up to 30 mg/kg.
Pentobarbital-induced sleeping time in mice was prolonged at doses of 10 mg/kg and higher.

In saline-loaded rats, chloride excretion was reduced at and above 1 mg/kg and urinary volume and sodium excretion were reduced at 10 mg/kg and higher.

In *in vitro* studies with isolated guinea pig ileum, the only effect of lumiracoxib was an inhibition of 5-HT-induced contractions at the highest concentration tested ($10^{-5}$M). Therefore water and electrolyte excretion were decreased at doses similar to or higher than therapeutic doses, and kidney function should be monitored in patients. There may also be a potential to interact with anaesthetics (increased pentobarbital-induced sleeping time, possibly as a result of inhibition of hepatic metabolism of pentobarbital by lumiracoxib).

**Pharmacodynamic Drug Interactions**
No studies were conducted.

**Assessor's Comment**
The selectivity and potency of lumiracoxib for COX-2 was investigated in *in vitro* enzyme, whole cell and whole blood assays, in comparison to celecoxib and/or rofecoxib and diclofenac. It showed greater selectivity than other selective COX-2 inhibitors in the human whole blood assay.

The anti-inflammatory, analgesic and anti-pyretic activities of lumiracoxib were also investigated in a number of *in vivo* animal models. It was shown to have equivalent activities compared to other COX-2 selective inhibitors and diclofenac.

Metabolites of lumiracoxib were also studied in *in vitro* assays. In a human whole blood assay, the potency of lumiracoxib and its 4'-hydroxy metabolite were comparable, although in other assays this metabolite was 10 to 30 times less potent than lumiracoxib. The 4'-hydroxy metabolite was also studied in *in vivo* assays, and found to have modest activity in the carrageenan-induced rat paw oedema assay.

In a rat tissue chamber model in which concentrations of compound in the chamber reportedly represent those in inflamed tissue, lumiracoxib entered the chamber faster that celecoxib and rofecoxib, and also was present at higher concentrations in the chamber 12 hours after dosing than in plasma. Therefore if this model reflects the situation in man, lumiracoxib may have a more rapid onset of action than the other COX-2 inhibitors tested.

Lumiracoxib exhibited less gastroenteropathic activity than the non-selective COX inhibitor diclofenac.
Renal effects were noted (reduced urinary $PGE_2$ in water-loaded rats and water and electrolyte excretion in saline-loaded rats), which can be expected as COX-2 is expressed constitutively in the kidney. Kidney function should be monitored in patients.

There were indications of a slight CNS effect in behavioural studies in mice at doses of 10 mg/kg and higher, as well as a prolongation of phenobarbital-induced sleeping time in mice at similar doses, which may indicate a potential to interact with anaesthetics.

No significant activity of lumiracoxib was observed in cardiovascular, respiratory or gastric studies.

The estimated $IC_{50}$ for hERG channel blockade was 51-fold the $C_{max}$ in man following a dose of 400 mg of lumiracoxib. Lumiracoxib decreased action potential parameters in sheep Purkinje fibres, suggesting it may have a potential to shorten QT interval. This occurred at a similar concentration to the $C_{max}$ in man. However, when plasma protein binding is taken into consideration, the free fraction in human plasma is about 50-fold less than the *in vitro* concentration at which action potential parameters were decreased. In telemetered monkeys, there were no notable effects on QT intervals at a dose of 500 mg/kg, at which the systemic exposure (3350 µg.h/ml) was over 100 times that in man following a therapeutic dose. More importantly, no effects on QT interval have been noted in the clinical trials.

## PHARMACOKINETICS

### Methods of analysis

Lumiracoxib concentrations in animal feed, plasma, blood or tissue were analysed by HPLC with UV detection or reverse isotope dilution or by LC/MS/MS and LC/MS methods. Metabolites were measured in plasma using LC/MS/MS and LC/MS techniques.

### Absorption

The pharmacokinetics following a single oral or intravenous dose were investigated in mouse, rat, rabbit and monkey. The main findings are tabulated below (Tables 3 and 4).

**Table 3: Pharmacokinetics of lumiracoxib following a single iv dose**

| Species | Dose (mg/kg) | CLp (L/h/kg) | Vdss (L/kg) | $t_{½}$ (h) | $t_{½}$* (h) |
|---|---|---|---|---|---|
| Mouse | 2 | 0.467 | 0.289 | 0.545 | 58.4 |
| Rat | 3 | 0.123 | 0.308 | 3.9 | 27 |
| Rabbit | 3 | 0.51 | 0.28 | 0.87 | 7.0 |
| Monkey | 3 | 0.077 | 0.16 | 3.9 | 35 |

* $t_{½}$ of radioactivity

Assessor's table

**Table 4: Pharmacokinetics of lumiracoxib following a single oral dose**

| Species | Dose (mg/kg) | $C_{max}$ (ng/ml) | $t_{max}$ (h) | $AUC_{(0-\infty)}$ (ng·h/ml) | $t_{½}$ (h) | $t_{½}$ * (h) | F (%) |
|---|---|---|---|---|---|---|---|
| Mouse | 5 | 6690 | 1.0 | 13000 | 1.08 | 13.5 | 100 |
| Rat | 10 | 5990 | 1.0 | 36400# | 4.4 | 56 | 45 |
| Rabbit | 20 | 11300 | 0.5 | 30000 | 2.0 | 14 | 72 |
| Monkey | 18.7 | 20100 | 1.8 | 82500 ∇ | 3.2 | 45 | 33-74 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Man ♦ | 400 mg | 7280 | 4.0 | 48400 | 6.54 | 186 | |

* $t_{½}$ of radioactivity, # $AUC_{(0-168)}$, ∇ $AUC_{(0-96)}$, ♦ figures from Study 0106
Assessor's table

In the mouse, pharmacokinetics and metabolism were studied after single intravenous and oral doses (gavage and dietary). The oral doses were completely absorbed. The terminal elimination half-lives of lumiracoxib in plasma were 0.545h and 1.08h following iv and gavage doses, respectively. Terminal elimination half-lives of radioactivity were longer (58.4h after an iv dose and 13.5h after the gavage dose). Metabolism was similar irrespective of route of administration.

In the rat, the oral dose was almost completely absorbed (90-100%). Bioavailability following the oral dose was about 45%, suggesting the presence of a first-pass effect. The terminal elimination half-lives of lumiracoxib in plasma were 3.9h and 4.4h following iv and oral doses, respectively. Metabolism was extensive. Terminal elimination half-lives of radioactivity in plasma were longer (27h after an iv dose and 56h after the gavage dose).

In the rabbit, the plasma elimination half-life of radioactivity was again longer than that of lumiracoxib. Lumiracoxib was the major circulating compound following an oral dose. Metabolism was similar after intravenous dosing.

There was much inter-individual variability in bioavailability of an oral dose of lumiracoxib in the monkey. Again the major circulating plasma component was the parent drug.

**Distribution**
In the rat following a single intravenous dose, the volume of distribution at steady state (308 ml/kg) was approximately equal to the volume of extracellular fluid in this species. Protein binding was high.

Whole body autoradiography in rats following a single iv or oral dose showed distribution of radioactivity mainly to the organs of excretion and metabolism (kidney, liver, gastrointestinal tract). No radioactivity was detected in brain or testis. *In vitro*, in the absence of plasma proteins, the extraction ratio in rat brain is about 28%, but in the presence of plasma proteins is reduced to about 3%.

In pregnant rats following an oral dose of $^{14}$C-lumiracoxib on day 10 and 17 of gestation, levels of radioactivity were higher only in liver and kidney than those in blood. Levels in the lung, uterus and implant (day 10) were similar to those in blood. On day 17, the foetus had ≤10% and placenta about 50% of maternal blood levels of radioactivity.
Blood:plasma concentration ratios of lumiracoxib in man, monkey and rat (0.5, 0.4 and 0.5, respectively) were independent of concentration between 0.1 and 10 µg/ml. *In vitro* protein binding of lumiracoxib was high (>99%) in all three species, and independent of concentration over the same range tested. Heparin had no effect on plasma protein binding in human plasma at 0.1 or 10 µg/ml. In a separate study with human plasma *in vitro*, the bound fraction was 0.996-0.997, with metabolite LBG667 (4'-hydroxy) showing a similar binding (0.995). *In vitro* plasma protein binding of metabolites LBK286 (4'-hydroxy, 5-carboxy) and LBH019 (5-carboxy) were lower, at 0.975-0.980 and 0.965-0.976, respectively.

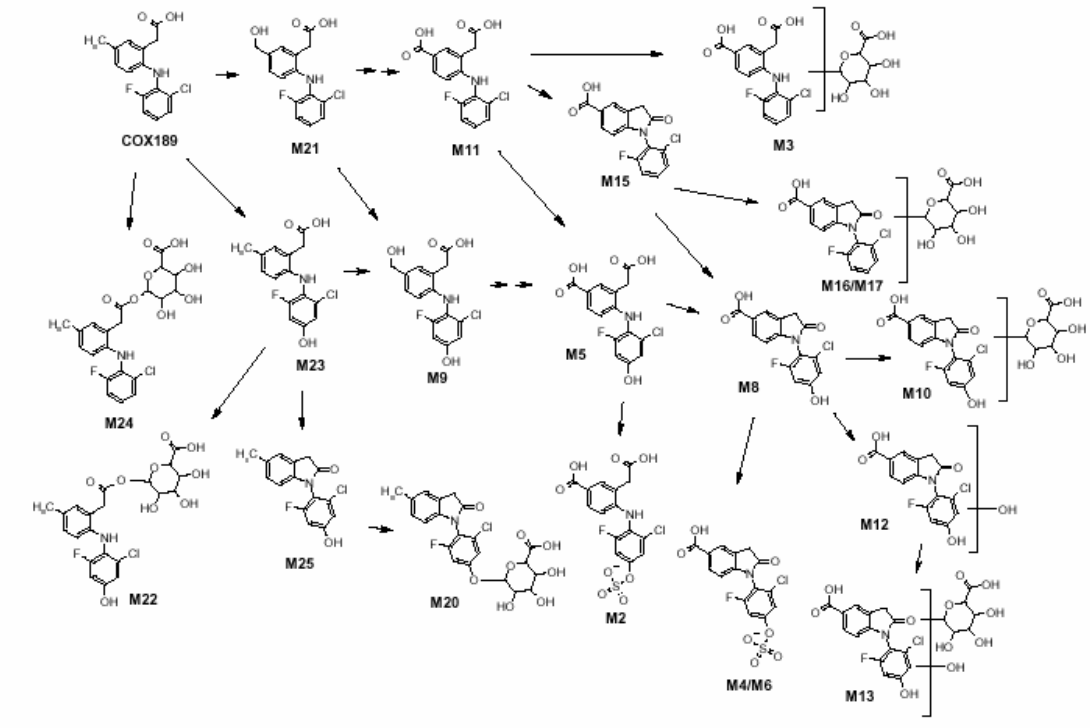
The *ex vivo* plasma protein binding of $^{3}$H-lumiracoxib was >0.98 in both normal subjects and in patients with renal failure undergoing haemodialysis.

At concentrations of 100 and 300 μg/ml, the fraction of lumiracoxib bound to human plasma proteins was 0.999 and 0.993, respectively. At these same nominal concentrations, the fraction bound to monkey plasma proteins was 0.998 and 0.988, respectively. There appeared to be a trend towards a decrease of protein binding at the higher concentration in both species.
In a further study, the bound fraction in human serum albumin was >0.98, whereas that in α1-acid glycoprotein was 0-0.053, suggesting the albumin is responsible for most of the plasma protein binding in human plasma.

In a study of distribution into inflamed vs normal tissue, lumiracoxib was administered (po) to rats that had been injected either with saline or carrageenan one hour earlier. Distribution of radioactivity was generally similar in the saline and carrageenan-treated animals, with most appearing in kidney and liver. However there was a slightly higher distribution of radioactivity into the inflamed footpad and dorsal subcutaneous layer of the carrageenan-treated rats (2.7 to 5.3 times higher after 1 and 4 hours post-dose). Lumiracoxib reduced paw oedema by 28% at 4h post-dose.

**Metabolism**
The metabolic pathways of lumiracoxib in man are shown in the figure below.

**Metabolite pathways of COX189 in humans**




Metabolism was studied as part of the single dose pharmacokinetic studies in mouse, rat, rabbit and monkey.

In mouse, the major metabolic pathways were hydroxylation of the dihaloaromatic ring and oxidative metabolism of the 5-methyl group to yield the corresponding 5-hydroxymethyl or 5-carboxy derivative. The major metabolite in plasma after an oral dose was M9 (5-hydroxymethyl phenol), followed by metabolites M7 (phenol glucuronide), M11 (5-carboxy), M23 (phenol) and M5 (5-carboxy phenol). Glucuronic acid and sulfate conjugation was also observed.

The major metabolic pathways in the rat include oxidative metabolism to yield several monohydroxylated metabolites and their corresponding sulphate and glucuronide conjugates. The acyl glucuronide of lumiracoxib and its apparent rearrangement products, as well as a glucuronic acid conjugate of the 4´-hydroxy metabolite were observed as biliary metabolites

In rabbit plasma, the major metabolite after an oral dose of lumiracoxib was M23 (phenol), but M7 (phenol glucuronide), M8 (5-carboxy lactam phenol), M11 (5-carboxy), M15 (5-carboxy lactam) and M21 (5-hydroxymethyl) were also present.

The major metabolite in monkey plasma was M11 (5-carboxy), followed by metabolites M5 (5- carboxy phenol), M15 (5-carboxy lactam) and M23 (phenol).
M11 and M5 were major metabolites in faeces.

In liver slices from rat, cynomolgus monkey and human, $^{14}$C-lumiracoxib was hydroxylated at the benzylic 5-methyl and dihalo-aromatic ring, with sulphate and glucuronide conjugates of the monohydroxylated metabolites also found.

In human liver microsomes, the major metabolic reaction is the hydroxylation of the dihaloaromatic ring of lumiracoxib, with the hydroxylation of the benzylic 5-methyl group occurring to a lesser extent. Investigations with human recombinant enzymes indicated that these reactions were catalysed by CYP2C9. Further conversion of the benzylic 5-hydroxymethyl to the carboxylic acid occurred when the reaction with the recombinant CYP2C9 was allowed to proceed. Lumiracoxib competitively inhibited CYP2C9 (Ki=7.0 µM), suggesting the possibility of pharmacokinetic drug-drug interactions *in vivo*. It had little or no effect on *in vitro* activities of CYP1A2, CYP2C8, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. A further study (DMPK(US) R02-306) showed that CYP1A2 and CYP2C19 were also very weakly active in the formation of 4'-hydroxy- and 5-hydroxymethyl-lumiracoxib.

Arochlor-induced rat liver S9 produced the hydroxylated metabolites seen previously (4'-hydroxy and 5-hydroxymethyl) as well as the lactam products formed by cyclisation of the oxidative metabolites (4'-hydroxy-5-carboxy lactam and 5-carboxy lactam).

Metabolism of $^{14}$C-lumiracoxib was studied in male volunteers following a single oral dose (400mg). The parent drug was the major circulating compound, but three major metabolites [M5 (4´-hydroxy-5-carboxy), M11 (5-carboxy), M23 (4´-hydroxy)] and at least two minor metabolites [M8 (4´-hydroxy-5-carboxy lactam) and M15 (5-carboxy lactam)] were observed. Plasma exposures ($AUC_{0\text{-}48h}$) for lumiracoxib, M5, M11 and M23 were 58.9, 12.5, 16.6 and 8.82 µg or µgEq.h/ml, respectively.

**Excretion**

The transfer of $^{14}$C-lumiracoxib and its metabolites into milk was investigated following a single oral dose of 10 mg/kg to lactating rats. Based on $AUC_{0-\infty}$ values, the overall milk:plasma concentration ratio of total radioactivity was 0.2. Projecting the rat data to humans, it is estimated that the maximum amount of COX189 and/or its metabolites that a breast-fed infant could be exposed to by ingesting 1 L of milk daily is 0.39% of a 400 mg adult dose.

Unchanged lumiracoxib was the main component in milk, and the metabolites identified were similar to those in plasma. The main metabolites were M7 (phenol glucuronide) and M15 (5-carboxy lactam), with smaller amounts of M5 (5-carboxy phenol), M11 (5-carboxy), M19 (phenol sulfate), M21 (5-hydroxymethyl) and M23 (phenol).

In the mouse, elimination of radioactivity was via the renal and biliary routes, with the larger proportion (66-69% compared with 19-24%) in the faeces. Unchanged lumiracoxib in urine was < 0.55% of the dose irrespective of route of administration, and in faeces, unchanged drug represented 3.24% and 2.38% of the dose after iv and gavage respectively.

In the rat, approximately 39% of the iv dose was eliminated in the urine, with 46% in the faeces.

In the rabbit, excretion occurred primarily via the urine, regardless of the dose route, with urinary excretion accounting for 84.1% and 78.8% of the intravenous and oral doses, respectively. Recovery in faeces represented 1.84% of the intravenous dose and 4.24% of the oral dose.

In monkey, excretion occurred primarily via the faeces. Following an oral dose, 6.49% and 87.8% of the dose was eliminated in the urine and faeces, respectively. In the faeces, unchanged parent drug accounted for 11.9% of the oral dose.

In man following an oral dose of 400 mg, an average of 54.1% of the radioactivity was recovered in the urine and 42.7% in the faeces. The major metabolites in both urine and faeces were M5 (4'-hydroxy- 5-carboxy) and M11 (5-carboxy), representing about 7.8% and 6.3% of the dose in urine, and 20.5% and 8.28% of the dose in faeces, respectively. Unchanged lumiracoxib accounted for 3.3% of the dose in urine and 2% in faeces. Conjugation of lumiracoxib directly with glucuronic acid to produce the acid glucuronide accounted for 2.5% of the dose in urine. No glutathione-derived metabolites (glutathione, cysteine or mercapturic acid conjugates) were detected in either urine or faecal samples.

**Pharmacokinetic drug interactions**

Monolayers of human colon adenocarcinoma cell line (Caco-2) grown on permeable filter were used to predict *in vivo* absorption of lumiracoxib. The apical to basolateral and basolateral to apical permeability at 120 min were calculated to be 72.3 x $10^{-5}$ and 113 x $10^{-5}$ cm/min, respectively, suggesting a high permeability for the compound *in vivo*.

Possible pharmacokinetic interactions between omeprazole, antacids (aluminium hydroxide/magnesium hydroxide) and lumiracoxib were studied in volunteers by examining changes in lumiracoxib glucuronic acid metabolite concentrations. There was much inter- and intra-subject variability and consequently no apparent pharmacokinetic drug interactions.

A similar study was conducted with fluconazole, a known inhibitor of CYP2C9. Again there was inter-individual variability. In 6/7 individuals, treatment with fluconazole increased lumiracoxib glucuronide, with a decrease in the remaining volunteer. The average change in exposure ($AUC_{0-48h}$) to lumiracoxib glucuronide when co-administered with fluconazole was 1.73 times (range 0.77 to 2.39-fold).

The effects of lumiracoxib on the *in vitro* plasma protein binding of a number of potential co-medications (salicylic acid, phenytoin, warfarin, nateglinide and tolbutamide) and *vice versa*, were investigated using human plasma. The bound fraction of lumiracoxib (>0.98) was unaffected by the presence of therapeutic concentrations of the other medications tested. Likewise, the bound fraction of the co-medications was unaltered in the presence of lumiracoxib.

**Other pharmacokinetic studies**
No other studies were reported.

**Assessor's Comment**
Orally administered lumiracoxib was extensively absorbed (90-100%) in all species, including man, with time to peak concentrations of lumiracoxib ranging from 0.5 to 4.0 hours.
The elimination half-life of lumiracoxib ranged from 1 to 6.5 hours after an oral dose in the species studied, with the half-life of radioactivity in the plasma being longer (13 to 14 hours in mouse and rabbit, 45 hours in monkey, 56 hours in rat and 186 hours in man).
Lumiracoxib is highly protein bound (>0.98), predominantly to albumin in human serum.

The parent drug is the predominant circulating compound in all species following an oral dose. In each species, metabolism is similar after intravenous and oral dosing, and is qualitatively similar in all species.
Biotransformation occurs primarily by the hydroxylation (usually at the 4' position) of the dihaloaromatic ring, and/or oxidation at the 5-methyl position to produce 5-hydroxymethyl and then 5-carboxy metabolites. Subsequent glucuronidation or sulphation of the oxidative metabolites may then occur, or cyclisation to the corresponding lactams. Direct glucuronidation of lumiracoxib may also occur, particularly in the rat, although this does not appear to be a major pathway in man. Of the species tested, the monkey showed most similarity to man with respect to metabolite profile.
The major metabolites in human plasma are 4'-hydroxy-5-carboxy (M5), 5-carboxy (M11) and 4'-hydroxy (M23), the latter being pharmacologically active. The potency of 4'-hydroxy –lumiracoxib is 10 to 30 times less than that of lumiracoxib in an *in vitro* enzyme assay, but equipotent in the human whole blood assay. However, plasma exposure to this metabolite is only 15% of that of the parent, therefore it probably does not contribute greatly to the overall pharmacological effect.
In man, CYP2C9 is the main enzyme responsible for the metabolism of lumiracoxib. A general increase in the exposure to lumiracoxib glucuronide in volunteers treated with fluconazole (CYP2C9 inhibitor) suggests that this may be a compensatory pathway when CYP2C9 is inhibited.
The potential for genetic polymorphism to affect metabolism of lumiracoxib has been investigated *in vitro* and *in vivo* and reported in the clinical dossier. Reportedly, no evidence has been found to suggest that a group of poor metabolisers of lumiracoxib exists in the general population

Routes of excretion varied across the species. In rabbits, excretion was mainly renal whereas in monkeys, faecal excretion was the predominant route. Mouse, rat and man excreted a dose by renal and faecal routes, with a slightly higher proportion in the faeces in mouse and rat, and a slight preference for urinary excretion in man.

Overall, the animal species chosen for the toxicity studies were appropriate for the purpose.

## TOXICOLOGY

### Single Dose Toxicity Studies

Mice received single oral doses of 100, 300, 600 or 1200 mg/kg. Clinical signs at 600 mg/kg and above included ataxia, reduced locomotor activity and impaired righting reflex. At 1200 mg/kg, additional signs included muscle flaccidity, shallow or laboured breathing and ptosis. There were also deaths, reduced body weight gain and food consumption in these groups. Dead animals had perforated or distended stomachs. The NOEL was 300 mg/kg.

Similar clinical signs and effects on body weight were observed in mice following acute intraperitoneal dosing. Doses were 10, 50, 250 or 750 mg/kg, with 50 mg/kg as the NOEL. Moribundity occurred in the high-dose group.

Rats received single oral doses of 50, 150, 500 or 1500 mg/kg. Effects at 500 mg/kg and above included mortality and moribundity, ataxia, decreased locomotor activity, impaired righting reflex, hypothermia, chromodacryorrhoea, intestinal ulceration and/or perforation and peritonitis. Effects at 150 mg/kg and above included decreased defaecation, decreased food consumption and body weight gain. Therefore the NOEL in this study was 50 mg/kg.
An acute intraperitoneal study was conducted in rats at doses of 10, 50, 250 and 1000 mg/kg. Mortality and moribundity, related to peritonitis or intestinal perforation, were restricted to the high dose group. At 250 mg/kg and above, effects were similar to those observed following acute oral dosing (ataxia, decreased locomotor activity, decreased food consumption and body weight gain, peritonitis). At 1000 mg/kg, additional signs included impaired righting reflex, hypothermia and absence of faeces. Therefore the NOEL was 50 mg/kg in this study.

### Repeated Dose Toxicity Studies

Pivotal toxicity studies were a 26-week oral study in rats and a 39-week study in monkeys, each with a 4-week recovery period. Four-week studies were also conducted in these species, and a number of dose range-finding studies were also carried out (including 2- and 13-week oral [dietary] studies in mice and rats, 2-week oral studies in monkey and intravenous rising dose studies in rat and monkey).

A 2-week oral (feed) range-finding study (Study No. 987095) was conducted in mice using doses of 10, 50, 150, 500 mg/kg/day. Findings at 150 mg/kg and above were similar to those observed in the acute studies, and histopathological changes in the stomach, liver, kidney, large and small intestines were noted. The NOEL was 50 mg/kg/day.

A 13-week oral (feed) range-finding study (Study No. 987141) was conducted in mice using doses of 10, 25, 50 and 100 mg/kg/day. There were no treatment-related effects on ocular, clinical chemistry or haematological parameters. Moribundity and mortality attributed to perforating gastrointestinal ulcers were present at and above 25 mg/kg/day, with decreased locomotor activity, decreased defaecation and hypothermia among the

clinical signs. At 50 mg/kg/day and above, impaired righting reflex, shallow breathing, decreased body weight gain and at 100 mg/kg/day tremors and ataxia were noted. Histologically, target organs were the gastrointestinal tract (especially colon, caecum and ileum) and kidneys. At all doses, there was intracytoplasmic vacuolation of parietal cells of the glandular stomach, the severity of which appeared to be dose-related. Nephropathy was noted in both sexes at 50 mg/kg/day and above, and reduced kidney weights. AUC increased over-proportionally to dose. On day 1, $AUC_{(12-36h)}$ values were 48047, 151718, 423142, 890773 ng.h/ml in males and 41108, 144729, 524562 and 1016908 ng.h/ml in females. There appeared to be no accumulation over the 13-week dosing period.

A 2-week oral dose range-finding study in rats used doses of 0, 10, 25, 75, 125 mg/kg/day with an additional group at 75 mg/kg/day for toxicokinetic analysis (Study No. 987050). Deaths occurred at 75 and 125 mg/kg/day. Clinical signs were similar to those in the acute studies. Ulceration and perforation of the GI tract and resulting peritonitis was observed at 75 mg/kg/day and above. $AUC_{(0-24)}$ after a single dose of 75 mg/kg was 480 µg.h/ml. The NOEL was 25 mg/kg/day.

Doses of 25, 50, 100, 200 mg/kg/day were administered as feed admixture in a 2-week dose range-finding in rats (Study No. 987096). Mortality/moribundity at and above 50 mg/kg/day were attributed to GI toxicity. Clinical signs were as in previous studies. Haematology and clinical chemistry showed increases in white blood cell counts, minimal decreases in red blood cell counts, haematocrit and Hb, minimal increases in reticulocytes and platelets, decreased albumin, total protein and albumin/globulin ratio. Changes were associated with perforation and peritonitis of the GI tract. Splenic enlargement in some individuals at 50 and 100 mg/kg/day was correlated with splenic erythropoiesis. Tubular dilation, indicative of minimal nephropathy, was noted in some animals at 50 and 200 mg/kg/day. As in the previous study, the NOEL was 25 mg/kg/day.

A 4-week oral (gavage) study, with a 4-week recovery period, was carried out in rats (Study No. 987075). Doses were 0, 5, 15 or 50 mg/kg/day. The only treatment-related findings were slight neutrophilia and increases in spleen weight at the top dose. Exposure increased with dose. $AUC_{(0-24)}$ values were 22300, 98400 and 335000 ng.h/ml in males and 25200, 107000 and 314000 ng.h/ml in females at 5, 15 and 50 mg/kg respectively, on day 1, with no accumulation after repeated dosing. There were no quantifiable levels in control rat plasma.
Given the results of studies 987096 and 987075, the dose at which gastrointestinal toxicity/perforation/death occurs is somewhere between 50 and 75 mg/kg/day.

A 13-week oral (dietary) dose range-finding study was carried out in rats (Study No. 997014). Doses were 0, 5, 10, 30 and 50 mg/kg/day. Mortalities occurred at 30 and 50 mg/kg/day. Clinical signs at 50 mg/kg/day included decreased locomotor activity, decreased defaecation, hunched posture, red lacrimation, ataxia, impaired righting reflexes and distended abdomen. Some of these findings also occurred at 30 mg/kg/day.

At 30 mg/kg/day and above, white blood cell counts increased, red blood cell counts, haematocrit, Hb and MCV decreased, and there were increased platelet counts and reticulocytosis. Decreased albumin, total protein and albumin/globulin ratio were also noted at 30 and 50 mg/kg/day. These findings were likely related to the observation of intestinal perforation in these groups, with enlargement of mesenteric lymph nodes. At 50 mg/kg/day, splenic enlargement was noted.

Increased absolute and relative liver weights were noted in females at 30 and 50 and in males (relative) at 50 mg/kg/day, and increased relative spleen weights in both sexes at 30 and 50 mg/kg/day.

The main target was the gastrointestinal tract, with perforating intestinal ulcers with secondary local and systemic inflammatory sequelae at 30 and 50 mg/kg/day (adhesions, hepatic inflammatory infiltrates, mesenteric lymphoid sinus histiocytosis and extramedullary haematopoiesis). The second target was kidney, with corticomedullary tubular dilation indicative of nephropathy at 30 mg/kg/day and above. The NOAEL was 10 mg/kg/day.

No quantifiable drug was present in selected control samples. The $AUC_{(0-24)}$ increased in proportion to dose at week 2. Values are given in Table 5, below. Generally levels in females were higher than in males. At 13 weeks, AUC was higher than in week 2 and increased over-proportionally to dose.

**Table 5: Systemic exposure of rats to lumiracoxib at week 2 of a 13-week oral (dietary) dose range-finding study**

| *Dose (mg/kg/day)* | *$AUC_{(0-24)}$ (ng.h/ml)* | |
|---|---|---|
| | *Males* | *Females* |
| 5 | 21435 | 29032 |
| 10 | 46009 | 41854 |
| 30 | 146980 | 204393 |
| 50 | 254501 | 278364 |

One of the pivotal studies was a 26-week oral study in rats with a 4-week recovery period (Study No. 997032). Doses were 3, 10, 30 and 60 (reduced to 50) mg/kg/day. The latter group was terminated early due to poor condition.

Death/moribundity occurred at 30 mg/kg/day and above as a result of intestinal ulceration and perforation. Distended abdomen, faecal changes, pale appearance and blood in faeces were observed. There was general improvement during recovery.

In males at 60 (50) mg/kg/day, there were treatment-related decreases in food consumption and alkaline phosphatase. Intestinal ulceration and secondary inflammation, often progressing to perforation and adhesions were found.

There were increased white blood cell counts at 60 (50) mg/kg/day and at 30 mg/kg/day and above, the following were noted: increased monocyte and neutrophil counts, enlarged spleen and lymph nodes, intestinal blood loss (suggested by changes in red blood cell parameters, low serum total protein and albumin levels, increased haematopoiesis in spleen and liver), granulopoiesis in bone marrow and lymphocyte/plasma cell hyperplasia in various, often enlarged, lymphoid organs. Leukocytosis in lung or spleen, sinus ectasia of the mesenteric lymph node, pancreatic oedema, inflammation and/or acinar hypertrophy were also seen at 30 mg/kg/day and above.

Adrenal cortical hypertrophy, lymphoid necrosis and atrophy in various lymphoid tissues and erosion/ulceration of the stomach at ≥ 30 mg/kg/day were considered secondary to the stress of ulcers. No macroscopic or microscopic changes were noted during the recovery period.

The NOEL was 3 mg/kg/day due to the finding of blood in faeces, altered red blood cell parameters, increased white blood cell count and neutrophils, splenic and liver extramedullary haematopoiesis and enlarged spleen in one male at 10 mg/kg/day.

Exposure was over-proportional to dose over the range 3 to 30 mg/kg/day. At 3 mg/kg/day, $AUC_{(0-24)}$ at weeks 1-2, 12 and 25 were 19018, 13175 and 19935 ng.h/ml in males and 14905, 16093 and 30920 ng.h/ml in females, respectively. At weeks 12 and 25 in the 10 and 30 mg/kg/day groups, accumulation of lumiracoxib was noted, which was greater in females. Accumulation at the top dose could not be evaluated due to the early termination of this group.

Lumiracoxib was detected in one control sample of those tested (2h sample in week 12). The level was 76.4 ng/ml and considered negligible compared to the levels found in the treated animals.

The systemic exposures at the end of this study, and their ratios to that in man following a therapeutic dose, are shown in Table 6 below.

An intravenous rising dose/2-week toxicity study (Study No. 01070109) was conducted in rats. Rising doses of 2, 10 and 40 mg/kg were given on days 1, 3 and 5, followed by a 2-week consecutive dosing phase at 2, 10 or 20 mg/kg/day. Skin lesions were observed at or near injection sites after rising doses of 20 or 40 mg/kg and in the consecutive phase at 10 and 20 mg/kg/day.

Moderate to marked neutrophilia and lymphopenia occurred at 20 mg/kg/day. There were increased liver and kidney weights in females at 20 mg/kg/day but no corresponding histopathology. Macroscopic findings were noted at injection site (tail) and sublumbar lymph node (enlargement at 10 mg/kg/day and above). Microscopic findings at the injection site included inflammation, venous thrombosis and epidermal ulceration, and in the sublumbar lymph nodes, haemorrhage/erythrophagocytosis at 20 mg/kg/day. An increased incidence of lymphoid hyperplasia at and above 10 mg/kg/day and plasma cell hyperplasia in females at 20 mg/kg/day were also noted. The changes were considered secondary to inflammation at the injection site. The AUC increased in proportion to dose at the two higher doses, and no accumulation was observed.

Doses of 0, 100, 300 or 1000 mg/kg/day were employed in a 2-week oral (gavage) dose range-finding study (Study No. 987051) in cynomolgus monkeys. The high-dose group was terminated early. At 300 mg/kg/day, haematocrit and associated red blood cell parameters were reduced and reticulocytes elevated. Therefore the NTEL was 100 mg/kg/day, at which the $AUC_{(0-24)}$ was in the range 684 to 1060 μg.h/ml

A 4-week oral (gavage) toxicity study with 4-week recovery period (Study No. 987076) was carried out in monkeys. Doses were 0, 20, 100 and 500 (reduced to 200) mg/kg/day. Mortality/moribundity occurred in the top dose group, with clinical signs of emesis, diarrhoea, reduced food consumption, decreased faeces, blood in faeces and body weight loss, which recovered during the recovery period.

There were no treatment-related ocular or electrocardiographic effects, or changes in urinalysis.

Haematocrit, haemoglobin and red blood cell count were decreased at 500 mg/kg/day on days 9 and 11, but had returned towards normal by day 23. Reticulocytes increased,

serum proteins and electrolytes decreased and triglycerides, BUN and creatinine increased in some individuals. BUN was elevated on day 23 at 100 and 500/200 mg/kg/day. All values returned to normal during the recovery period.

Necropsy revealed enlarged spleens and increased spleen weight in males, and some enlarged lymph nodes in both sexes at the high dose.

Microscopically, gastrointestinal mucosal damage was noted at the high dose (erosions, ulcers, haemorrhage, inflammation and increased mitosis in intestinal epithelium. Haematopoiesis was increased in two males (secondary to reduced red cell parameters). Changes in liver (hypertrophy of Kupffer cells and periportal infiltrates of leukocytes), spleen (lymphoid and histiocytic hyperplasia and granulocytic infiltration in red pulp) and adrenal (haemorrhage and cortical necrosis, in females only) were consistent with a reaction to antigenic and/or septic challenge. Decreased vacuolation of the adrenal cortex, thymic atrophy, degeneration and giant cell formation in the testes and renal and hepatic vacuolation were considered secondary to stress and general debilitation in the moribund animals. Tubular dilation of the outer cortex of the kidney was present in both sexes. Similar findings were not present in the recovery animals.

Exposure was less than proportional to dose. At the NTEL of 20 mg/kg/day, $AUC_{(0-24)}$ was in the range 117 to 123 μg.h/ml at the end of the dosing period.

An intravenous rising dose/2-week toxicity study (Study No. 0170110) was conducted in cynomolgus monkey. Rising doses of 4, 20, 40 mg/kg were given on days 1, 3 and 5, followed by a 2-week consecutive dosing phase at 4, 20 or 40 mg/kg/day. Some animals in the latter group were not dosed on days 7, 8 and/or 11 due to multiple skin lesions at or near injection sites. This group was sacrificed early, on day 12, because of the skin lesions. Skin lesions at or near the injection sites occurred in all groups, but the severity was greater at 40 mg/kg/day. Corresponding findings included perivascular inflammation and/or epidermal ulceration identified by macro- and/or microscopic evaluations and alterations in plasma protein. A NOEL was not determined in this study. Animals were exposed to lumiracoxib in a dose-proportional manner. There were no sex differences and no accumulation.

A pivotal 39-week oral toxicity study was conducted in cynomolgus monkeys, with a 4-week recovery period (Study No. 997036). Lumiracoxib was administered by gavage at doses of 0, 10, 40 or 150 mg/kg/day.

There were no effects on food consumption, ophthalmoscopy, electrocardiography or urinalysis. There were apparently no gross or microscopic findings related to treatment. One high dose female was moribund during week 33, the cause of which was not obvious from gross or microscopic examination, although it was anaemic.

There were decreases in body weight gain in mid-dose females and both sexes at the high-dose, which were reversible.

Increases in BUN occurred in mid-dose females and both sexes at the high-dose, but serum creatinine and renal histology were unaltered. Decreased haematocrit and haemoglobin and increased liver weights were noted at the high dose, which were reversible during the recovery period.

Toxicokinetic evaluations were carried out on samples obtained during weeks 1, 14 and 24. Exposure was dose-proportional, similar in males and females and there was no

evidence of accumulation. At the NOEL of 10 mg/kg/day, $AUC_{(0-24)}$ values ranged from 44700 to 64609 ng.h/ml in males and from 51019 to 64634 ng.h/ml in females, with $C_{max}$ values of 9398-25156 ng/ml (males) or 10657-18972 ng/ml (females). At the NTEL of 40 mg/kg/day, $AUC_{(0-24)}$ values were 314977-501126 ng.h/ml in males and 245670-382061 ng.h/ml in females. $C_{max}$ values at the NTEL were 47102-91217 ng/ml in males and 55133-124516 ng/ml in females.

The table below (Table 6) shows the systemic exposure in rats and monkeys at the end of the pivotal toxicity studies, and the ratios to that in man following a therapeutic dose of lumiracoxib.

**Table 6: Systemic exposure and safety margins in pivotal toxicity studies**

| Species and study duration | Dose (mg/kg/day) | • AUC(0-24) (ng.h/ml) | Findings | Exposure ratio* |
|---|---|---|---|---|
| Rat 26-week | 3 | 25428 | NOEL | 0.82 |
| | 10 | 111302 | NOAEL | 3.6 |
| | 30 | 384347 | GI lesions and mortality | 12.4 |
| Monkey 39-week | 10 | 54667 | NOEL | 1.8 |
| | 40 | 373399 | NOAEL | 12.0 |
| | 150 | 1178241 | No GI lesions | 38 |
| Monkey 4-week | 500/200 | 1145000 | GI lesions and mortality | 37 |

• AUC at last time point, combined male and female means
* calculated as ratio of AUC to that in man after 400 mg dose (31 µg.h/ml)
Assessor's Table

**Genotoxicity Studies**
Lumiracoxib was negative in an Ames test conducted in *Salmonella typhimurium* strains TA1535, TA97a, TA98, TA100 and TA102 either with or without metabolic activation at concentrations up to 5000 µg/plate (Study No. 981692).

Four chromosomal aberration tests were carried out in V79 Chinese hamster cells with and without metabolic activation.

In the first of these (Study No. 981811), there were increases in structural chromosome aberrations above the historical negative control range in the absence of metabolic activation, but these were not statistically significant and occurred at concentrations that were cytotoxic. It was concluded that both in the absence and presence of S9, lumiracoxib was not clastogenic in this study.

In the second study in V79 Chinese hamster cells (Study No. 991838), a statistically significant increase in aberrant cells was noted in the presence of metabolic activation, but at cytotoxic concentrations.

The third study (Study No. 0112102) was carried out in conjunction with Study No. 0112101, in which it was spiked with two by-products. In Study 0112102, lumiracoxib induced chromosome aberrations after 3 hours of treatment both with and without metabolic activation, at cytotoxic concentrations.

The fourth chromosomal aberration test in V79 Chinese hamster cells (Study No. 001832) employed two different metabolic activation systems (S9 from rat livers pre-

treated or not pre-treated with Arochlor 1254). There were no differences between the activation systems, both producing significant increases in aberrations at cytotoxic concentrations in one of two assays.

Chromosome aberration was studied in cultured human peripheral blood lymphocytes (Study No. 001851). There were no increases in aberrant cells after 20 hours. After 3 hours, in the absence and presence of rat S9, there was an increase in aberrant cells at high, cytotoxic concentrations, although these were not reproducible and lumiracoxib was considered to be non-clastogenic.

In a bone marrow micronucleus test in rats (Study No. 981874), there were no increases in micronuclei following oral doses of up to 500 mg/kg. At this dose, $AUC_{(0-24)}$ was 3331.1 µg.h/ml and 2883.9 µg.h/ml in males and females, respectively. The $C_{max}$ values were 193.5 and 173.2 µg/ml in males and females, respectively.

Induction of micronuclei was investigated in rat liver *in vivo* (Study No. 002001). One of two independent observers noted a small but significant increase in micronuclei at both doses (50 and 100 mg/kg ) at 72 hours. The study was repeated using 25, 50 and 100 mg/kg doses. There was no increase in micronuclei in hepatocytes in this repeat study.

Lumiracoxib did not induce elevated DNA migration in an *in vivo* comet assay in liver cells of rats treated orally with doses of 50, 100 or 500 mg/kg (Study No. 003986).

Therefore in the battery of genotoxicity studies conducted, lumiracoxib produced negative results in an Ames test, and in three *in vivo* studies in the rat (bone marrow and liver micronucleus tests and a liver comet assay). It produced positive results (significant increases in chromosomal aberrations) in three of four chromosome aberration studies in V79 Chinese hamster cells. These increases were found at cytotoxic concentrations, at which cell survival was less than 50% of the control value. There were no increases in clastogenicity in the absence of cytotoxicity. In an *in vitro* assay in human peripheral blood lymphocytes, increased (non-reproducible) aberrations were also noted only at cytotoxic concentrations.

**Carcinogenicity Studies**

**Long-term Studies**

Two-year studies were conducted in mice and rats.

In the mouse study, lumiracoxib was administered orally via feed admixtures to CD-1 [Crl:CD-1 (ICR)BR] mice (60/sex/group) at target daily doses of 0, 1, 2.5, 5 or 10→12 mg/kg/day. The high dose was increased to 12 mg/kg/day at the start of week 5. Doses were based on the 13-week dietary dose range-finding study.

Increased mortality in the high dose group resulted in sacrifice of the survivors after a minimum of 94 weeks treatment.

There were no effects on body weight, food consumption, palpable masses or ophthalmology during the in-life portion of the study.

Deaths occurred in all groups treated with lumiracoxib (4, 2, 10 and 56 animals in the 1, 2.5, 5 and 10→12 mg/kg/day groups, respectively). Survival remained at > 50% until week 65 in males and week 78 in females, reducing to about 27% at week 94 when the group was terminated. Survival was considered adequate to assess carcinogenic

potential. Clinical signs noted prior to death or sacrifice included thin appearance, pale eyes and decreased locomotor activity. Similar signs were also noted in some animals that survived to study termination.

There was a dose-related increase in gastrointestinal ulceration, necrosis and perforation. Macroscopic and microscopic findings in the abdominal cavity and gastrointestinal tract were consistent with peritonitis (inflammation in the peritoneal cavity with adhesions between abdominal organs resulting from erosion, ulceration, necrosis and perforation of the intestine or stomach) particularly at the higher dose levels (≥ 5 mg/kg/day).

There were no increases in either benign or malignant tumours in mice treated with up to 5 mg/kg/day for 104 weeks or 10→12 mg/kg/day for up to 94 weeks.

Lumiracoxib was not quantifiable in plasma collected from control animals. Most animals in the 1 and 2.5 mg/kg/day groups and all animals in the 5 and 10 →12 mg/kg/day groups had measurable lumiracoxib concentrations. Exposure was generally similar between males and females, and in weeks 4 and 26, and appeared to be more than proportional to dose. In week 4, the $AUC_{(0-24)}$ values in males were 1656, 7522, 10093 and 51883 ng.h/ml and in females were 3064, 9431, 19386 and 56942 ng.h/ml at doses of 1, 2.5, 5 and 10 mg/kg/day, respectively.

Based on the test article-related mortality and moribundity in this study, the NOEL was < 1 mg/kg/day. However, lumiracoxib was not carcinogenic in mice when administered via feed admixtures for at least 94 weeks.

In the rat study, lumiracoxib was administered orally via feed admixtures to Wistar Hannover (HsdBrl:WH) rats (60/sex/group) at target daily doses of 2, 4, 8 or 16 mg/kg/day. There was a positive trend for increased mortality, which was significantly higher at the high dose than in controls. Intestinal ulceration, perforation and/or peritonitis were observed in these animals and considered a contributory cause of mortality.

Clinical signs at the top dose included pale appearance, dehydration, slightly decreased locomotor activity and reduced/absent faeces. Reduced faeces were also noted in females at 4 and 8 mg/kg/day.

At all doses there was an increase in foot sores, which was identified microscopically as pododermatitis. The cause was undetermined and the significance unknown.

Lumiracoxib had no effect on food consumption, ophthalmology or palpable mass formation during the study.

At doses ≥8 mg/kg/day, lumiracoxib produced intestinal ulceration and changes secondary to ulceration including inflammation of the intestine at the site of ulceration, perforation and leakage of intestinal contents into the peritoneal cavity with subsequent inflammation and adhesions of the surfaces of abdominal organs. Additional findings secondary to inflammation included leukocytosis, increased bone marrow granulopoiesis and lymphoid hyperplasia in lymph nodes. Plasma cell hyperplasia in lymph nodes, extramedullary haematopoiesis, increased liver necrosis, epididymal sperm granulomas and increased renal tubular pigment were also noted at 16 mg/kg/day.

All treated animals were exposed to lumiracoxib. Exposure increased with dose, and females showed a higher exposure than males at each dose. The $AUC_{(0-24h)}$ values were 7450, 17100, 36400 and 78000 ng.h/ml in males and 13000, 27500, 47300 and 115000 ng.h/ml in females at 2, 4, 8 and 16 mg/kg/day, respectively, in week 4. By week 53, the $AUC_{(0-24h)}$ values were 10900, 23100, 50900 and 111000 ng.h/ml in males and 15600, 34900, 70900 and 157000 ng.h/ml in females at 2, 4, 8 and 16 mg/kg/day, respectively. Lumiracoxib was not detected in any of the control samples tested.

Lumiracoxib was not carcinogenic in rats when administered for two years at doses up to 16 mg/kg/day. The high dose was poorly tolerated, with gastrointestinal toxicity resulting in an increased number of deaths.

**Short or Medium Term Studies**
No such studies have been conducted.

**Other Studies**
There are no other studies.

**Reproductive and developmental toxicity**
The reproductive and developmental toxicity studies conducted are summarised in the table below (Table 7).

**Table 7: Reproductive and developmental toxicity studies with lumiracoxib**

| Study Type | Duration of Treatment | Dose Levels (mg/kg/day) |
|---|---|---|
| Fertility and early embryonic development in rats (Study 997024) | ♂ 29 Days Pre-Mating through mating until sacrifice (49 to 53 days in total)<br>♀ 14 Days Pre-Mating to Gestation Day 6 | 10, 30, 50→60 |
| Developmental toxicity in rats including toxicokinetic analysis (Study 997008) | Gestation Day 6 to Gestation Day 17 | 10, 30, 50 |
| Range-finding in rabbits (Study 987101) | Gestation Day 7 to Gestation Day 20 | 10, 30, 100 |
| Developmental toxicity in rabbits including toxicokinetic analysis (Study 997009) | Gestation Day 7 to Gestation Day 20 | 10, 25, 50, 75, 250, 500 |
| Prenatal and postnatal development in rats (Study 007063) | Gestation Day 6 to Lactation Day 20 | 20, 60, 200 |
| Range-finding in neonatal/juvenile rats (Study 0270018) | Post-partum Week 1 to Post-partum Day 27 | 3, 10, 30<br>3, 10, 20, 30 |

Assessor's table

**Fertility and early embryonic development**
An oral fertility and early embryonic development study was conducted in rats (Study No. 997024). Males were dosed with 0, 10, 30 and 60→50 mg/kg/day from day 29 prior to mating (top dose lowered after 10 days) and females at 0, 10, 30 and 50 mg/kg/day from 2 weeks prior to mating. At the top dose in both sexes, there were deaths and/or moribund sacrifices, clinical signs including piloerection, decreased activity, ataxia, reduced or absent faeces, and necropsy findings of fluid-filled abdominal cavities and intestinal adhesions.

Male reproductive parameters were not affected therefore the NOEL for male reproductive performance and fertility was 60→50 mg/kg/day.

In females, reproductive effects were noted as follows:
At 50 mg/kg/day: ↓ number of corpora lutea

At ≥ 30 mg/kg/day: ↓ number of implantation sites
↓ viable foetuses
↑preimplantation loss

Therefore the NOEL for female reproductive performance and fertility was 10 mg/kg/day.

**Embryo-foetal development**
Oral doses of 0, 10, 30 or 100 mg/kg/day were administered to pregnant rats from gestation day 6 to 17 in an embryo-foetal development study (Study No. 997008). Satellite animals were used for toxicokinetic analysis.

The following findings were noted:
At 100 mg/kg/day: ↓ maternal body weight and food consumption
↓ implantation sites,
↓ number of viable foetuses
↓ foetal weights

At ≥ 30 mg/kg/day: mortality/moribund sacrifice
decreased locomotor activity, piloerection
decreased or absent faeces
fluid-filled abdominal cavities
intestinal adhesions, haemorrhages and erosions.

There were no maternal effects at 10 mg/kg/day and no teratogenicity at any dose. The NOEL for embryo-foetal development was 30 mg/kg/day.

Toxicokinetic analysis showed exposure increased less than proportional to dose. Mean $AUC_{(0-24)}$ values were 79892, 146558 and 176970 ng.h/ml at 10, 30 and 100 mg/kg/day, respectively.

An oral embryo-foetal development dose range-finding study was conducted in rabbits from gestation day 7 to 20 at doses of 0, 10, 25, 50, 75, 100, 250 and 500 mg/kg/day (Study No. 987101). Maternal and embryotoxicity were evident at doses ≥ 250 mg/kg/day, with moribund sacrifice of one dam at 500 mg/kg/day, and complete resorption of all embryos at this dose.

An oral embryo-foetal developmental study (Study No. 997009) was conducted in rabbits from gestation days 7 to 20 at doses of 0, 20, 60 and 200 mg/kg/day.

Maternal toxicity (red substance in cage pan) was noted at all doses levels. Additional findings were as follows:
At 200 mg/kg/day: ↓ food consumption, body weights and body weight gains

At ≥ 60 mg/kg/day: dose-related ↑ in resorptions
↓ in viable foetuses
delayed ossification of sternebrae and phalanges

At 200 mg/kg/day, the decreased body weights and body weight gains were attributed increased resorptions. At this high dose, the resorptions were generally attributed to early resorptions, whereas those at 60 mg/kg/day were mostly attributed to late resorptions.

Lumiracoxib was not considered to be teratogenic in rabbits.

Lumiracoxib was measurable in all treated females. The mean $AUC_{(0-24)}$ values at 20, 60 and 200 mg/kg/day were 37259, 153754 and 648755 ng.h/ml, respectively. These values showed a trend towards dose over-proportionality.

Lumiracoxib was quantifiable only in pooled litters from dams at 200 mg/kg/day and in one animal at 60 mg/kg/day (LOQ 11.9 ng/g). At 200 mg/kg/day, the mean concentration in foetal tissue was 21.8 ± 3.2 ng/g. In dams at this time (about 24 hours post-dose), the plasma concentration of lumiracoxib was 411 ± 110 ng/ml.

A NOEL for dams was not established in this study (< 20 mg/kg/day). The NOEL for embryo-foetal development was 20 mg/kg/day.

**Prenatal and postnatal development, including maternal function**
An oral pre- and post-development study was conducted in the rat at doses of 0, 3, 10, 30 mg/kg/day from gestation day 6 to lactation day 20 (Study No. 007063). Maternal effects occurred at all doses. Clinical signs included pale appearance (3 and 30 mg/kg/day), ataxia, hunched posture (10 mg/kg/day), emaciation, cool to touch and rough coat (≥ 10 mg/kg/day). These signs generally occurred around parturition and resulted in loss of litters. Two females died at 30 mg/kg/day.

At all doses, gestation was slightly prolonged and the number of still-born pups increased. At necropsy, pale internal organs were noted at all doses. At 10 mg/kg/day, intestinal adhesions were present, and at 30 mg/kg/day there were haemorrhagic foci of the stomach, intestinal perforations and blood and nodules on the intestines. Pup mortality increased in all treated groups on days 0 to 4 post-partum. The $F_1$ generation were unaffected by treatment with respect to body weight, clinical signs, morphological development, learning and memory assessments, necrospy findings or fertility. A NOEL was not established for dams or their offspring in this study.

**Studies in which offspring (juveniles) are dosed and/or further evaluated**
An oral dose range-finding study has been conducted in neonatal and juvenile rats (Study No. 0270018). Neonate/juveniles were dosed at 0, 3, 10, 20 or 30 mg/kg/day from the first week post-partum to day 27 post-partum. These doses were well-tolerated, with no deaths, clinical signs, effects on body weight or necropsy findings in the

juveniles. However, a high dose not exceeding 30 mg/kg/day was recommended for the definitive oral neonatal and juvenile development study in the rat, due to mortality noted at 30 mg/kg/day in previous repeat-dose toxicology studies in adult animals. The definitive study, to support paediatric studies, is ongoing and consequently not reported in this present dossier.

**Local tolerance**
An iv single dose local tolerance study in female cynomolgus monkey was reported (Study No. 0270020). The study employed a 30 minute infusion (control, or 20 mg/kg salt, equivalent to 17.7 mg/kg base, administered in 0.1M glycine buffer, pH 9.0) to mimic potential clinical trial iv administration. No clinical signs (including injection site reactions), or effects on body weight or food consumption were noted. There was some minor bruising in both groups, due to manipulation. No local irritation or systemic toxicity was noted in this study. This is in contrast to intravenous rising dose toxicity studies in rats and monkeys, where skin lesions were observed at or near injection sites after rising doses of 4 (monkeys), 20 or 40 mg/kg.

**Other toxicity studies**
Lumiracoxib was screened in a rat whole embryo culture assay for teratogenic and/or embryotoxic potential. No teratogenic effects were observed. Embryotoxicity was observed at 300 μg/ml. The NOAEL for embryonic growth, dysmorphogenesis and differentiation was 100μg/ml.

**Antigenicity**
No studies were conducted.

**Immunotoxicity**
An oral immunotoxicity study (Study No.0110086) was conducted in rats. Groups of rats (two groups at each dose level) received oral doses of 0, 3, 10 or 30 mg/kg/day of lumiracoxib for 4 weeks. One group at each dose was immunised with 50 μg Keyhole limpet haemocyanin (KLH) in adjuvant (Alugel) 16 and 8 days before necropsy. The other groups received adjuvant only.

Four high-dose animals died, with body weight loss and microscopic evidence of inflammation in the gastrointestinal tract with adhesions to the liver. Inflammation of the stomach was noted in two high-dose animals at the end of the dosing period. There were no other lumiracoxib-related effects on body weight, food consumption, organ weights or macroscopic or microscopic examination.

Increased granuloma formation at the injection site was attributable to immunisation with KLH in adjuvant, and an increase in serum KLH-specific IgG and IgM titres was also noted.

Microscopically, there was lymphoid activation in spleen and lymph nodes in immunised rats, but there were no differences in distribution between the control and high-dose animals. There were no lumiracoxib-related changes in KLH-specific IgG and IgM titres, haematology parameters or splenocyte phenotypes.

Toxicokinetic analyses confirmed that animals treated with lumiracoxib were exposed to the parent compound. No quantifiable levels were observed in samples from control animals. There were no marked sex differences. Exposure increased (up to two-fold) between days 1-2 and days 26-27. Overall, there was a trend towards an over-proportional increase in exposure with increasing dose.

The NOEL in this study was 10 mg/kg/day, based on toxicity at 30 mg/kg/day, but there was no apparent immunotoxicity in this study.

Contact photoallergenic potential was assessed in a local lymph node assay in female BALB/c mice (Study No. 0117057). Lumiracoxib (20%, 5% or 1.25% solutions) was applied to the ears and for each concentration, one group of mice was exposed to UVA light (10J/$cm^2$). Another group received vehicle and TCSA (tetrachlorosalicyl-anilide) was used as the positive control.
Lumiracoxib does have a structural alert for skin sensitisation (aromatic primary or secondary amine). At 1.25%, there was a statistically significant increase in ear weight in the irradiated animals when compared with the non-irradiated control and also at 5% in comparison to vehicle control. However, there was no dose-dependent increase in ear weight, and LN weights and cell counts were not increased in all lumiracoxib groups. Therefore in this assay, lumiracoxib did not have photoallerginic potential.

**Dependence**
No studies were conducted.

**Metabolites**
No toxicity studies were conducted with metabolites.

**Studies on impurities**
Genotoxicity studies and repeated-dose toxicity studies were carried out on batches of lumiracoxib containing impurities that required qualification.

Impurity 534-00 is the bromo 6-fluoro isomer of lumiracoxib, and is specified in the drug substance at a level of 0.2%. An Ames test and a 4-week toxicity study were conducted on TOX4/COX189 (batch 02/1). TOX4/COX189 was a mixture of 99% lumiracoxib and 1% of impurity 534-00. The Ames test (Study No. 0212008) was negative at concentrations up to 5000 μg/plate.

In the 4-week oral study, TOX4/COX189 or TOX5/COX189 (100% lumiracoxib, Batch no. 02/1) was administered orally via gavage at daily doses of 30.3 or 30 mg/kg/day, respectively, for at least 4 weeks. One rat in each treated group died (gastrointestinal pathology). Clinical signs were limited to stained/wet fur. There were no effects on body weights or food consumption and no toxicologically significant effects on urinalysis, haematology or clinical chemistry.

Treatment-related lesions (intestinal ulceration and secondary lesions) occurred in both treated groups at similar incidences. Exposure to lumiracoxib appeared similar between the treated groups. The presence of impurity 534-00 at a level of 1% did not alter the toxicological profile of lumiracoxib.

For new medicinal products with a maximum daily dose of 400mg, the qualification threshold for impurities is 0.2%. Two degradation products, 519-99 (aldehyde) and 520-99 (alcohol), are specified at higher levels in the Finished Product Specification and therefore require qualification. These were qualified in *in vitro* genotoxicity and repeated-dose toxicity studies.

TOX1/COX189 batch 00/1 (Ce E-2841/118) containing 92.8% lumiracoxib, 2.2% of 519-99 and 5.1% 520-99 was negative in an Ames test (Study No. 0112006) at concentrations up to 5000 μg/plate. This same batch was assayed in a chromosome

aberration test in V79 Chinese hamster cells (Study No. 0112101). Study 0112102 with unspiked lumiracoxib was carried out in parallel. In the presence of metabolic activation, and after a 3 hour treatment in the absence of metabolic activation, structural chromosome aberrations were significantly increased at the highest cytotoxic concentration. There were no significant increases in polyploidy. This is not considered to indicate an *in vivo* genotoxic hazard. Comparison of these results with those from study 0112102 indicate that the by-products 519-99 and 520-99 are not clastogenic under these conditions.

A 4-week oral toxicity study was conducted in rats in order to qualify these two degradation products (Study No. 017015). Lumiracoxib was administered by gavage at 50.2 mg/kg/day (COX189, batch 0013005), and in the presence of 519-99 (aldehyde) and 520-99 (alcohol) at 53.9 mg/kg/day (TOX1/COX189). Clinical signs were similar in both treatment groups and comparable to those reported in the previous toxicity studies. However, mortality was greater in males treated with TOX1/COX189 (15/20) in comparison with those dosed with COX189 (10/20).

Both TOX1/COX189 and COX189 produced similar effects on haematology and chemistry (↑ WBC, neutrophil, monocyte and eosinophil counts, ↓ RBC counts, Hb concentration and haematocrit, ↑ reticulocytes, ↓ total protein and albumin and ↓ calcium [in males]).

Liver weights increased in females to a greater extent with COX189 alone. Spleen weight increased in COX189-treated animals, but in males treated with TOX1/COX189, the increase was much greater.

Macroscopic findings with both test articles were similar and included adhesions of the abdominal organs and fluid in the abdominal cavity.

Microscopic changes were also similar in both treated groups and to those seen previously (including transmural necrosis of the jejunum and/or ileum, perforation and peritonitis, serosal inflammation and fibrin deposition on abdominal organs.

Exposure to lumiracoxib was similar for animals administered COX189 or TOX1/COX189. The mean $AUC_{(0-24)}$ for animals receiving COX189 were 326 and 380 µg.h/ml in males and females respectively, and for those receiving TOX1/COX189 were 408 and 390 µg.h/ml in males and females, respectively.

Therefore the toxicokinetic and pathology results suggest that the effects of COX189 and TOX1/COX189 are similar. However, the in-life results suggest that the toxicity of TOX1/COX189 may be greater than that of COX189 in male rats, with increased spleen weights and increased mortality.

A further 4-week gavage toxicity study (Study No. 0170143) was conducted in rats, including the degradation products 519-99 and 520-99.

TOX3/COX189 (Batch no. 01/1, containing 98.9% COX189) was administered orally at doses of 15.2 or 30.3 mg/kg/day, and TOX2/COX189 (Batch no. 01/1, containing 94.8% COX189, 1.9% 519-99 and 1.9% 520-99), was administered orally at doses of 15.8 or 31.6 mg/kg/day.

One animal in each of the high dose groups was sacrificed in a moribund condition. The only effects on body weights were in these animals. Food consumption showed variable effects and was not always statistically significant.

There were no differences between the effects on haematological or clinical chemistry parameters in the animals treated with TOX3/COX189 and those treated with TOX2/COX189, and neither formulation produced toxicologically significant effects on these parameters.

Compound-induced pathology findings were similar in animals given high doses of TOX3/COX189 and TOX2/COX189, and were similar to those previously observed (perforating intestinal ulcers, adhesions of most abdominal organs, intestinal contents in the abdominal cavity, and enlarged adrenals and lymph nodes). Microscopically, findings included inflammation of many abdominal organs, increased hematopoiesis in the spleen and granulopoiesis in bone marrow and lymphoid and plasma cell hyperplasia in various lymph nodes. The incidence and/or severity of stomach erosions, vacuolation of the squamous epithelium of the limiting ridge and of eosinophilic inclusions was also similar between groups treated with the two batches.

Toxicokinetic evaluation revealed that exposure to lumiracoxib was similar in animals given TOX3/COX189 and TOX2/COX189. Mean $AUC_{(0-24)}$ of lumiracoxib in males was 111 and 308 µg.h/ml at 15.2 and 30.3 mg/kg/day TOX3/COX189, respectively, and 154 and 314 µg.h/ml at 15.8 and 31.6 mg/kg/day TOX2/COX189, respectively. In females, mean $AUC_{(0-24)}$ values were 105 and 229 µg.h/ml at 15.2 and 30.3 mg/kg/day TOX3/COX189, respectively, and 92 and 279 µg.h/ml at 15.8 and 31.6 mg/kg/day TOX2/COX189, respectively.

The presence of 519-99 and 520-99 did not alter the toxicity profile of lumiracoxib at the levels used in this study.

**Ecotoxicity/environmental risk**

The potential environmental risk associated with the use of lumiracoxib was evaluated. Following oral administration, only 5% of the dose is excreted in unchanged form. The metabolites 4´-hydroxy and glucuronide conjugate are the major concerns for environmental risk assessment; the 4´-hydroxy metabolite possesses pharmacological activity similar to the parent and the glucuronide conjugate could be de-conjugated to parent compound during the sewage treatment process due to microbial activity. Lumiracoxib possesses low water solubility, low lipophilicity and non-biodegradability, which suggest it may persist in the environment.

Predicted environmental concentrations (PECs) in the various environmental compartments were calculated based on the total amount of lumiracoxib, 4´-hydroxy metabolite and glucuronide conjugate, assuming zero removal from the compartment.

PECs due to human use show that lumiracoxib could be present in the surface water at the level of 32 ng/l. This is higher than the action limit (PECsw >1 ng/l) according to the guidance document III 5504/94 and further assessment was undertaken. The predicted no effect concentration (PNEC) on aquatic organisms, of which Daphnia appears most sensitive, was calculated. The ratio of predicted environmental concentrations in sewage/surface water (PECsw/PECsw) and PNEC was calculated to be < 1. Based on this ratio, the environmental risk posed by use of this compound is considered to be of no immediate concern and no further assessment is required.

**Assessor's overall conclusions on toxicology**

The effects of lumiracoxib in acute toxicity studies in rats and mice included ataxia, reduced locomotor activity, impaired righting reflex and intestinal ulceration and/or perforation. Mortality and moribundity were associated with gastrointestinal toxicity.

Pivotal repeated-dose toxicity studies were conducted in rats (26-week oral study) and monkeys (39-week oral study). Dose range-finding studies were also conducted in rats, monkeys, mice and pregnant rabbits.

In mice administered lumiracoxib in feed for 2 or 13 weeks, target organs were the gastrointestinal tract and kidneys, with perforating gastrointestinal ulcers and renal tubular dilation observed in both studies.

Similar findings were noted in the 2- and 13-week dietary studies in rats, with perforating intestinal ulcers and their sequelae leading to death and moribundity, and tubular dilation again noted in the kidneys.

In 2-, 4- and 26-week oral rat studies in which the dose was given by gavage instead of in the diet, the kidney did not appear to be affected.

Lumiracoxib was relatively well-tolerated in the 4-week study, with only slight increases in spleen weight at the top dose of 50 mg/kg/day. In the 2- and 26-week studies, gastrointestinal toxicity was evident, with dose-dependent perforating gastrointestinal ulcers leading to mortality. As in the previous studies, there were additional pathological findings such as perforations and adhesions that were attributed to the gastrointestinal toxicity. Following a 4-week recovery period at the end of the 26-week study, no gastrointestinal lesions were noted.

In the 26-week study, the NOEL was 3 mg/kg/day, due to the finding of some haematology changes in one animal at 10 mg/kg/day. At this dose, systemic exposure was less than that in man. The NOAEL was 10 mg/kg/day, at which systemic exposure was 2.0 to 3.6 times than in man. At 30 mg/kg/day, a dose causing GI lesions and mortality, systemic exposure was 10.6 or 12.4 times higher than that in man, at weeks 12 and 25, respectively. The SPC section 5.3 states the exposure multiple at the dose causing GI lesions.

The gastrointestinal tract and kidney were also identified as target organs in the monkey, although lumiracoxib was better tolerated in this species than in rodents. In a 4-week study, intestinal ulcers resulted in death (and the reduction of the high dose from 500 to 200 mg/kg/day). Secondary findings were similar to those found in rats. Gastrointestinal lesions were not seen in the 39-week study in monkeys.

BUN was increased in the 2-, 4- and 39-week monkey studies. Renal tubular dilation and increased serum creatinine were noted only in the 4-week study at the high dose.

No treatment-related effects were noted after the 4-week recovery periods following the 4-week and 39-week studies. In the 39-week study, the NOEL was 10 mg/kg/day, due to the finding of increased BUN at 40 mg/kg/day. At this dose, systemic exposure at week 24 was 1.8 times that in man. As the increase in BUN was minimal and did not correspond to changes in serum creatinine or renal pathology, the NOAEL was 40 mg/kg/day, at which systemic exposure was 12 times than in man. At 150 mg/kg/day there were no GI lesions and the systemic exposure at week 24 was 38 times that in man. However there were GI lesions at the top dose in the 4-week monkey study, at

which systemic exposure was similar, that is, about 38 times higher than that in man after a therapeutic dose. The SPC section 5.3 again states the exposure multiple at the dose causing GI lesions.

Findings of increased liver weights in the 39-week monkey study and in the 2-week i.v. study and 13-week dietary study in rats, were not associated with any clinical chemistry or histopathological evidence of hepatoxicity.

Therefore the two main target organs for lumiracoxib are the gastrointestinal tract and the kidney.

Lumiracoxib was negative in an Ames test and in *in vivo* studies for clastogenicity. Positive results were noted in *in vitro* studies for chromosome aberrations, but only at concentrations that produced cytotoxicity. No structural alerts for genotoxicity were reported using two computer-based systems (DEREK and MCase).

Carcinogenicity studies were carried out in mice and rats. Gastrointestinal toxicity was responsible for deaths, particularly at the higher doses, but survival was considered sufficient to enable assessment of the carcinogenic potential. No increases in the incidence of tumours were noted following treatment with lumiracoxib. At the highest doses in these studies, the systemic exposure was 2.4 (mouse) and 4.3 (rat) times that in man following a therapeutic dose.

In male rats, reproductive parameters were unaffected by lumiracoxib at doses up to 60→50 mg/kg/day. In females, decreases in numbers of corpora lutea, implantation sites and viable foetuses, and increased preimplantation loss, occurred at ≥ 30 mg/kg/day.

The SPC, section 4.4, contains the following warning:
"Use of lumiracoxib, as with any drug known to inhibit COX-2, is not recommended in women attempting to conceive".

In embryo-foetal developmental studies, gastrointestinal toxicity was evident in the rat at ≥ 30 mg/kg/day, although embryo-foetal toxicity (decreases in implantation sites, number of viable foetuses and in foetal weights) was evident only at 100 mg/kg/day. At the NOEL for embryo-foetal toxicity (30 mg/kg/day), systemic exposure to lumiracoxib (146558 ng.h/ml) was 4.7 times that in man following a 400 mg dose (31000 ng.h/ml). There were no teratogenic effects in the rat.

In the rabbit, decreases in viable foetuses were associated with dose-related increases in resorptions at ≥ 60 mg/kg/day. Delayed ossification of sternebrae and phalanges were noted in foetuses at ≥ 60 mg/kg/day. Lumiracoxib did not appear to be teratogenic in the rabbit. At the NOEL for embryo-foetal development (20 mg/kg/day), systemic exposure (37259 ng.h/ml) was 1.2 times that in man following a 400 mg dose. The mean concentration of lumiracoxib in pooled rabbit foetuses from the 200 mg/kg/day group was 21.8 ng/g tissue, which represents only 5% of the maternal plasma concentration (411 ng/ml) measured at the same time point.

In a pre- and post-natal development study in rats, gestation was prolonged slightly and the number of stillborn pups increased. Pup mortality increased on postpartum days 0-4. A NOEL was not established in this study. In keeping with other drugs of this class, the proposed SPC contraindicates lumiracoxib during the last trimester of pregnancy

because of its potential to cause uterine inertia and premature closure of the ductus arteriosus.

Lumiracoxib did not produce immunotoxic effects in a 4-week study in rats, and a local lymph node assay in mice did not suggest a photoallergenic potential.

Proposed specifications for impurities in the DSS and FPS required that 534-00, a by-product of the synthesis (bromo-derivative), and degradation products 520-99 and 519-99, (an alcohol and aldehyde, respectively) should be qualified. A batch of lumiracoxib containing 1% 534-00 was negative in an Ames test and no more toxic in a repeated-dose toxicity study than lumiracoxib alone.

A batch containing 2.2% of 519-99 and 5.1% 520-99 was negative in an Ames test and produced similar effects in an *in vitro* chromosome aberration test as the parent compound. This batch was potentially more toxic in a repeated-dose toxicity study than an unspiked batch, with increased mortality in male rats in the group receiving the spiked batch. A further repeated-dose study using a batch containing 1.9% of each of 519-99 and 520-99 showed similar toxicity to an unspiked batch of lumiracoxib and therefore these degradation products may be considered qualified at this level.

The applicant conducted an environmental risk assessment. The physicochemical properties of lumiracoxib suggest that it may persist in the environment. However, calculated PEC/PNEC ratios were < 1 and therefore no further assessment is required.

Overall this was a good preclinical dossier. The studies have demonstrated that lumiracoxib is a selective COX-2 inhibitor, targeting the gastrointestinal tract and kidney in toxicity studies.

There are no objections on preclinical grounds to the grant of a marketing authorisation for this product.

# 5. CLINICAL ASPECTS

*Because of the complex regulatory history of these products, the assessment report below is composed of the original national clinical assessment from 2003, with the findings from the Committee for Safety of Medicines (CSM). This is followed by the assessment of additional clinical data provided in 2004 during and subsequent to the Mutual Recognition Procedure.*

## ORIGINAL CLINICAL ASSESSMENT - 2003

### 1. INTRODUCTION

'PREXIGE' 200mg tablets are ovaloid, red, film-coated tablets with “NVR” debossed on one side and 'OC' on the other side and each tablet contains 200mg lumiracoxib.

'PREXIGE' 400mg tablets are ovaloid, red, film-coated tablets with “NVR” debossed on one side and 'OD' on the other side and each tablet contains 400mg lumiracoxib.

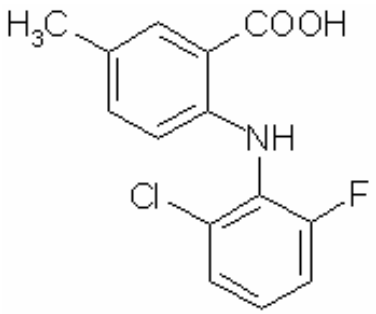
200mg tablets have 50% drug load and 400mg tablets have 65% drug load

COX is also known as prostaglandin endoperoxide synthase and it exhibits two activities - cyclo-oxygenase which is responsible for cyclisation of arachidonic acid to form prostaglandin $G_2$ and hydroperoxidase which is responsible for reduction of prostaglandin $G_2$ to prostaglandin $H_2$. COX exists as two isoforms - COX-1 and COX-2 isoforms.

Lumiracoxib (also coded as COX 189) is a novel nonsteroidal anti-inflammatory drug (NSAID). Like all NSAIDs, lumiracoxib inhibits the enzyme cyclo-oxygenase (COX). The novelty of lumiracoxib arises because it represents the latest in a new pharmacological class of NSAIDs that are highly selective inhibitors of the inducible isoform (COX-2) of the enzyme cyclo-oxygenase. COX-2 is the isoform that is responsible for the biosynthesis of prostaglandins that mediate inflammation, pain, and fever.

Currently, there are three other COX-2 selective inhibitors approved throughout the EU and intended for oral administration. These are rofecoxib (a furanone derivative), celecoxib (a pyrazole derivative) and etoricoxib (bipyridine derivative).

In contrast, lumiracoxib is a phenyl acetic acid derivative. Structurally, therefore, lumiracoxib is not related to any of the approved COX-2 selective inhibitors.




**Lumiracoxib**

Chemically, lumiracoxib is optically inactive and is characterised as 2-[(2-chloro-6-fluorophenyl)amino]-5-methyl benzeneacetic acid.

Molecular weight: 293.72
Empirical formula: $C_{15}H_{13}Cl\,FNO_2$

**Additional Information:**
During the Assessment of the clinical documentation for lumiracoxib, the UK Clinical Assessor did NOT have any point that required clarification by more detailed information from the applicant. However, the applicant was requested to provide information on any further reports of hepatotoxicity in an on-going TARGET study.

The UK Biostatistical Assessor did NOT have any point that required clarification by more detailed information from the applicant.

## 2. SUMMARY OF CLINICAL ASSESSMENT

The following is the summary of the clinical assessment of lumiracoxib.

### 2.1 Pharmacodynamics

Results from in vitro and ex-vivo set of studies investigating inhibition (%) of PGE2 and TxB2 synthesis, coagulation-induced TxB2 production, platelet aggregation and effects on on gastric and intestinal mucosa support the claim that lumiracoxib is a COX-2 selective inhibitor.

### 2.2 Pharmacokinetics

Bioavailability of oral lumiracoxib is calculated at 74.0 ± 8.6 %. There is a substantial variability with coefficients of variation for AUC being 19.1% for IV and 22.8% for oral administration. Following oral administration of 200mg dose, coefficients of variation within and between individuals were 22% and 28% respectively. The corresponding figures for AUC were 11% and 26%. Dose-normalised Cmax and AUC are higher in the Japanese by 43% and 22% respectively.

It is bound almost exclusively to albumin ≥ 98% and independent of concentration. Kinetics of lumiracoxib are linear to doses of 800mg. At doses of 1200mg or higher, there is marked loss of dose proportionality with under-exposure. 200mg FMI (50% drug load) is bioequivalent to 400mg FMI (65% drug load).

Lumiracoxib is metabolised by oxidation by CYP2C9. Clearance was independent of dose, gender or age with no evidence of accumulation. One of its metabolites, 4-hydroxy-lumiracoxib, is pharmacologically active and almost as potent and COX-2 selective as the parent drug.

Compared to fasting condition, administration of lumiracoxib after a high fat meal resulted in a reduction in AUC and Cmax of about 16% and 19% respectively. This difference, however, is unlikely to be of any clinical significance.

### 2.3 Pharmacokinetics in Special Populations

There are no significant influences on pharmacokinetics of lumiracoxib arising from age, gender, ethnicity, CYP2C9 polymorphism due to the common *2 allele or moderate hepatic impairment.

It is possible that individuals who are homozygous for *3 allele would have very high plasma levels but this genotype is extremely rare in Western Caucasian population.

Exposure to lumiracoxib is lower in patients with end stage renal disease compared to normal subjects. Compared to normal subjects, mean exposure to 4'-hydroxy-lumiracoxib is not significantly increased in ESRD patients and exposure to 4'-hydroxy-5-carboxy-lumiracoxib is increased substantially (by about 7 times). Dialysis has no effect on plasma exposure to lumiracoxib or these metabolites.

Pharmacokinetics in juvenile patients with rheumatoid arthritis would have been helpful but this has not been investigated.

## 2.4 Drug Interactions

There is no evidence of an interaction with contraceptive pill, omeprazole or antacids.

A risk of interactions arising from protein binding in rare individuals cannot be excluded. This is most likely with phenytoin or salicylic acid.

A decrease in protein binding of phenytoin from 91.4 % to 89.1 % could increase the free fraction from 8.6 % to 10.9 % - an increase of 27 %. A decrease in protein binding of salicylic acid from 99.3 % to 94.0 % could increase the free fraction from 0.7 % to 6.0 % - an increase of 857 %. Therefore, high Cmax in such individuals could predispose them to a potential interaction resulting from displacement of phenytoin and salicylic acid – the former resulting in phenytoin toxicity and the later resulting in loss of COX-2 selectivity.

Drugs that are likely to be used by the target population include prednisolone and aspirin. No interaction studies have been carried out against these drugs. Neither is there an interaction study with digoxin or lithium. The Applicant has already included a statement on the potential for an interaction with lithium.

Lumiracoxib appears to increase the prothrombin time in patients stabilised on warfarin. Compared to placebo treatment, recovery of the S-7-OH warfarin metabolite in urine was about 25% lower in subjects treated with lumiracoxib.

Celecoxib (a substrate of CYP2C9 had also produced only minimal changes in the pharmacokinetics or the pharmacodynamics of warfarin and yet, there were post-marketing reports describing patients on warfarin who had increased anticoagulation and (in some cases) bleeding complications after treatment with celecoxib was started. Effect of lumiracoxib is slightly greater but it seems to have been dealt with adequately in the SPC.

## 2.5 Dose Selection for Phase III Pivotal Studies

### Osteoarthritis

In an extensive dose-finding programme, no distinction could be made between 50mg BD, 100mg BD, 200mg BD and 400mg QD doses of lumiracoxib. The lowest dose used, 50mg BD, is effective and doses lower than this have not been investigated. Among the four doses, 50mg BD is consistently superior to 100mg BD dose. In fact, for some secondary endpoints (HAQ score at 4 weeks, WOMAC physical function score), 100mg BD was statistically no different from placebo.

The only advantage for lumiracoxib 400mg QD is earlier onset of effect compared to lumiracoxib 50mg BD or 100mg BD (week 1 versus week 2). However, this advantage may be more than offset by any dose-related clinical and laboratory safety.

### Primary dysmenorrhoea

No specific study – dose selection extrapolated from studies in acute pain in post-dental surgery patients.

**Acute pain**
The model used is acute pain in post-dental surgery patients. It is difficult to distinguish clearly between 100mg and 200mg doses of lumiracoxib since these two doses have not been compared directly. On balance, a dose of 200mg appears better than 100mg dose. When 200mg and 400mg doses are compared, the weight of evidence overall favours the use of 400mg daily dose.

## 2.6 Efficacy in osteoarthritis

It is noted that two doses - 200mg QD and 400mg QD - were investigated for OA of the knee but only the higher dose was investigated for OA of the hip.

Lumiracoxib 200mg and 400mg QD are effective in relieving pain in osteoarthritis of knee. 400mg QD is effective in relieving pain in osteoarthritis of the hip joints. There are no reasons to believe that 200mg QD dose will not be effective at the hip joints.
Both doses are as effective as celecoxib 200mg QD and rofecoxib 25mg QD. It should be noted that the current EU approved dose of celecoxib is 200mg QD which may be increased to 200mg BD while the current EU approved dose of rofecoxib is 12.5mg QD which may be increased to 25mg QD.

The data show that lumiracoxib is effective in the treatment of primary osteoarthritis of the hand and that the two doses are equally effective. 400mg daily dose had no superiority over 200mg dose in any parameter at any time point (week 2 or week 4).

The data show that the efficacy of lumiracoxib is maintained over at least 52 weeks.
The two doses – 200mg and 400mg daily – are equally effective in this regard with no different at any time point.

There is no difference between 200mg and 400mg QD doses of lumiracoxib. The risk/benefit ratio for a 400mg dose is unfavourable (dose-related clinical and laboratory safety, particularly the gastro-intestinal, neurological and psychiatric adverse events and hepatic and renal safety of lumiracoxib.

## 2.7 Efficacy of in Rheumatoid arthritis

The efficacy of lumiracoxib in RA is questionable.

The dose selection studies (0105 and 2312) had investigated doses ranging from 50mg BD to 1200mg QD. None of the doses investigated were found to be effective in RA.
Although 800mg and 1200mg QD doses did not differ significantly from naproxen 500mg BD, a dose of lumiracoxib that is superior to placebo could not be identified.

In the two major well-controlled studies, one failed to produce any evidence of efficacy (0114) while the other showed that the lower dose (200mg QD) was more effective than the higher dose of 400mg QD.

When the data from the two major well-controlled studies are combined, the pooled results are statistically significant for the primary endpoint but the findings are driven by one (smaller) study and show the lack of consistency between the two studies. Even the combined results show lack of statistical significance for 4 secondary parameters on 200mg dose and 1 secondary parameter on 400mg dose.

## 2.8 Efficacy in Primary dysmenorrhoea

A single 400mg dose of lumiracoxib is effective in treating the symptoms of primary dysmenorrhoea. The indication should be restricted to the population studied (that is, patients with moderate to severe primary dysmenorrhoea).

## 2.9 Efficacy Acute pain

It is concluded that lumiracoxib 400mg QD is an effective analgesic for very short-term use. The indication should be restricted to the population studied (that is, patients with moderate to severe pain following dental or orthopaedic surgery).

## 2.10 Clinical safety of lumiracoxib

Lumiracoxib appears to have an acceptable profile of clinical safety. The pattern of events reported with lumiracoxib is typical of COX-2 selective inhibitors that have been approved to date.

As far as the comparison between 200mg QD and 400mg QD doses is concerned, there is a greater frequency of drug-related adverse events with the higher dose in dataset 1 and 7. These events include a range of GI, neurological and psychiatric events.

In dataset 7 in RA, the % of patients who discontinued due to an adverse event was 5.9% with 200mg QD dose and 7.8% with 400mg QD dose.

At present, there is no evidence of serious hypersensitivity reactions or greater nephrotoxicity following the use of lumiracoxib.

## 2.11 Laboratory safety of lumiracoxib

Lumiracoxib is a mild to moderate hepatotoxin and a moderate nephrotoxin.

While it is recognised that the pharmacokinetics of lumiracoxib parent drug are not influenced by renal impairment, one needs to consider the pharmacodynamic effects of lumiracoxib in patients with compromised renal function. It is also noted that exposure to lumiracoxib is lower in patients with end stage renal disease compared to normal subjects. Compared to normal subjects, mean exposure to 4'-hydroxy-lumiracoxib is slightly increased in ESRD patients and exposure to 4'-hydroxy-5-carboxy-lumiracoxib is increased markedly (by about 7 times).

## 2.12 Electrocardiographic safety of lumiracoxib

There are very minor electrocardiographic, particularly QTc interval, changes but given the presence of changes in the placebo group and absence of any dose-effect relationship, these data provide sufficient reassurance. These data show that lumiracoxib has no effect on parameters of cardiac conduction or ventricular action potential duration. There is no evidence of any concern at present.

## 2.13 Gastrointestinal safety of lumiracoxib

Lumiracoxib has improved gastrointestinal safety compared to classical non-selective NSAIDs and comparable to other coxibs.

Relative to the 200mg QD dose, 400mg QD dose of lumiracoxib is associated with a greater frequency of gastrointestinal effects in terms of pre-specified gastrointestinal events, laboratory data for haematocrit and haemoglobin and symptomatic ulcers in long-term OA and short-term RA dataset.

## 2.14 Prothrombotic effects of lumiracoxib

The CPMP is undertaking a class review of the cardiac safety of COX-2 selective inhibitors. This is prompted by the concerns that COX-2 selective inhibitors may have prothrombotic activity.

There is a slightly greater percentage of patients in the lumiracoxib 200/400 combined group with a pre-defined cardiovascular event when compared with placebo. Individual assessment by treatment group for the larger groups showed a slightly greater rate for APTC endpoints for lumiracoxib 200mg QD (0.5%) and 400mg QD (0.4%), compared with placebo (0.2%) and celecoxib 200mg QD (0.3%). Patients with increased vascular risk had an increased event rate, and that the combined lumiracoxib 200/400mg group showed an APTC event rate of 0.65% compared with 0.22% for placebo.

It is noteworthy that a dataset of only 12-months duration at the most should uncover a point estimate that is indicative of slightly greater prothrombotic risk associated with lumiracoxib relative to placebo.

The sample size and the duration of the studies are such that 95% confidence intervals of the risk WILL be wide and encompass unity.

There is a biological plausibility to the prothrombotic risk and a small increase in risk especially in those with high cardiovascular risk cannot be excluded. Use of low dose aspirin reduces this risk.

More importantly, this slight increase in prothrombotic risk has to be seen in the context of considerable improvement in gastrointestinal risk conferred by lumiracoxib over the classical NSAIDs.

It is therefore appropriate to include a caution on the use of lumiracoxib in patients with ischaemic heart disease.

## 2.15 Hepatic safety of lumiracoxib

The data on hepatic effects of lumiracoxib are a matter of concern. The frequency of abnormal serum transaminases is relatively high and dose-related within the proposed therapeutic range. The results from datasets 1 and 9 clearly show that this frequency is greater with 400mg dose than with 200mg dose.

It is noted that even in the clinical trials, there was one case of concomitant elevation of ALT/AST >3ULN and bilirubin >3 mg/dl in the lumiracoxib 200mg QD group.
Of greater concern, however, are the 4 reports of hepatitis associated with 400mg QD dose of lumiracoxib in TARGET study. This study does not include a 200mg dose.

The Applicant needs to address this potential for serious hepatotoxicity by recommending that liver function tests should be measured before starting therapy with lumiracoxib and at monthly interval thereafter for the first 6 months.

## 2.16 Nephrotoxicity of lumiracoxib

There is also an increased concern that COX-2 selective inhibitors may have a greater potential for nephrotoxicity in view of the constitutional role of COX-2 in maintaining renal homeostasis. Recently, the prescribing information for valdecoxib in the US was amended to draw attention to serious hypersensitivity reactions reported with its use.

Relative to 200mg QD dose, the 400mg QD dose of lumiracoxib has a higher frequency of patients with respect to post-baseline increase in serum creatinine concentration of > 35.36 μmol/L (0.4 mg/dl) above baseline value, potassium levels
> 6.0 mmol/L or oedema.

Available data are consistent with a notion that lumiracoxib may be more nephrotoxic that other coxibs and therefore, the drug should be contraindicated in patients with moderate to severe renal dysfunction. There is also need for an appropriate warning to the effect that medically appropriate supervision should be maintained when using lumiracoxib in the elderly and in patients with mild renal dysfunction. Serum creatinine should be measured before starting therapy with lumiracoxib and at monthly interval thereafter for the first 6 months. There should also be a statement on patients at risk (those with pre-existing renal dysfunction, uncompensated heart failure, or cirrhosis and those receiving diuretics or ACE inhibitors).

## 2.17 Myelotoxicity of lumiracoxib

Available data are consistent with a notion that lumiracoxib treatment is not associated with significant myelotoxicity compared to other coxibs or classical NSAIDs. There is no evidence of any concern at present.

## 2.18 Articular structure and the effect of lumiracoxib

The assessor concludes that lumiracoxib does not have any adverse effect on articular structure over a 1-year period. There is no evidence of any concern at present.

The rate of joint space narrowing in osteoarthritis reported in the literature ranges from -0.06 mm per year to -0.23 mm per year.

In a population of 691 patients treated by rofecoxib and diclofenac, the mean rate of change in minimal joint space width over one year of treatment was:

- -0.14 mm per year for 12.5mg rofecoxib
- -0.27 mm per year for 25mg rofecoxib
- -0.18 mm per year for diclofenac group.

There was no statistically significant difference among these groups.

## 2.19 Summary of Product Characteristics

Major changes proposed by the Clinical Assessor for consideration by the Committee are:

1. Removing the indication in rheumatoid arthritis
2. The indication in primary dysmenorrhoea should be restricted to the population studied (that is, patients with moderate to severe primary dysmenorrhoea).
3. The indication in acute pain should be restricted to the population studied (that is, patients with moderate to severe pain following dental or orthopaedic surgery).
4. Downward revision to the posology for osteoarthritis
5. Additional or amended contraindications in respect of patients with renal or hepatic dysfunction.
6. Inclusion of a caution for use in patients with ischaemic heart disease
7. Inclusion of an advice to monitor renal and liver function tests at baseline and every month for the first 6 months.
8. Addition of other adverse drug events and drawing attention to the greater frequency of certain events with 400mg QD dose relative to 200mg QD dose.
9. Revisions to the texts of section 5.1 on Pharmacodynamics to reflect better and briefly the data from the clinical trials.

## 3. PHARMACODYNAMICS

### * Summary of Pharmacodynamics

The Applicant has summarized the data as follows:

1. At clinically relevant doses, as well as doses up to 1200mg QD, lumiracoxib is COX-2 selective.

2. In terms of gastroduodenal erosions determined by endoscopy, lumiracoxib is not different from placebo but it is statistically significantly different from naproxen.

### 3.1 Primary Pharmacodynamics

The applicant has submitted a number of studies, characterising the primary pharmacodynamics of lumiracoxib in man. The tissues used for these studies are:

Human whole blood assays for ex vivo studies
Studies 0101, 1101, 0107, 2311, 2314

In vivo measurements of daily excretion of TxB2 metabolite
Study 2314

In vivo measurements of platelet aggregation
Studies 0102, 2312

Gastric mucosal biopsies for ex vivo studies
Study 2311

The parameters used for measurement of COX activity are as follows:

| | |
|---|---|
| *COX-1 Activity:* | Serum $TxB_2$ |
| | TxB2 metabolite (6-keto-PGF1-$\alpha$) |
| *COX-2 Activity:* | LPS-induced $PGE_2$ synthesis |

Study 0101 Ex-vivo inhibition (%) of PGE2 and TxB2 synthesis following single dose:

| | PGE2 | | TxB2 | |
|---|---|---|---|---|
| | 1 hour | 4-hours | 1 hour | 4-hours |
| Placebo | - 56.6 | - 57.2 | - 23.4 | - 41.0 |
| 25mg | 87.3 | 81.5 | 36.7 | - 47.1 |
| 50mg | 61.5 | 94.0 | 58.9 | 39.3 |
| 100mg | 89.7 | 99.5 | 47.7 | 29.0 |
| 200mg | 89.7 | 99.5 | - 63.9 | - 58.3 |
| 400mg | 91.6 | 99.5 | -68.3 | - 303.6 |
| 800mg | 98.9 | 98.2 | 46.7 | 10.9 |

Near complete inhibition of COX-2 is observed at 100mg Fitting the concentration data to an Emax model, the following parameters were derived:

| | Estimate | SE | CV (%) |
|---|---|---|---|
| Emax (%) | 100.5 | 1.6 | 1.6 |
| EC50 (ng/ml) | 54.5 | 8.4 | 15.5 |

Study 0107

This study compared ex vivo coagulation-induced TxB2 production to assess in vivo inhibition of COX-1 on day 6 at predose, 2 and 4 hours post-dose. This study also compared effects on gastric and duodenal mucosa.

Geometric means (ng/ml) for thromboxane production in three treatment groups at the three timepoints are shown below:

| | Post 12th dose | Post 13th dose (2h) | Post 13th dose (4h) |
|---|---|---|---|
| Placebo | 31.81 | 41.73 | 45.75 |
| Lumiracoxib 200mg BD | 40.08 | 44.03 | 39.61 |
| Naproxen 500mg BD | 8.14 | 1.20 | 2.19 |

Counts of subjects with various types of gastric antral lesions at day 8 were as follows:

| | Normal | Petechiae | Erosions | Ulcers |
|---|---|---|---|---|
| Placebo | 17 | 2 | 1 | 0 |
| Lumiracoxib 200mg BD | 9 | 11 | 0 | 0 |
| Naproxen 500mg BD | 2 | 17 | 0 | 1 |

Counts of subjects with various types of duodenal lesions at day 8 were as follows:

| | Normal | Petechiae | Erosions | Ulcers |
|---|---|---|---|---|
| Placebo | 20 | 0 | 0 | 0 |
| Lumiracoxib 200mg BD | 20 | 0 | 0 | 0 |
| Naproxen 500mg BD | 7 | 0 | 13 | 0 |

The above results show that lumiracoxib is not significantly different from placebo. Naproxen is statistically significantly different from lumiracoxib or placebo.

Study 2311

This was a 3-peroid crossover randomised, placebo-controlled study to evaluate the effect of lumiracoxib on gastric and intestinal mucosa. Effect on inhibition of COX-1 (coagulation-induced TXB2 in ex vivo whole blood assay) and COX-2 (LPS-induced PGE2 in ex vivo whole blood assay) was also measured.

Total number of erosions from all sites on day 9

| | Period 1 | Period 2 | Period 3 | Total |
|---|---|---|---|---|
| Placebo | 0 | 6 | 4 | 10 |
| Lumiracoxib 800mg QD | 0 | 0 | 0 | 0 |
| Naproxen 500mg BD | 106 | 43 | 106 | 255 |

Total number of erosions from gastric sites on day 9

| | Period 1 | Period 2 | Period 3 | Total |
|---|---|---|---|---|
| Placebo | 0 | 4 | 3 | 7 |
| Lumiracoxib 800mg QD | 0 | 0 | 0 | 0 |
| Naproxen 500mg BD | 103 | 36 | 92 | 231 |

Gastric biopsy results on adjusted mean production (pg/mg) of PGE2

| | Mean | 95% CI |
|---|---|---|
| Placebo | 221.46 | 179.80, 272.78 |
| Lumiracoxib 800mg QD | 156.29 | 126.92, 192.45 |
| Naproxen 500mg BD | 67.86 | 55.09, 83.58 |

Production of TXB2 and PGE2 in whole blood assay

| | PGE2 (pg/ml) | TxB2 (ng/ml) |
|---|---|---|
| Placebo | 20654.15 | 421.81 |
| Lumiracoxib 800mg QD | 4729.53 | 293.87 |
| Naproxen 500mg BD | 7054.53 | 12.68 |

Thus, lumiracoxib has a small clinically insignificant inhibitory effect on COX-1 compared to placebo. Both lumiracoxib and naproxen caused significant inhibition of COX-2.

Study 0102

Platelet aggregation was evaluated in this multiple dose study in 40 healthy volunteers. Doses used were placebo, 50mg BD, 100mg BD, 200mg BD, 300mg BD and 400mg QD. Subjects received a single dose followed by an evaluation for 48 hours. This was followed by 9 additional days of multiple dosing.

Measurements of platelet aggregation were made at baseline and throughout various time points during the study.

There was no evidence of inhibition of ADP- or collagen-stimulated platelet aggregation in 39 of the 40 subjects.
One subject on 100mg BD who exhibited slightly above the normal time for platelet function before the administration of first dose also had values above the normal range at a few time points during the study.

Study 2312

Platelet aggregation was assessed in a subset of patients using the ADP, collagen or arachidonate activation. This was measured at baseline and at 2, 6 and 12 hours post-dose on days 0, 14 and 28 of the study. Doses of lumiracoxib were 800mg and 1200mg daily for 28 days.

There was little or no change from baseline in ADP- or collagen-stimulated platelet aggregation on day 28 by either dose of lumiracoxib or by naproxen 500mg BD.

Arachidonic acid induced platelet aggregation was inhibited by naproxen but lumiracoxib 1200mg had no effect.

## 3.2 Secondary Pharmacodynamics

Preclinical studies have showed that lumiracoxib has hardly any potential to block the hERG potassium current.

***Assessor's Comments on Pharmacodynamics:***

These results support the claim that lumiracoxib is a COX-2 selective inhibitor.

## 4. PHARMACOKINETICS

Following studies are summarised below:

| Objective | Studies |
|---|---|
| Single dose PK | 0101, 1101, 0123 (HV) |
| Multiple doses PK of therapeutic doses | 0102, 1103 (HV)<br>0104, 0112, 2316 (OA)<br>0105, 0111, 2312 (RA) |
| Dose proportionality | 0101, 1101 |
| Intra-subject and inter-subject variability | 2330 |
| Mass balance and PK following single dose of 14C-lumiracoxib in encapsulated form | 0106 |
| Comparative and absolute bioavailabilities | 2331 |
| Bioequivalence | 0121, 2315, 2330 |
| Effect of food | 0121, 1102, 2315 |

HV = Healthy volunteers

### * Summary of Pharmacokinetics

The Applicant has summarized the data as follows:

1. After an intravenous dose the mean plasma clearance of lumiracoxib is 7.7 ± 1.5 L/h and the $V_{ss}$ is 9.0 ± 1.7 L
2. In healthy subjects the mean absolute oral bioavailability of lumiracoxib 200mg final market image (FMI) tablet is 74.0 ± 8.6% and the mean terminal half life observed in plasma is 3.98 ± 1.37 h; $t_{max}$ is typically about 2 h post dose.
   After a dose of 400mg, mean plasma concentrations are high at 15 minutes post dose; > 600 ng/ml.
3. Following oral administration, the AUC of lumiracoxib is linear and dose proportional in the dose range 25-800mg
4. On multiple oral administration with once a day regimens the pharmacokinetics of lumiracoxib are time independent and no accumulation or auto-induction is observed at doses up to 1200mg QD and for periods up to 91 days. The peak to trough fluctuation (100 x [($C_{max}$-$C_{min}$)/$C_{av}$g]) is high being about 700-800%.
5. Mean systemic availability is largely unchanged when lumiracoxib is administered with a high fat meal
6. Compared to release in the stomach the relative bioavailability of lumiracoxib is consistently high following release in the proximal small bowel, distal small bowel and colon, indicating that absorption is uniform throughout the small intestine and colon.
7. After an oral dose of 14C-lumiracoxib, about 54% of administered radioactivity is excreted in urine and about 43% in faeces. Only about 5% of administered lumiracoxib is excreted as unchanged drug
8. Lumiracoxib is metabolised by CYP2C9 to form 4'-hydroxy-lumiracoxib, 5-carboxy-lumiracoxib and 4'-hydroxy-5-carboxy-lumiracoxib; in addition various conjugates (glucuronides and sulfates) are formed of these metabolites. Only 4'-hydroxy-lumiracoxib has similar activity and similar selectivity to that of lumiracoxib. Based on plasma concentrations (15% of the AUC of lumiracoxib) the contribution of this metabolite to efficacy is thought to be small

9 Lumiracoxib is highly bound to plasma proteins albumin. The blood to plasma ratio is about 0.5, indicating little distribution into blood cells.

10. In RA patients, high plasma concentrations of lumiracoxib are achieved rapidly ($t_{max}$ of about 2 h) and by 24 h post dose plasma concentrations were low, being typically less than 5% of the $C_{max}$. In contrast concentrations of lumiracoxib in synovial fluid are higher than plasma by about 5 h post dose and remained substantially higher than

those in plasma for the remainder of the dose interval, lending support to the use of lumiracoxib in once a day regimens

## 4.1 Single dose pharmacokinetics

Studies 0101, 1101, 0123

Study 0101

A randomised double blind parallel group study in healthy volunteers
Mean age 26.2 years, height 175.1 cm and weight 71.1 kg
Sampling time 72 hours post-dose
Fasting condition
N = 48 = 42 Caucasians, 2 Blacks, 1 Oriental and 3 others
Subjects entered in a group of 8 (6 active and 2 placebo) with timelagged ascending dose level.

Pharmacokinetic parameters (Mean ± SD)

| Dose (mg) | Cmax ng/ml | AUC(0-α) ng.hr/ml | AUC(0-α) ng.hr/ml per 25mg | Median Tmax (hrs) | Half-life (hr) |
|---|---|---|---|---|---|
| 25 | 645 ± 220 | 2530 ± 619 | 2530 | 2.5 | 2.9 ± 1.9 |
| 50 | 1930 ± 776 | 5480 ± 1550 | 2740 | 2.0 | 3.6 ± 2.6 |
| 100 | 2420 ± 1130 | 8350 ± 2220 | 2088 | 2.5 | 3.4 ± 1.6 |
| 200 | 4180 ± 1510 | 16700 ± 4640 | 2088 | 3.0 | 4.5 ± 1.2 |
| 400 | 6740 ± 2060 | 40900 ± 9150 | 2557 | 2.3 | 6.2 ± 1.9 |
| 800 | 1088 ± 1620 | 78800 ± 16000 | 2462 | 2.8 | 6.0 ± 1.3 |

Dose recovery was of the order of 82%. Lumiracoxib was the major circulating component in plasma with three major and two minor metabolites. Elimination was primarily metabolic with only small fraction excreted unchanged. Excretion involved renal and biliary routes.

| Dose (mg) | Unchanged drug recovery in urine (% of dose) | Renal clearance L/hr |
|---|---|---|
| 25 | 1.45 | 0.15 |
| 50 | 1.14 | 0.11 |
| 100 | 1.17 | 0.15 |
| 200 | 1.22 | 0.15 |
| 400 | 1.01 | 0.10 |
| 800 | 0.76 | 0.08 |

Study 1101

Design as above.
**Japanese** healthy volunteers
Mean age 22 years, height 173 cm and weight 60.5 kg

Pharmacokinetic parameters (Mean ± SD)

| Dose (mg) | Cmax ng/ml | AUC(0-α) ng.hr/ml | AUC(0-α) ng.hr/ml per 25mg | Median Tmax (hrs) | Half-life (hr) |
|---|---|---|---|---|---|
| 25 | 1036 ± 486 | 2783 ± 827 | 2783 | 2.5 | 2.0 ± 0.5 |
| 50 | 2147 ± 433 | 6201 ± 1232 | 3100 | 3.5 | 2.6 ± 0.9 |
| 100 | 3619 ± 1397 | 12340 ± 3057 | 3085 | 2.5 | 4.8 ± 1.2 |
| 200 | 6677 ± 1241 | 24608 ± 2815 | 3076 | 3.0 | 4.1 ± 1.4 |

| | | | | | |
|---|---|---|---|---|---|
| 400 | 8600 ± 2169 | 46921 ± 5503 | 2933 | 2.0 | 5.3 ± 1.9 |
| 800 | 16412 ± 5148 | 89213 ± 20507 | 2788 | 2.3 | 5.7 ± 2.1 |

| Dose (mg) | Unchanged drug recovery in urine (% of dose) | Renal clearance L/hr |
|---|---|---|
| 25 | 0.15 | 0.016 |
| 50 | 0.15 | 0.014 |
| 100 | 0.16 | 0.015 |
| 200 | 0.16 | 0.015 |
| 400 | 0.17 | 0.015 |
| 800 | 0.10 | 0.010 |

Dose-normalised Cmax and AUC are higher in the Japanese by 43% and 22%, respectively.

## 4.2 Intra- and Inter-Subject Variability

In Study 2330, bioequivalence of the lumiracoxib 400mg FMI tablet (65% drug-load) compared to 2 x 200mg FMI tablet (50% drug-load) was assessed in 44 subjects, each subject receiving both treatments on two occasions.

Intra- and inter-subject coefficients of variation for Cmax and AUC0-t at both the 200mg and 400mg doses are given in the table below. The coefficients of variation were obtained from the results of the mixed model analysis of log-transformed AUC0-t and Cmax by assuming the CV is approximately 100 x standard deviation, where the standard deviation is estimated on the logarithmic scale.

| | Coefficient of Variation (%) | |
|---|---|---|
| | Intra-subject | Inter-subject |
| AUC0-t | | |
| 200mg | 11 | 26 |
| 400mg | 10 | 24 |
| Cmax | | |
| 200mg | 22 | 28 |
| 400mg | 29 | 25 |

## 4.3 Dose-proportionality study

Studies 0101 and 1101

These two studies are discussed above and show a close trend for dose proportionality in the range of 25mg to 800mg daily of lumiracoxib.

## 4.4 Multiple doses pharmacokinetics

Studies 0102, 1103 (HV), 0104, 0112, 2316 (OA) and 0105, 0111, 2312 (RA)

Study 0102 in healthy volunteers

48-hours evaluation after a single dose followed by 9 additional days of multiple dosing. 40 subjects (8 per group [6 active + 2 placebo] dosed in time-lagged manner with ascending doses)

Mean parameters were as follows:

| | Day 1 | Day 12 |
|---|---|---|

| | Cmax ng/ml | AUC(0-α) ng.hr/ml | AUC(0-τ) ng.hr/ml | Cmax ng/ml | AUC(0-τ) ng.hr/ml |
|---|---|---|---|---|---|
| 50mg BD | 957 | 4870 | 3910 | 1170 | 5020 |
| 100mg BD | 2030 | 9300 | 8660 | 2330 | 10400 |
| 200mg BD | 4730 | 20600 | 18900 | 3880 | 17400 |
| 300mg BD | 3950 | 23700 | 20300 | 3840 | 21800 |
| 400mg QD | 5900 | 36000 | 34000 | 6250 | 31300 |

The pharmacokinetics are fairly dose-proportional and independent of time; there being no accumulation over time.

Study 1103 in healthy volunteers

Multiple dosing in **Japanese** subjects

Eight volunteers per group (6 active drug and 2 placebo)

| | Cmax ng/ml | AUC(0-α) ng.hr/ml | Half-life hr | Clearance L/hr |
|---|---|---|---|---|
| | **Day 1** | | | |
| 200mg QD | 4442 | 19193 | 4.1 | 10.5 |
| 400mg QD | 8186 | 34609 | 3.9 | 12.1 |
| 400mg BD | 4688 | 17269 | 1.7 | 11.7 |
| | **Day 5** | | | |
| 200mg QD | 4857 | 20726 | 4.0 | 9.8 |
| 400mg QD | 9023 | 35424 | 3.5 | 11.5 |
| 400mg BD | 4912 | 18089 | 2.7 | 11.5 |

These data are consistent with the data in another study (above) with single dose. There is dose proportionality and time-independence, there being no evidence of accumulation

Study 2316 in osteoarthritis

Dosing for 28 days in OA patients
16 patients

Pharmacokinetic parameters (Mean ± SD)

| Dose (mg) | Cmax ng/ml | AUC(0-6) ng.hr/ml | AUC(0-τ) ng.hr/ml | Median Tmax (hrs) |
|---|---|---|---|---|
| | **Day 28** | | | |
| 100QD | 3312 ± 876 | 8346 ± 1775 | 11107 ± 2486 | 1.1 |

The data suggest that the drug is absorbed rapidly. The parameters are consistent with dose-proportionality within the range 100-800mg QD of lumiracoxib.

Study 0104 in osteoarthritis

76 of the 5583 patients had PK/PD profiles (52 on lumiracoxib). Dosing for 28 days in OA patients.

Pharmacokinetic parameters (Mean ± SD)

| Dose (mg) | Cmax ng/ml | AUC(0-6) ng.hr/ml | AUC(0-τ) ng.hr/ml | Median Tmax (hrs) |
|---|---|---|---|---|
| | **Day 0** | | | |
| 50BD | 914 ± 343 | 2690 ± 956 | | 2.0 |
| 100BD | 1787 ± 601 | 5220 ± 1810 | | 2.5 |
| 200BD | 4207 ± 2164 | 11731 ± 3570 | | 3.0 |
| 400QD | 5536 ± 1798 | 17246 ± 5279 | | 3.0 |
| | **Day 28** | | | |
| 50BD | 1009 ± 594 | 2768 ± 1257 | 3838 ± 1318 | 2.0 |
| 100BD | 1862 ± 630 | 6009 ± 1886 | 8088 ± 2876 | 2.0 |
| 200BD | 4378 ± 3099 | 11089 ± 3024 | 14322 ± 3087 | 2.0 |
| 400QD | 4788 ± 2642 | 15311 ± 5587 | 25750 ± 9196 | 2.0 |

The data suggest that steady state is reached on day 1 of drug administration. There is dose proportionality with no evidence of accumulation on 50mg, 100mg and 200mg BD and 400mg QD regime.

The relatively higher values of Cmax and AUC for 400mg QD dose, relative to 200mg BD dose, may simply reflect rapid absorption. The difference between the two regimes decreases with time.

There was no evidence of gender related effect on clearance.
There was a slight decrease in clearance with age.

Study 0112 in osteoarthritis

62 of the 1702 patients had PK/PD profiles (35 in 200mg and 27 in 400mg group).
Dosing for 91 days in OA patients

Pharmacokinetic parameters (Mean ± SD)

| Dose (mg) | Cmax ng/ml | AUC(0-6) ng.hr/ml | AUC(0-τ) ng.hr/ml | Median Tmax (hrs) |
|---|---|---|---|---|
| | **Day 0** | | | |
| 200QD | 6517 ± 4435 | 15284 ± 8751 | | 2.0 |
| 400QD | 9289 ± 4874 | 24974 ± 11940 | | 2.0 |
| | **Day 28** | | | |
| 200QD | 6289 ± 4136 | 13004 ± 7072 | 17077 ± 9403 | 2.0 |
| 400QD | 8914 ± 3921 | 23106 ± 9683 | 31171 ± 13316 | 2.0 |
| | **Day 91** | | | |
| 200QD | 6617 ± 4874 | 14377 ± 7410 | 19123 ± 9419 | 2.0 |
| 400QD | 8519 ± 3518 | 20782 ± 8011 | 28803 ± 16519 | 2.0 |

Clearance was independent of dose, gender or age with no evidence of accumulation.

| Two subjects (400mg QD) had very high | Cmax | and | AUC(0-6): |
|---|---|---|---|
| Subject 18 from centre 109 | 17929 | | 52816 |
| Subject 6 from centre 1104 | 24668 | | 53252 |

Studies 0105, 0111 and 2312 in rheumatoid arthritis

In general, the pharmacokinetic profile in patients with rheumatoid arthritis was similar to that observed in patients with osteoarthritis.

The only difference was uncovered in studies 0105 and 2312 in which there was a **clear evidence of non-proportionality** for both the AUC and Cmax at doses higher than 800mg. The data from this study are shown below:

*Study 0105*

65 patients dosed for 28 days

Pharmacokinetic parameters (Mean ± SD)

| Dose (mg) | Cmax ng/ml | AUC(0-6) ng.hr/ml | AUC(0-τ) ng.hr/ml | Median Tmax (hrs) |
|---|---|---|---|---|
| | **Day 0** | | | |
| 50BD | 999 ± 382 | 2913 ± 1004 | | 2.1 |
| 100BD | 1957 ± 835 | 5991 ± 2000 | | 2.1 |
| 200BD | 3119 ± 1570 | 10523 ± 4278 | | 2.7 |
| 400QD | 7243 ± 2595 | 20656 ± 4690 | | 2.0 |
| | **Day 28** | | | |
| 50BD | 1068 ± 340 | 3027 ± 980 | 3780 ± 1265 | 2.0 |
| 100BD | 1764 ± 695 | 5304 ± 1718 | 6722 ± 2065 | 2.0 |
| 200BD | 3607 ± 2138 | 11599 ± 5175 | 15605 ± 5713 | 2.0 |
| 400QD | 6094 ± 2141 | 19425 ± 5010 | 30961 ± 4626 | 3.0 |

*Study 2312*

Once a day dosing

| Dose (mg) | Cmax ng/ml | AUC(0-12) ng.hr/ml | AUC(0-τ) ng.hr/ml |
|---|---|---|---|
| | **Day 0** | | |
| 800mg | 25367 | 68893 | |
| 1200mg | 20029 | 77279 | |
| | **Day 14** | | |
| 800mg | 20126 | 59624 | 63995 |
| 1200mg | 21359 | 69957 | 75370 |
| | **Day 28** | | |
| 800mg | 18884 | 60494 | 64733 |
| 1200mg | 20175 | 69974 | 75894 |

Compared to 800mg dose, the AUC(0-τ) for 1200mg dose was only 17% higher with Cmax only 7% higher at day 28.

## 4.5 Absolute bioavailability

Study 2331

Single center open label study in healthy volunteers given 200mg FMI tablet and up to 100mg IV infusion of 13C-lumiracoxib over 30 minutes

N = 15 = 12M and 3F (mean age 38.2 years) (all Caucasians)

Pharmacokinetics following oral and IV lumiracoxib

| | IV Infusion | Oral administration |
|---|---|---|
| AUC(0-α) μg.hr/ml | 13343 ± 2544 | 20036 ± 4564 |
| Cmax ng/ml | 14625 ± 4194 | 5964 ± 2132 |
| Tmax hr | 0.5 | 2.3 |
| Half-life hr | 2.17 ± 0.34 | 3.98 ± 1.37 |
| Clearance L/hr | 7.7 ± 1.5 | |
| Volume of Distribution L | 9.0 ± 1.7 | |

Bioavailability was calculated at 74.0 ± 8.6 %

Coefficients of variation for AUC were 19.1% for IV and 22.8% for oral administration

## 4.6 Effect of Food

200mg dose as tablet in Study 0121

| Fasted | Fed | Ratio | 90% CI for ratio |
|---|---|---|---|
| Cmax ng/ml | | | |
| 4317.7 | 3977.3 | 81.14 | 63.97, 102.94 |
| AUC(0-t) ng/hr/ml | | | |
| 14852 | 12467 | 83.50 | 78.06, 89.31 |
| AUC(0-α) ng/hr/ml | | | |
| 14991 | 12614 | 83.71 | 78.35, 89.43 |
| Tmax (hr) | | | |
| 2.5 | 3.0 | | |

Thus, compared to fasting condition, administration of lumiracoxib after a high fat meal resulted in a reduction in AUC and Cmax of about 16% and 19% respectively.

Data from other studies are summarized below for comparison:

| Study | Dose | Parameter | Ratio | CI |
|---|---|---|---|---|
| 0121 | 200mg | AUC | 83.7 | 78.4. 89.4 |
| 0121 | 200mg | Cmax | 81.1 | 64.0, 102.9 |
| 2315 | 400mg | AUC | 96.4 | 90.1, 103.1 |

| | | | | |
|---|---|---|---|---|
| 2315 | 400mg | Cmax | 107.3 | 85.7, 134.2 |

This difference, however, is unlikely to be of any clinical significance.

## 4.7 Absorption

Study 0123

This randomised, open-label, 4-ways crossover study evaluated the relative bioavailability of lumiracoxib released at specific sites within the gastrointestinal tract. 100mg lumiracoxib in polyethylene glycol suspension in a capsule with MBq $^{99m}$Tc-DTPA added to confirm release.

Pharmacokinetic parameters (Mean ± SD)

| Site | Cmax ng/ml | AUC(0-α) ng.hr/ml | AUC(0-t ng.hr/ml | Median Tmax (hrs) |
|---|---|---|---|---|
| Stomach | 1390 ± 513 | 6146 ± 944 | 6011 ± 940 | 2.0 |
| Proximal small bowel | 1628 ± 663 | 6603 ± 2186 | 6355 ± 2321 | 1.0 |
| Distal small bowel | 2413 ± 996 | 6842 ± 1473 | 6691 ± 1525 | 1.0 |
| Ascending colon | 1109 ± 612 | 4983 ± 1145 | 4736 ± 1144 | 1.0 |

Ratios (95% CI) of parameters relative to release in stomach

| Site | Cmax ng/ml | AUC(0-α) ng.hr/ml | AUC(0-t ng.hr/ml |
|---|---|---|---|
| Stomach | 1 | 1 | 1 |
| Proximal small bowel | 1.077<br>0.770, 1.506 | 1.041<br>0.856, 1.268 | 1.013<br>0.821, 1.251 |
| Distal small bowel | 1.517<br>1.049, 2.194 | 1.099<br>0.886, 1.364 | 1.092<br>0.866, 1.376 |
| Ascending colon | 0.815<br>0.572, 1.160 | 0.848<br>0.690, 1.042 | 0.820<br>0.657, 1.023 |

Apart from the low bioavailability when released in ascending colon, the exposure is comparable when the drug is released in small bowel and in stomach

## 4.8 Distribution

The blood to plasma ratio is about 0.5 and independent of concentration.

Plasma protein binding of lumiracoxib was investigated in human plasma in vitro in the concentration range 0.05 to 100 μg/ml.

It is bound almost exclusively to albumin ≥ 98% and independent of concentration.

The binding profile is unaltered in patients with end stage renal disease or in patients with moderate hepatic impairment.

In one open-label study (0122), there was no evidence that binding in synovial fluid differed from that in plasma.

In study 0122, after multiple dosing in patients with rheumatoid arthritis, mean concentrations of lumiracoxib and its metabolites in plasma and synovial fluid after last dose of 400mg were as follows:

*Lumiracoxib*

| Hours⇒ | 0 | 1 | 2 | 4 | 6 | 8 | 10 | 24 | 28 |
|---|---|---|---|---|---|---|---|---|---|
| Plasma | 155 | 5022 | 5724 | 3553 | 1839 | 1131 | 819 | 147 | 111 |
| Synovial fluid | 454 | 526 | 932 | 1033 | 2864 | 1546 | 864 | | 87 |

*4-OH-lumiracoxib*

| Hours⇒ | 0 | 1 | 2 | 4 | 6 | 8 | 10 | 24 | 28 |
|---|---|---|---|---|---|---|---|---|---|
| Plasma | 145 | 420 | 178 | 144 | 683 | 433 | 74 | | 27 |
| Synovial fluid | 138 | 150 | 44 | 66 | 406 | 315 | 84 | | 10 |

The equilibrium half-life is estimated at 3.3 hours and a large peak following a single dose may ensure a rapid distribution of lumiracoxib to this effect compartment.

## 4.9 Metabolism

Study 0106

Metabolism of lumiracoxib involves oxidation of:

- 5-methy group to yield 5-hydroxy-methyl-lumiracoxib which is then further metabolised to 5-carboxy-lumiracoxib and
- dihaloaromatic ring to yield 4-hydroxy-lumiracoxib.

Both 5-carboxy-lumiracoxib and 4-hydroxy-lumiracoxib are further metabolised to yield 5-carboxy-4-hydroxy-lumiracoxib.

These oxidative metabolites are subject to conjugation by glucuronic acid. Direct glucuronidation of lumiracoxib is relatively minor (2-3%).

In vitro studies:

The involvement of major cytochromes in the metabolism of lumiracoxib was investigated in vitro using human baculovirus-insect-cell-expressed supersomes.

The results showed that the formation of various metabolites is catalysed as follows:

| | | |
|---|---|---|
| 4-OH-lumiracoxib | CYP2C9 | (main) |
| | CYP1A2 | (4.31%) |
| | CYP2C19 | (2.55%) |
| 5-OH-methyl-lumiracoxib | CYP2C9 | (main) |
| | CYP1A2 | (0.94%) |
| | CYP2C19 | (1.08%) |

No other CYP isozymes were involved.

The proposed metabolic pathways are shown in the figure overleaf.

In vivo Study 0106

Studies using radiolabelled product indicated the presence of a number of metabolites in the urine but three major circulating metabolites.

Plasma exposure to drug-related components relative to lumiracoxib are as follows (see figure overleaf):

| | | |
|---|---|---|
| Total radioactivity: | 153 | . |
| Lumiracoxib: | 58.90 | |
| 5-COOH | 16.60 | (also known as metabolite M11) |
| 4-OH-5-COOH | 12.50 | (also known as metabolite M5) |
| 4-OH | 8.82 | (also known as metabolite M23) |
| 5-COOH-lactam | 5.91 | |
| 4-OH-5-COOH lactam | 4.10 | |

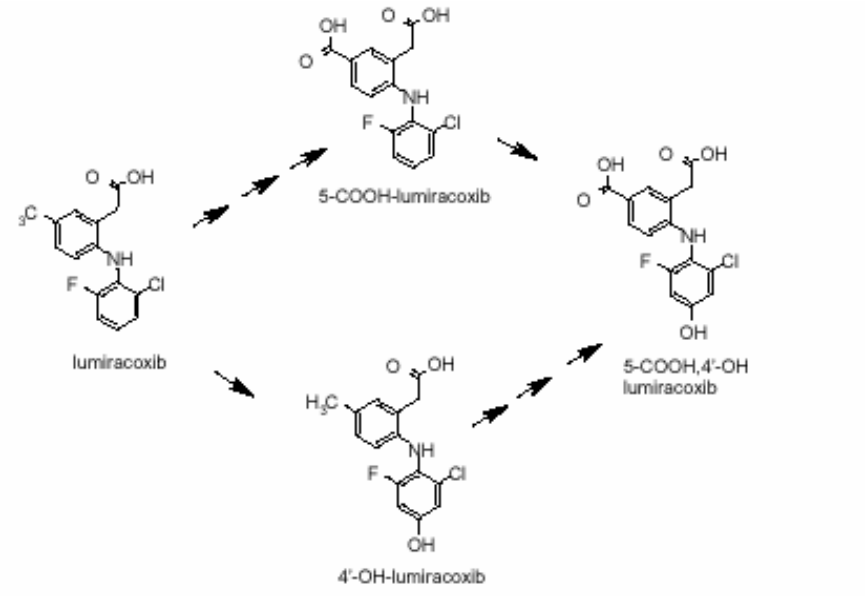
## 4.10 Excretion

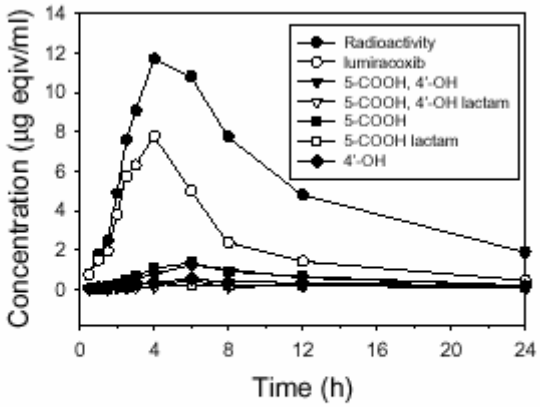
Following an oral dose of 400mg $^{14}$C-lumiracoxib to 4 healthy male volunteers, the excretion pattern observed was:

54% radioactivity in urine and 43% in faeces with a total recovery of 97% by 168 hours
Unchanged lumiracoxib accounted for 3.3% and 2.0% of the dose in urine and faeces respectively.

Renal clearance ranges 0.05-0.2 L/h

**Major human plasma metabolites of lumiracoxib**






Plasma concentrations of lumiracoxib, radioactivity and metabolites following oral administration of [$^{14}$C]-lumiracoxib to healthy subjects [study 0106

## 4.11 Activity of metabolites

4-hydroxy-lumiracoxib is as potent and COX-2 selective as lumiracoxib.

In whole blood assay:

| | IC50 for inhibition of PGE2 (µM) | IC50 for inhibition of TxB2 (µM) |
|---|---|---|
| Lumiracoxib | 0.1 | 66 |
| 4-OH-lumiracoxib | 0.1 | 77 |
| Di-carboxylic acid metabolites | Observed inhibition was not concentration-dependent and never exceeded 40 % in the range of 3-300 µM | Observed inhibition was not concentration-dependent and never exceeded 25% in the range of 3-300 µM |

In vitro enzyme inhibition assay (See Report RD-2002-50325 in module 4.2.1.1):

| | IC50 for inhibition of COX-2 (µM) | IC50 for inhibition of COX-1 (µM) |
|---|---|---|
| Lumiracoxib | 0.16 | 3.2 |
| 4-OH-lumiracoxib | 5 | 36 |

## 4.12 Bioequivalence

Study 0121

Early studies with lumiracoxib used a capsule formulation. However, the formulation used in the clinical trials is the final market image (FMI) tablet.

Study 0121

This study tested the bioequivalence of the 100mg capsule (x2) to the FMI 200mg tablet. Mean values for bioequivalence parameters were as follows:

| | Capsule Form (A) | FMI tablet Form (B) | Ratio B/A (95% CI) |
|---|---|---|---|
| Cmax ng/ml | 3283 | 4317 | 0.766 (0.604, 0.972) |
| AUC(0-t) | 14892 | 14852 | 1.005 |

| | | | |
|---|---|---|---|
| ng.hr/ml | | | (0.940, 1.075) |
| AUC(0-α) ng.hr/ml | 15029 | 14991 | 1.005 (0.941, 1.074) |
| Tmax | 2.0 | 2.5 | |

Thus, the two forms perform almost identically except for Cmax. The Applicant has used the normal bioequivalence criteria for AUC (80-125) and the extended limits (70-143) for Cmax. Therefore, as fax as Cmax is concerned, the two forms are not bioequivalent. This is important since the applicant has relied on higher Cmax following once daily administration as a means to ensure the higher distribution of the drug into synovial fluid.

Notwithstanding, the above observations are theoretical since the formulation used in clinical trials is the FMI tablets. The tablet formulation used in major efficacy trials was 200mg tablet with 50% drug load.

Study 2315

This study tested the bioequivalence of the FMI 400mg tablet to the FMI 200mg tablet.

Geometric mean values for bioequivalence parameters for the two tablets – both with 50% drug load - were as follows:

| | (A) 200mg x 2 | (B) 400mg x 1 | Ratio B/A (90% CI) |
|---|---|---|---|
| Cmax ng/ml | 7983 | 6721 | 0.842 (0.673, 1.053) |
| AUC(0-t) ng.hr/ml | 28121 | 26999 | 0.960 (0.897, 1.028) |
| AUC(0-α) ng.hr/ml | 28270 | 27172 | 0.961 (0.898, 1.028) |
| Tmax | 1.8 | 2.5 | |

This study shows that a lower Cmax after a 400mg tablet relative to 2 x 200mg tablets.

Geometric mean values for bioequivalence parameters for the two tablets – 200mg with 50% drug load and 400mg with 65% drug load - were as follows:

| | (A) 200mg x 2 | (B) 400mg x 1 | Ratio B/A (90% CI) |
|---|---|---|---|
| Cmax ng/ml | 7983 | 8131 | 1.019 (0.814, 1.274) |
| AUC(0-t) ng.hr/ml | 28121 | 28672 | 1.020 (0.952, 1.091) |
| AUC(0-α) ng.hr/ml | 28270 | 28831 | 1.020 (0.953, 1.091) |
| Tmax | 1.8 | 2.0 | |

This study shows that 200mg FMI (50% drug load) is bioequivalent to 400mg FMI (65% drug load). This was confirmed in a replicate design study 2330.

Overall, as far as the AUC is concerned, the study shows bioequivalence of 400mg 50% drug load tablet or 400mg 65% drug load tablet with 200mg 50% drug load tablet.

As far as Cmax is concerned, only 400mg 65% drug load tablet is just about bioequivalent with 200mg 50% drug load tablet.

Study 2330

| | (A)<br>200mg 50% drug load tablet x 2 | (B)<br>400mg 65% drug load tablet x 1 | Ratio B/A<br>(90% CI) |
|---|---|---|---|
| Cmax<br>ng/ml | 9261.1 | 8557.2 | 0.92<br>(0.86, 0.99) |
| AUC(0-t)<br>ng.hr/ml | 43765.5 | 42334.0 | 0.97<br>(0.94, 0.99) |
| AUC(0-$\alpha$)<br>ng.hr/ml | 44008.9 | 42496.1 | 0.97<br>(0.94, 0.99) |

***Assessor's Comments on Pharmacokinetics:***

Bioavailability was calculated at 74.0 ± 8.6 %

Coefficients of variation for AUC were 19.1% for IV and 22.8% for oral administration

Kinetics of lumiracoxib are linear to doses of 800mg.

At doses of 1200mg or higher, there is marked loss of dose proportionality with under-exposure.

200mg FMI (50% drug load) is bioequivalent to 400mg FMI (65% drug load).

Lumiracoxib is metabolised by oxidation by CYP2C9. 4-hydroxy-metabolite of lumiracoxib is pharmacologically active and almost as potent and COX-2 selective as the parent drug.

Compared to fasting condition, administration of lumiracoxib after a high fat meal resulted in a reduction in AUC and Cmax of about 16% and 19% respectively. This difference, however, is unlikely to be of any clinical significance.

## 5. PHARMACOKINETICS IN SPECIAL POPULATIONS

Following studies are summarised below:

| Special population studied | Studies |
|---|---|
| Females versus males | Pooled analysis |
| Elderly versus young adults | Pooled analysis |
| Hepatic impairment | 0137 |
| Renal impairment | 0136 |
| CYP2C9 Poor metabolisers | Pooled analysis |
| Ethnicity | Pooled analysis<br>0101, 1101 |

### * Summary of Pharmacokinetics in special populations:

The Applicant has summarized the data as follows:

1. The exposure of older subjects (≥ 65 years) to lumiracoxib is 15% higher than in younger subjects. Thus based on pharmacokinetic data no dose adjustment is necessary in the elderly. Studies in children have not yet been conducted.
2. Gender and ethnic origin do not affect the pharmacokinetics of lumiracoxib. Body weight appears to influence exposure to lumiracoxib with a patient of 100 kg expected to have an AUC of about 0.78 times that of a patient of 75kg. At doses of 200mg or 400mg, efficacy of lumiracoxib relative to placebo was maintained regardless of BMI category.
3. On the basis of plasma exposure to lumiracoxib and pharmacogenetic analysis, no evidence has been found to suggest that exposure to lumiracoxib is increased in subjects with genotypes of CYP2C9 associated with reduced metabolic clearance.
4. Exposure to lumiracoxib is lower in patients with end stage renal disease compared to normal subjects. Compared to normal subjects, mean exposure to 4'-hydroxy-lumiracoxib is not significantly increased in ESRD patients and exposure to 4'-hydroxy-5-carboxy-lumiracoxib is increased substantially (by about 7 times). Dialysis has no effect on plasma exposure to lumiracoxib or these metabolites.
5. There is no difference in the exposure to lumiracoxib between normal subjects and subjects with moderate hepatic impairment

### 5.1 Effect of Age

The exposure (AUC) data from a total of 57 patients > 65 years of age (of whom 8 were > 75 years old) were compared to that from 387 patients < 65 years age.

It was estimated that the elderly have a mean increase of 15% in exposure.

### 5.2 Effect of Gender

From the pooled analysis, it was determined that relative to 249 males, the 193 females had a slightly greater exposure (6 % in AUC and 11% in Cmax) to lumiracoxib.

### 5.3 Effect of Hepatic Dysfunction

Study 0137

Single dose, open label, parallel group study
400mg lumiracoxib

Patients with moderate hepatic impairment (Child-Pugh score 7-9) compared to matched healthy controls – 8 in each group

Mean pharmacokinetic parameters:

| | Cmax ng/ml | AUC(0-t) ng/hr/ml | AUC(0-α) ng/hr/ml |
|---|---|---|---|
| | **Lumiracoxib** | | |
| Hepatically impaired | 6689 | 29036 | 29198 |
| Healthy controls | 7486 | 28654 | 28746 |
| | **Ratio** | | |
| **Hepatic/Healthy** | 0.86 | 1.01 | 1.01 |

Correlation analysis was performed to examine relationship with specific hepatic function tests (albumin, total bilirubin and PT). No correlation was observed for either Cmax or AUC.

* **No studies have been performed in patients with severe hepatic impairment**

## 5.4 Effect of Renal Dysfunction

Study 0136

Single dose, open label, parallel groups study
200mg lumiracoxib

Patients with end-stage renal disease compared to matched healthy volunteers
8 in each group

Mean pharmacokinetic parameters were as follows:

| | Cmax ng/ml | AUC(0-t) ng.hr/ml | AUC(0-α) ng.hr/ml |
|---|---|---|---|
| | **Lumiracoxib** | | |
| ESRD post-dialysis | 3165 | 11074 | 11181 |
| ESRD with dialysis | 3039 | 10644 | 10751 |
| Healthy controls | 4719 | 14213 | 14323 |
| | **4-OH-lumiracoxib** | | |
| ESRD post-dialysis | 278.3 | 2918.4 | 3637.2 |
| ESRD with dialysis | 259.3 | 2456.7 | 3044.8 |
| Healthy controls | 351.6 | 2156.5 | 2477.1 |
| | **5-caroboxy-4-OH-lumiracoxib** | | |
| ESRD post-dialysis | 1459.9 | 46239.1 | |
| ESRD with dialysis | 1513.7 | 43757.5 | |
| Healthy controls | 743.7 | 6297.7 | |

Ratios of the mean pharmacokinetic parameters were as follows:

| | Cmax ng/ml | AUC(0-t) ng.hr/ml | AUC(0-α) ng.hr/ml |
|---|---|---|---|
| | **Lumiracoxib** | | |
| ESRD post-dialysis versus healthy controls | 0.66 | 0.73 | 0.73 |
| ESRD dialysis before versus dialysis after dose | 0.99 | 1.00 | 1.00 |
| | **4-OH-lumiracoxib** | | |
| ESRD post-dialysis versus healthy controls | 0.74 | 1.17 | 1.35 |
| ESRD dialysis before versus dialysis after dose | 1.04 | 1.24 | 1.22 |
| | **5-caroboxy-4-OH-lumiracoxib** | | |
| ESRD post-dialysis versus healthy controls | 2.45 | 9.36 | |

| | | | |
|---|---|---|---|
| ESRD dialysis before versus dialysis after dose | 1.01 | 1.10 | |

There was no difference between normal and renal failure subjects in terms of ex-vivo protein binding of lumiracoxib (≥ 98%).

Thus, averaging the pre- and post-dialysis values, it is evident that renal failure results in:

- a decreased systemic exposure to lumiracoxib (24% for AUC and 35% for Cmax)
- an increased exposure to the primary active metabolite (4-OH-lumiracoxib) (AUC is increased by 35% and Cmax is decreased by 24%).

Haemodialysis has no effect on the pharmacokinetics of lumiracoxib or its primary metabolite.

Given that 4-OH-lumiracoxib is equipotent as lumiracoxib, it is anticipated that renal failure has no influence on response and no dose adjustment is necessary on pharmacokinetic considerations.

## 5.5 Ethnic Influences on Pharmacokinetics of Lumiracoxib

The influence of ethnicity was investigated from the data across the program.

| | | Point estimates of AUC relative to Caucasians |
|---|---|---|
| Caucasians | n = 392 | 100 % |
| Blacks/Afro-Americans | n = 19 | 116 % |
| Hispanics | n = 31 | 108 % |
| Japanese | n = 30 | 110 % |

## 5.6 Pharmacogenetic Influences on Pharmacokinetics of Lumiracoxib

In vitro catalytic data are shown in the table below:

| | Vmax (pmol $P450^{-1}$ $min^{-1}$) | |
|---|---|---|
| | 4-hydroxylation | 5-methyl-hydroxylation |
| CYP2C9*1 | 5.52 | 2.14 |
| CYP2C9*2 | 4.42 | 0.996 |
| CYP2C9*3 | 1.50 | 0.676 |

| | Km (μM) | |
|---|---|---|
| | 4-hydroxylation | 5-methyl-hydroxylation |
| CYP2C9*1 | 4.87 | 8.85 |
| CYP2C9*2 | 3.60 | 5.92 |
| CYP2C9*3 | 5.80 | 8.78 |

| | Vmax/Km (μL $min^{-1}$ pmol $P450^{-1}$) | |
|---|---|---|
| | 4-hydroxylation | 5-methyl-hydroxylation |
| CYP2C9*1 | 1.130 | 0.242 |
| CYP2C9*2 | 0.947 | 0.168 |
| CYP2C9*3 | 0.192 | 0.077 |

The catalytic efficiency of variant alleles is 70-84% for CYP2C9*2 and 23-32% for CYP2C9*3. This suggests that only individuals carrying the CYP2C9*3 allele may develop high plasma levels of lumiracoxib.

In a polled analysis of 496 subjects who received lumiracoxib, there were 6 who were observed as falling outside the normal distribution of dose-normalised exposure. These 6 had Cmax in the range 10595 to 17854 ng/ml

Four of these 6 were available for genotyping and they were:

| | |
|---|---|
| *1/*1 | 3 |
| *1/*3 | 1 |

In addition, 97 subjects with pharmacokinetic data were genotyped and the results were as follows:

| | CYP2C9 genotype | | | | | |
|---|---|---|---|---|---|---|
| | *1/*1 | *1/*2 | *1/*3 | *2/*2 | *2/*3 | *3/*3 |
| N | 63 | 22 | 9 | 2 | 1 | 0 |
| Mean AUC ng.hr/ml | 35523 | 34835 | 42261 | 34909 | 24571 | - |

There appears to be no gene-dose effect.

## 5.7 Pharmacokinetics in children

Juvenile rheumatoid arthritis (JRA) may attract the use of lumiracoxib.

However, the applicant has not studied the use of the drug or its pharmacokinetics in children.

***Assessor's Comments on Pharmacokinetics is Special Populations:***

There are no significant influences on pharmacokinetics of lumiracoxib arising from age, gender, ethnicity, CYP2C9 polymorphism due to the common *2 allele or moderate hepatic impairment.

It is possible that individuals who are homozygous for *3 allele would have very high plasma levels but this genotype is extremely rare in Western Caucasian population.

Exposure to lumiracoxib is lower in patients with end stage renal disease compared to normal subjects. Compared to normal subjects, mean exposure to 4'-hydroxy-lumiracoxib is not significantly increased in ESRD patients and exposure to 4'-hydroxy-5-carboxy-lumiracoxib is increased substantially (by about 7 times). Dialysis has no effect on plasma exposure to lumiracoxib or these metabolites.

Pharmacokinetics in juvenile patients with rheumatoid arthritis would have been helpful but this has not been investigated. The drug is not recommended for use in children. It should be contraindicated rather than "not indicated".

## 6. INTERACTIONS WITH DRUGS

Following studies are summarised below:

| Interaction under study | Studies |
|---|---|
| Lumiracoxib-methotrexate | 0108 |
| Lumiracoxib-warfarin | 0134 |
| Lumiracoxib-oral contraceptives | 2326 |
| Lumiracoxib-omeprazole and antacids | 0135 |
| Lumiracoxib-fluconazole | 2313 |

### ∗ Summary of Drug Interaction studies

The Applicant has summarized the data as follows:

1. Lumiracoxib has no effect on the pharmacokinetics of methotrexate, or S-warfarin, but in subjects stabilized on warfarin, lumiracoxib appears to slightly increase the prothrombin time.
2. Lumiracoxib has no effect on the pharmacokinetics or pharmacodynamics (efficacy) of a typical oral contraceptive regimen consisting of ethinyl estradiol and levonorgestrel.
3. Omeprazole, Al/Mg hydroxide antacid (Maalox) or fluconazole, (an inhibitor of CYP2C9) have no significant effect on the pharmacokinetics of lumiracoxib.
4. Based on studies *in vitr*o, interactions involving plasma protein binding are not expected to have any clinically relevant effects on lumiracoxib or co-administered drugs

### ∗ In vitro study characterising the inhibitory potential of lumiracoxib

The inhibitory potential of lumiracoxib (0-200 μM) towards six human liver microsomal cytochrome P-450 (CYP) activities was evaluated (Report DMPK(US) R99-535 in module 4, subsection 4.2.2.4)

The results were as follows:

| CYP | Probe reaction | Lumiracoxib $IC_{50}$ value | $IC_{50}$ value | Positive inhibitor |
|---|---|---|---|---|
| 1A2 | Phenacetin O-deethylase | >200 μM | 0.7 μM | Fluvoxamine |
| 2C9 | Diclofenac 4'-hydroxylase | ~10 μM | 0.6 μM | Sulfaphenazole |
| 2C19 | Mephenytoin 4'-hydroxylase | >50 μM | 22 μM | Sulfone of omeprazole |
| 2D6 | Bufuralol 1'-hydroxylase | >200 μM | 0.8 μM | Quinidine |
| 2E1 | Chlorzoxazone 6-hydroxylase | >200 μM | <0.1 μM | 4-Methylpyrazole |
| 3A4/5 | Midazolam 1'-hydroxylation | >50 μM | <0.1 μM | Ketoconazole |
| 2C8 | Paclitaxel 6α-hydroxylation | >200 μM | 1.3-1.8 μM | Quercetin [Ki] |

**The data suggest that lumiracoxib does not inhibit any of the drug metabolising CYP isoforms at clinically relevant concentrations and there is a wide margin of safety.**

### In vitro protein-binding interactions

This was investigated to evaluate the displacement of some key narrow therapeutic or clinically relevant drugs from protein by lumiracoxib:

| | Protein binding in presence of lumiracoxib concentration (μg/ml) | | |
|---|---|---|---|
| | 0 | 2 | 20 |
| Protein binding of | Mean % | Mean % | Mean % |
| Nataglinide | | | |

| | | | |
|---|---|---|---|
| 1 μg/ml | 98.9 | 99.1 | 99.0 |
| 10 μg/ml | 99.0 | 99.0 | 98.9 |
| Phenytoin | | | |
| 5 μg/ml | 91.4 | **89.1** | 89.6 |
| 30 μg/ml | 92.7 | 88.7 | 89.3 |
| Salicylic acid | | | |
| 30 μg/ml | 99.3 | **94.0** | 92.3 |
| 300 μg/ml | 77.6 | 80.2 | 75.4 |
| Tolbutamide | | | |
| 20 μg/ml | 95.4 | 97.6 | 95.6 |
| 200 μg/ml | 97.1 | 95.8 | 96.5 |
| Warfarin | | | |
| 0.3 μg/ml | 98.9 | 99.0 | 98.3 |
| 3 μg/ml | 99.0 | 99.0 | 98.1 |

It appears that at therapeutic concentrations of lumiracoxib, protein-binding interactions are unlikely in most individuals.

However, it is noted that in study 0112 described in section 4.4, there were

| two subjects (400mg QD) had very high | Cmax | and | AUC(0-6): |
|---|---|---|---|
| Subject 18 from centre 109 | 17929 | | 52816 |
| Subject 6 from centre 1104 | 24668 | | 53252 |

These Cmax are close to 2 μg/ml

A decrease in protein binding of phenytoin from 91.4 % to 89.1 % could increase the free fraction from 8.6 % to 10.9 % - an increase of 27 %.

A decrease in protein binding of salicylic acid from 99.3 % to 94.0 % could increase the free fraction from 0.7 % to 6.0 % - an increase of 857 %.

Therefore, high Cmax in such individuals could predispose them to a potential interaction resulting from displacement of phenytoin and salicylic acid – the former resulting in phenytoin toxicity and the later resulting in loss of COX-2 selectivity.

**∗ In vivo studies**

The sponsor evaluated the potential for drug interactions with:

- fluconazole, a drug that modulates CYP2C9 pathway
- drugs that might be anticipated to be used concurrently in the target populations (methotrexate, warfarin, oral contraceptives, omeprazole and antacids)

**6.1 Study with drugs modulating CYP2C9 pathway (015)**

Fluconazole is a powerful inhibitor of CYP2C9

2-period, open-label randomised, crossover study in 13 subjects.

Sequence 1: 3-day fluconazole with 400mg on day 1 and 200mg on days 2-3. On day 4, subjects received lumiracoxib 400mg with fluconazole 200mg

Sequence 2: 3-day without any drug. On day 4, subjects received lumiracoxib 400mg without any drug.

After a washout period of 16 days in the former and 13 days in the later group, the subjects received the alternate treatment.

Results:

| | Lumiracoxib | Lumiracoxib + fluconazole | Ratio of geometric mean |
|---|---|---|---|
| | AUC(0-4) (ng.h/ml) | | |
| Mean ± SD | 39408 ± 12100 | 46405 ± 12120 | |
| Geometric mean | 37693 | 44904 | 1.19 * |
| | AUC(0-$\alpha$) (ng.h/ml) | | |
| Mean ± SD | 39663 ± 12150 | 46941 ± 12815 | |
| Geometric mean | 37952 | 45341 | 1.19 * |
| | Cmax (ng/ml) | | |
| Mean ± SD | 9185 ± 2493 | 10282 ± 2282 | |
| Geometric mean | 8944 | 9959 | 1.11 |

* $p < 0.001$

There was a mean difference of +6337 pg/ml in change of serum level of TxB2 from baseline (90% CI for the difference between the two treatments ranged from –26820 to +39494 pg/ml). This difference was not statistically significant.

Given the concentration to which lumiracoxib maintains its COX-2 selectivity, this interaction is considered to be clinically insignificant.

## 6.2 Methotrexate Interaction Study 0108

A multicentre, double blind, randomised, placebo-controlled, two-way crossover design in 18 patients.

Each patient had a 21-day screening period, three baseline periods, a 24 h pharmacokinetic profile of methotrexate alone on Day 1, followed by a 14-day treatment period with randomised treatment sequences of methotrexate/lumiracoxib and methotrexate/placebo, each for seven consecutive days, and a study completion evaluation after end of study.

Each patient had 24-h pharmacokinetic profiles on Study Days 1, 8, and 15 with administration of methotrexate alone, and after multiple doses of 400mg lumiracoxib QD and the matching placebo, respectively.

Concentrations of methotrexate and 7-OH-Methotrexate and 7-OH-methotrexate: On days 1, 8 and 15, blood was withdrawn at predose and at 9 times post dose up to 24 h. Urine was collected quantitatively from 0-24 h on days 1, 8 and 15.

Blood samples were collected for lumiracoxib at trough times on days 4, 7, 11 and 14 and at predose and 6 times post dose on days 8 and 15.

Key plasma pharmacokinetic parameters for methotrexate (arithmetic mean ± SD) following administration alone, with placebo and with lumiracoxib (normalized to a 1mg dose of methotrexate)

| | Methotrexate | Methotrexate lumiracoxib | Methotrexate + placebo |
|---|---|---|---|
| Methotrexate PK | | | |
| AUC0-t (ng h/ml) | 108.00 ± 46.79 | 110.23 ± 46.26 | 101.82 ± 30.52 |
| Cmax (ng/ml) | 26.72 ± 9.47 | 27.50 ± 10.09 | 22.62 ± 8.89 |
| tmax (h) | 1.5 (0.5-4.0) | 1.0 (0.5-6.0) | 1.0 (0.5-6.0) |

Key plasma pharmacokinetic parameters (arithmetic mean ± SD) for 7-OH-methotrexate following administration alone, with placebo and with lumiracoxib (normalized to a 1mg dose of methotrexate).

| | Methotrexate | Methotrexate + lumiracoxib | Methotrexate + placebo |
|---|---|---|---|
| 7-OH-Methotrexate PK | | | |
| AUC0-t (ng h/ml) | 49.37 ± 20.63 | 36.25 ± 20.61 | 50.41 30.66 |
| Cmax (ng/ml) | 4.43 ± 3.36 | 3.64 ± 2.94 | 4.77 ± 4.23 |
| tmax (h) | 6.0 (4.0-8.0) | 6.0 (1.0-12.0) | 6.0 (0.5-12.0) |

Amount excreted (Ae) of methotrexate and 7-OH-methotrexate in urine (arithmetic mean ± SD) following administration of methotrexate alone, with placebo and with lumiracoxib (normalized to a 1mg dose of methotrexate).

| Amount excreted in urine | Methotrexate | Methotrexate + lumiracoxib | Methotrexate + placebo |
|---|---|---|---|
| Methotrexate (µg) | 652 ± 224 | 623 ± 264 | 644 ± 197 |
| 7-OH-methotrexate (µg) | 24 ± 12 | 28 ± 12 | 28 ± 14 |

Administration of lumiracoxib at doses of 400mg QD had no clinically significant effect on the plasma pharmacokinetics, plasma protein binding or urinary excretion of methotrexate.

Mean plasma exposure of the 7-OH-methotrexate metabolite was lower in the lumiracoxib dose group compared to placebo.

Compared to placebo, lumiracoxib had no effect on urinary recovery of 7-OH-methotrexate.

## 6.3 Warfarin Interaction Study 0134

A single-centre, randomised, placebo-controlled, open-label, parallel group study in healthy volunteers.

Subjects received a loading dose and were then dose titrated to a maintenance dose of racemic warfarin to produce a stable prothrombin time. Subjects were then randomised to receive either lumiracoxib 400mg QD or matched placebo for five days together with their maintenance dose of racemic warfarin.

PK samples were drawn on the last dose titration day (day 8) of warfarin and the last day of co-administration (day 13) for determination of R-warfarin and S-warfarin pharmacokinetics.

Male and female subjects aged 18-65. All subjects to be in good health as determined by past medical history, physical examination, electrocardiogram, laboratory tests and urinalysis. Only subjects genotyping as extensive metabolisers *(CYP2C9*1/*1* or *CYP2C9*1/*2)* were included.

Minimum of 13 days treatment (comprised of warfarin titration phase followed by 5 days of co-administration of warfarin and lumiracoxib/placebo) and 5 days post treatment wash-out (safety monitoring) per subject

**Information on maintenance dose of warfarin.**

| Dose (mg) | 3 | 3.5 | 4 | 4.5 | 5 | 5.5 | 6 |
|---|---|---|---|---|---|---|---|

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Placebo group (n) | 3 | 1 | 2 | 0 | 6 | 0 | 0 |
| Lumiracoxib group (n) | 1 | 1 | 1 | 2 | 3 | 2 | 2 |

Results:
Pharmacokinetic parameters (normalized to a 1mg dose) of R-warfarin and S-warfarin on day 13 following 5 day's treatment with either lumiracoxib or placebo (arithmetic mean and SD)

| | Placebo | Lumiracoxib |
|---|---|---|
| R-warfarin | | |
| AUCτ (ng.h/ml) | 2907.1 ± 484.2 | 2977.8 ± 540.4 |
| Cmax (ng/ml) | 162.9 ± 24.1 | 173.3 ± 47.3 |
| S-warfarin | | |
| AUCτ (ng.h/ml) | 1887.6 ± 446 | 2003.9 ± 431 |
| Cmax (ng/ml) | 119.6 ± 22.5 | 128.7 ± 38.5 |

Ratios of pharmacokinetic parameters of R-warfarin and S-warfarin on day 13 (following 5 day's treatment with either lumiracoxib or placebo) to day 8 (arithmetic mean ± SD).

| | Placebo | Lumiracoxib |
|---|---|---|
| R-warfarin | | |
| AUCτ (ng.h/ml) | 0.99 ± 0.10 | 0.99 ± 0.08 |
| Cmax (ng/ml) | 0.99 ± 0.15 | 1.10 ± 0.20 |
| S-warfarin | | |
| AUCτ (ng.h/ml) | 0.98 ± 0.11 | 0.99 ± 0.07 |
| Cmax (ng/ml) | 0.99 ± 0.13 | 1.07 ± 0.18 |

Summary of results for AUCτ and Cmax (S- and R- warfarin)

| Analysis parameter | Adjusted ratio (Lumiracoxib vs Placebo) | 95% CI |
|---|---|---|
| S-warfarin | | |
| AUCτ | 1.022 | 0.944, 1.105 |
| Cmax | 1.076 | 0.947, 1.222 |
| R-warfarin | | |
| AUCτ | 1.008 | 0.934, 1.087 |
| Cmax | 1.092 | 0.951, 1.254 |

Prothrombin times (arithmetic mean ± SD) on study day 8 (mean of morning and previous evening's determinations) and day 13 (mean of morning and evening determinations) with either placebo or lumiracoxib treatment.

| | Day 8 (Baseline) | Day 13 |
|---|---|---|
| Lumiracoxib | 17.5 ± 1.9 | 19.9 ± 2.5 |
| Placebo | 17.8 ± 3.4 | 17.6 ± 3.0 |

There was some evidence of a **significant lowering of S-7-hydroxy warfarin** in urine (Ae0-t) with co-administration of lumiracoxib compared to placebo.

| | Ae (mg) Placebo group | | Ae (mg) Lumiracoxib group | |
|---|---|---|---|---|
| | Day 8 | Day 13 | Day 8 | Day 13 |
| Median | 1.07 | 1.07 | 1.07 | 0.75 |
| Min-Max | 0-1.67 | 0.59-1.59 | 0-2.08 | 0-1.55 |

For both analyses of prothrombin time and INR, there was **evidence of a significant** difference with co-administration of lumiracoxib compared to co-administration of placebo. Prothrombin time is about 2.7 seconds longer with co-administration of lumiracoxib compared to placebo.

## 6.4 Oral Contraceptive Interaction Study 2326

A double blind, randomised, 3-periods crossover study in 35 healthy females. The study started with 82 subjects but the rest discontinued for non-safety related reasons.

Study included a 42-day screening period, 2 months stabilisation period, 12-h baseline period followed by three treatment periods.

Pharmacokinetics of the contraceptive pill was evaluated during day 21 of the two treatment periods (2 and 3).

The contraceptive pill used was Triphasil 28 (ethinyl estradiol + levonorgestrel).

Treatment A: Single dose of lumiracoxib 400mg on day 1
Treatment B: Once daily omeprazole for 4 days followed by a coadministration of lumiracoxib 400mg and omeprazole 20mg on day 5
Treatment C: Single dose of lumiracoxib 400mg on day 1 immediately followed by 20 ml dose of Aluminium hydroxide/magnesium hydroxide liquid ("Maalox")

Results:
Parameters for Ethinyl estradiol

| | | CP + Lumiracoxib | CP + Placebo | Mean ratio (90% CI) |
|---|---|---|---|---|
| Tmax | h | 1.5 | 1.5 | |
| Cmax | mg/ml | 109.8 | 107.3 | 1.05 (1.00, 1.10) |
| Cmin | ng/ml | 20.15 | 18.51 | 1.13 (1.01, 1.26) |
| Cave | ng/ml | 39.71 | 37.37 | |
| AUC(0-12) | ng.h/ml | 639.6 | 602.7 | 1.07 (1.04, 1.12) |
| AUC(0-24) | ng.h/ml | 949.8 | 893.3 | 1.08 (1.04, 1.12) |
| CLss/F | L/h | 35.12 | 38.26 | |

Parameters for Levonorgestrel

| | | CP + Lumiracoxib | CP + Placebo | Mean ratio |
|---|---|---|---|---|
| Tmax | h | 1.5 | 1.5 | |
| Cmax | mg/ml | 4.48 | 4.74 | 0.94 (0.88, 1.02) |
| Cmin | ng/ml | 1.73 | 1.74 | 0.98 (0.91, 1.06) |
| Cave | ng/ml | 2.36 | 2.41 | |
| AUC(0-12) | ng.h/ml | 32.7 | 33.2 | 0.98 (0.94, 1.03) |
| AUC(0-24) | ng.h/ml | 56.6 | 57.7 | 0.99 (0.93, 1.05) |
| CLss/F | L/h | 2.42 | 132.8 | |

## 6.5 Omeprazole and Antacids Interaction Study 0135

An open label, randomised, 3-periods crossover study in 12 healthy volunteers

Treatment A: Single dose of lumiracoxib 400mg on day 1
Treatment B: Once daily omeprazole for 4 days followed by a coadministration of lumiracoxib 400mg and omeprazole 20mg on day 5
Treatment C: Single dose of lumiracoxib 400mg on day 1 immediately followed by 20 ml dose of Aluminium hydroxide/magnesium hydroxide liquid ("Maalox")

Results:

| | Cmax ng/ml | AUC(0-α) ng.h/ml | Tmax (h) |
|---|---|---|---|
| Lumiracoxib | 9235 ± 1956 | 36748 ± 7732 | 2.4 |
| Lumiracoxib + Omeprazole | 8808 ± 2294 | 34877 ± 8404 | 3.0 |
| Lumiracoxib + Maalox | 10451 ± 3243 | 35496 ± 5718 | 1.8 |

Ratio (and 90% CI)

| | Cmax ng/ml | AUC(0-α) ng.h/ml |
|---|---|---|
| Lumiracoxib vs Lumiracoxib + Omeprazole | 0.95 (0.81, 1.12) | 0.95 (0.89, 1.01) |
| Lumiracoxib vs Lumiracoxib + Maalox | 1.11 (0.81, .1.32) | 1.00 (0.94, 1.06) |

Thus, neither omeprazole nor Maalox influence exposure to lumiracoxib.

***Assessor's Comments on Drug Interaction Potential of Lumiracoxib:***
There is no evidence of an interaction with contraceptive pill, omeprazole or antacids.

Drugs that are likely to be used by the target population include prednisolone and aspirin. No interaction studies have been carried out against these drugs. Neither is there an interaction study with digoxin or lithium.

The Applicant has already included a statement on the potential for an interaction with lithium.

Lumiracoxib appears to increase the prothrombin time in patients stabilised on warfarin. Compared to placebo treatment, recovery of the S-7-OH warfarin metabolite in urine was about 25% lower in subjects treated with lumiracoxib.

Celecoxib (a substrate of CYP2C9 had also produced only minimal changes in the pharmacokinetics or the pharmacodynamics of warfarin and yet, there were post-marketing reports describing patients on warfarin who had increased anticoagulation and (in some cases) bleeding complications after treatment with celecoxib was started. Effect of lumiracoxib is slightly greater but it seems to have been dealt with adequately in the SPC.

A risk of interactions arising from protein binding in rare individuals cannot be excluded. This is most likely with phenytoin or salicylic acid.

A decrease in protein binding of phenytoin from 91.4 % to 89.1 % could increase the free fraction from 8.6 % to 10.9 % - an increase of 27 %. A decrease in protein binding of salicylic acid from 99.3 % to 94.0 % could increase the free fraction from 0.7 % to 6.0 % - an increase of 857 %.

Therefore, high Cmax in such individuals could predispose them to a potential interaction resulting from displacement of phenytoin and salicylic acid – the former resulting in phenytoin toxicity and the later resulting in loss of COX-2 selectivity.

# 7. DOSE-RESPONSE RELATIONSHIP

## 7.1 Dose Selection in Osteoarthritis (OA)

Three studies have been submitted (0104, 2316 and 2301) covering a dose range from 50mg BD to 400mg QD

Study 0104

Double blind, randomised, parallel groups, international multicentre, double-dummy and placebo-controlled study

Placebo
50mg BD, 100mg BD, 200mg BD and 400mg QD lumiracoxib
75mg BD diclofenac as extended-release tablet

583 patients with OA of the knee or the hip (ACR criteria) for at least 3 months
Patients were included if they had a pain intensity of at least 40 mm on VAS in the affected joint in the previous 24 hours or had their disease controlled with NSAIDs or simple analgesics.

Dosing for 28 days in OA patients

Primary efficacy endpoint was the overall joint pain intensity over the previous 24 hours in the most affected joint after 4 weeks on a 100 mm VAS.

Secondary efficacy endpoints were overall joint pain intensity at each visit, patient's and physician's global assessment of disease, HAQ and WOMAC LK3.1 questionnaires)

Baseline demography

| | Mean age years | M / F (%) | Duration of disease (years) | Race W / B (%) |
|---|---|---|---|---|
| Placebo | 61.4 | 33.7 / 66.3 | 8.0 | 96.9 / 1.0 |
| Lumiracoxib 50mg BD | 61.5 | 32.3 / 67.7 | 7.4 | 94.9 / 3.1 |
| Lumiracoxib 100mg BD | 59.9 | 30.5 / 69.5 | 6.6 | 93.8 / 1.0 |
| Lumiracoxib 200mg BD | 59.4 | 25.0 / 75.0 | 6.9 | 91.9 / 5.1 |
| Lumiracoxib 400mg QD | 60.0 | 41.8 / 58.2 | 6.3 | 91.9 / 4.0 |
| Diclofenac 75mg BD | 59.7 | 31.9 / 68.1 | 6.3 | 93.6 / 3.2 |

Mean (± SD) results in primary endpoint at baseline and week 4 were:

| | N = | Baseline | Week 4 | P value vs placebo |
|---|---|---|---|---|
| Placebo | 96 | 67.9 ± 12.74 | 50.2 ± 24.57 | |
| Lumiracoxib 50mg BD | 96 | 66.9 ± 13.97 | 38.3 ± 24.32 | 0.001 |
| Lumiracoxib 100mg BD | 95 | 64.7 ± 14.31 | 38.4 ± 24.38 | 0.001 |
| Lumiracoxib 200mg BD | 96 | 67.0 ± 13.00 | 37.4 ± 25.39 | < 0.001 |
| Lumiracoxib | 98 | 66.9 ± 12.98 | 33.7 ± 23.74 | < 0.001 |

| | | | | |
|---|---|---|---|---|
| 400mg QD | | | | |
| Diclofenac 75mg BD | 93 | 66.1 ± 13.73 | 34.3 ± 23.24 | < 0.001 |

| | Estimated difference | Upper 95% Confidence limit | p |
|---|---|---|---|
| Lumiracoxib 400QD - Placebo | - 15.9 | - 7.5 | < 0.0001 |
| Lumiracoxib 200BD – Placebo | - 12.1 | - 3.9 | = 0.0009 |
| Lumiracoxib 50BD – Placebo | - 11.0 | - 3.4 | = 0.0014 |
| Lumiracoxib 100BD - Placebo | - 8.8 | - 2.1 | = 0.0052 |

Mean overall joint pain intensity at baseline and change during treatment

| | Baseline | Week 1 | Week2 | Week 4 |
|---|---|---|---|---|
| Placebo | 67.9 | - 9.7 | - 13.7 | - 17.7 |
| Lumiracoxib 50mg BD | 66.9 | - 19.5 * | - 22.6 * | - 28.6 * |
| Lumiracoxib 100mg BD | 64.7 | - 19.2 * | - 21.2 * | - 26.3 * |
| Lumiracoxib 200mg BD | 67.0 | - 22.0 * | - 24.1 * | - 29.6 * |
| Lumiracoxib 400mg QD | 66.9 | - 26.0 *ab | - 27.5 * | - 33.2 * |
| Diclofenac 75mg BD | 66.1 | - 27.9 *abc | - 30.4 *abc | - 31.8 * |

* p < 0.05 vs placebo a = p < 0.05 vs 50mg BD b = p < 0.05 vs 100mg BD
c = p < 0.05 vs 200mg BD

Mean (± SD) results on Patient's Global Assessment of Disease Activity:

| | N = | Baseline | Week 4 | P value vs placebo |
|---|---|---|---|---|
| Placebo | 96 | 62.5 ± 18.05 | 50.0 ± 22.95 | |
| Lumiracoxib 50mg BD | 96 | 63.1 ± 17.49 | 38.8 ± 21.48 | < 0.001 |
| Lumiracoxib 100mg BD | 95 | 62.0 ± 18.48 | 37.8 ± 22.18 | < 0.001 |
| Lumiracoxib 200mg BD | 96 | 64.0 ± 17.31 | 37.5 ± 24.00 | < 0.001 |
| Lumiracoxib 400mg QD | 98 | 63.7 ± 16.49 | 35.6 ± 24.08 | < 0.001 |
| Diclofenac 75mg BD | 93 | 62.2 ± 16.15 | 34.4 ± 22.96 | < 0.001 |

Mean (± SD) results on Physician's Global Assessment of Disease Activity:

| | N = | Baseline | Week 4 | P value vs placebo |
|---|---|---|---|---|
| Placebo | 96 | 60.4 ± 15.71 | 47.3 ± 22.12 | |
| Lumiracoxib 50mg BD | 96 | 59.1 ± 15.67 | 37.3 ± 20.24 | < 0.001 |
| Lumiracoxib 100mg BD | 95 | 56.6 ± 17.14 | 33.4 ± 20.39 | < 0.001 |
| Lumiracoxib 200mg BD | 96 | 61.3 ± 14.68 | 34.3 ± 20.01 | < 0.001 |
| Lumiracoxib 400mg QD | 98 | 59.6 ± 15.09 | 33.1 ± 21.30 | < 0.001 |

| | | | | |
|---|---|---|---|---|
| Diclofenac 75mg BD | 93 | 57.2 ± 15.62 | 33.4 ± 18.47 | < 0.001 |

Percentage of patients taking rescue medications

| | N = | % who took rescue medication | % who took > 2 tablets per day | P value vs placebo |
|---|---|---|---|---|
| Placebo | 96 | 67.7 | 24.0 | |
| Lumiracoxib 50mg BD | 96 | 56.3 | 6.3 | = 0.042 |
| Lumiracoxib 100mg BD | 95 | 56.8 | 8.4 | = 0.084 |
| Lumiracoxib 200mg BD | 96 | 60.4 | 10.4 | = 0.156 |
| Lumiracoxib 400mg QD | 98 | 50.0 | 9.2 | = 0.002 |
| Diclofenac 75mg BD | 93 | 47.9 | 4.3 | = 0.002 |

Percentage of patients discontinuing

| | N = | Due to adverse event | Due to serious adverse event | Due to laboratory abnormality |
|---|---|---|---|---|
| Placebo | 97 | 3.1 | 1.0 | 0 |
| Lumiracoxib 50mg BD | 98 | 3.1 | 0 | 0 |
| Lumiracoxib 100mg BD | 96 | 3.1 | 0 | 0 |
| Lumiracoxib 200mg BD | 99 | 4.0 | 0 | 2.0 |
| Lumiracoxib 400mg QD | 99 | 5.1 | 0 | 1.0 |
| Diclofenac 75mg BD | 94 | 13.8 | 0 | 0 |

Conclusion:
This study has essentially failed to distinguish between any of the 4 doses of lumiracoxib.

This study shows that the lowest dose used, 50mg BD, is effective but it is difficult to see how this can be quantified as the lowest effective dose since there is no information on doses lower than 50mg BD.

Among the four doses, 50mg BD is consistently superior to 100mg BD dose. In fact, for some secondary endpoints (HAQ score at 4 weeks, WOMAC physical function score), 100mg BD was statistically no different from placebo.

The only advantage for lumiracoxib 400mg QD is earlier onset of effect compared to lumiracoxib 50mg BD or 100mg BD (week 1 versus week 2).

PK/PD analysis showed a very flat correlation between mean VAS change from baseline and either plasma concentration (in the range 1000 to 5000 ng/ml) or AUC at day 0 and day 28. Likewise, the relationship over 6-hours post dose was also flat.

This flat relationship may result from the distribution of the drug into an effect compartment with slower kinetics than that in plasma.

Study 2316

Double blind, randomised, parallel groups, international multicentre, double-dummy and placebo-controlled study

Placebo
100m QD

244 patients with OA of the knee or the hip (ACR criteria) for at least 3 months
Patients were included if they had a pain intensity of at least 40 mm on VAS in the affected joint in the previous 24 hours.

Dosing for 28 days in OA patients

Primary efficacy endpoint was the overall joint pain intensity over the previous 24 hours in the most affected joint after 4 weeks on a 100 mm VAS.

Secondary efficacy endpoints were overall joint pain intensity at each visit, patient's and physician's global assessment of disease and patient's functional status after 4 weeks using DPDA subscales of WOMAC VA3.1 questionnaire.

Baseline demography

| | Mean age years | M / F (%) | Duration of disease (years) | Race W / B (%) |
|---|---|---|---|---|
| Placebo | 62.4 | 12.3 / 87.7 | 5.6 | 100 / 0 |
| Lumiracoxib 100mg QD | 62.8 | 19.7 / 80.3 | 6.1 | 100 / 0 |

Mean results (all ITT- LOCF) in primary endpoint at baseline and week 4 were:

| | N = | Baseline | Week 4 | Mean diff (95% CI) p value |
|---|---|---|---|---|
| Placebo | 122 | 65.51 | 47.69 | - 8.41 (-13.97, -2.84) p = 0.003 |
| Lumiracoxib 100mg QD | 122 | 64.79 | 39.29 | |

Mean overall joint pain intensity at baseline and change during treatment

| | Baseline | Week 1 | Week2 | Week 4 |
|---|---|---|---|---|
| Placebo | 65.5 | - 9.3 | - 14.6 | - 16.8 |
| Lumiracoxib 100mg QD | 64.8 | - 13.4 * | - 19.1 * | - 24.6 ** |

* $p < 0.05$ vs placebo * $p < 0.01$ vs placebo

Mean results on Patient's Global Assessment of Disease Activity:

| | N = | Baseline | Week 4 | Mean diff (95% CI) p value |
|---|---|---|---|---|
| Placebo | 122 | 63.12 | 48.87 | - 8.81 |
| Lumiracoxib 100mg QD | 122 | 63.85 | 40.05 | (- 14.11, - 3.52) p = 0.001 |

Mean results on Physicians Global Assessment of Disease Activity:

| | N = | Baseline | Week 4 | Mean diff (95% CI) p value |
|---|---|---|---|---|
| Placebo | 122 | 59.01 | 45.97 | - 7.96 |
| Lumiracoxib 100mg QD | 122 | 60.27 | 37.99 | (- 13.03, - 2.93) p = 0.002 |

Mean results on WOMAC Pain

| | N = | Baseline | Week 4 | Mean diff (95% CI) p value |
|---|---|---|---|---|
| Placebo | 122 | 10.38 | 8.58 | - 1.09 |
| Lumiracoxib 100mg QD | 122 | 9.87 | 7.49 | (- 1.98, - 0.19) p = 0.017 |

Mean results on WOMAC Stiffness

| | N = | Baseline | Week 4 | Mean diff (95% CI) p value |
|---|---|---|---|---|
| Placebo | 122 | 4.48 | 3.50 | - 0.34 |
| Lumiracoxib 100mg QD | 122 | 4.16 | 3.17 | (- 0.75, +0.07) p = 0.105 |

Mean results on WOMAC DPDA Functional Subscale

| | N = | Baseline | Week 4 | Mean diff (95% CI) p value |
|---|---|---|---|---|
| Placebo | 122 | 36.68 | 30.74 | - 3.17 |
| Lumiracoxib 100mg QD | 122 | 35.47 | 27.57 | (-5.97, - 0.36) p = 0.027 |

Mean results on rescue medications

| | | N | Rate (%) | Odds ratio | p |
|---|---|---|---|---|---|
| Visit 2-3 | Placebo | 117 | 60.7 | | |
| | Lumiracoxib | 118 | 54.2 | 0.77 | 0.357 |
| Visit 3-4 | Placebo | 118 | 63.6 | | |
| | Lumiracoxib | 121 | 57.9 | 0.80 | 0.437 |
| Visit 4-5 | Placebo | 111 | 75.7 | | |
| | Lumiracoxib | 118 | 65.3 | 0.61 | 0.116 |

Patients with AE and withdrawal rate

| | N = | % With AE | % With SAE | % Withdrawing |
|---|---|---|---|---|
| Placebo | 122 | 18.0 | 0.8 | 1.6 |
| Lumiracoxib 100mg QD | 122 | 19.7 | 0 | 1.6 |

100mg daily dose is an effective dose. It is not possible to compare it with 50mg BD dose.

Study 2301

This was a 1-week multicentre study comparing the short-term analgesic effect of placebo (n = 75), 400mg lumiracoxib (n = 144) and 200mg BD celecoxib (n = 145).

The primary endpoint was Pain Intensity Difference from baseline. Pain intensity was measured on a 100-mm VAS

Results:

| | Placebo | 400mg lumiracoxib | 200mg BD celecoxib |
|---|---|---|---|
| Mean actual PID for 3-5 hours post-dose | 13.4 | 19.8 | 16.8 |
| Responders at 3h | 9.3 % | 12.5 % | 5.5 % |
| AEs in | 13 % | 15 % | 11 % |
| Drug-related AEs | 8 % | 6 % | 6 % |

Lumiracoxib was statistically significantly superior to placebo.
Celecoxib was NOT statistically significantly superior to placebo.
Lumiracoxib was not inferior to celecoxib.

## 7.2 Dose Selection in Rheumatoid Arthritis (RA)

Two studies have been submitted (0105 and 2312) covering a dose range from 50mg BD to 1200mg QD

Both these studies are also supportive efficacy studies

Study 0105

Double blind, randomised, parallel groups, international multicentre, double-dummy and placebo-controlled study

Placebo
50mg BD, 100mg BD, 200mg BD and 400mg QD lumiracoxib
75mg BD diclofenac as extended-release tablet

571 patients with RA of the for at least 3 months
Patients were included if they had a pain intensity of at least 40 mm on VAS or had their disease controlled with NSAIDs or simple analgesics

Dosing for 28 days in RA patients

Primary efficacy endpoint was the RA pain intensity over the previous 24 hours after 4 weeks on a 100 mm VAS.

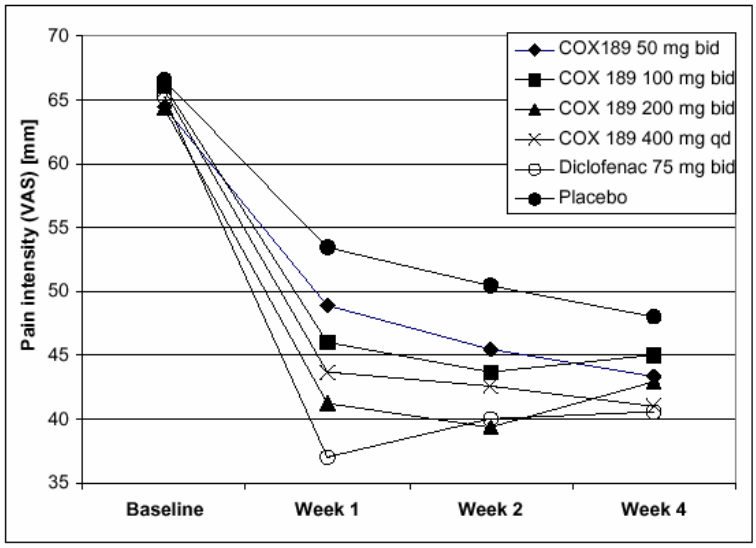
Secondary efficacy endpoints were pain intensity at each visit, patient's and physician's global assessment of disease, number of tender and swollen joints, CRP level and % responders according to ACR20, HAQ and RAQoL questionnaire.

Baseline demography

| | Mean age years | M / F (%) | Duration of disease (years) |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Placebo | 54.6 | 31.1 / 68.7 | 9.2 |
| Lumiracoxib 50mg BD | 55.1 | 14.7 / 85.5 | 11.5 |
| Lumiracoxib 100mg BD | 53.4 | 28.9 / 71.1 | 9.2 |
| Lumiracoxib 200mg BD | 55.5 | 20.4 / 79.6 | 9.7 |
| Lumiracoxib 400mg QD | 54.2 | 23.0 / 77.0 | 10.5 |
| Diclofenac 75mg BD | 53.5 | 23.1 / 76.9 | 8.7 |

Mean overall RA Pain intensity by visit (all ITT patients LOCF)




Mean (± SD) results in primary endpoint at baseline and weeks 1- 4 were:

| | N = | Baseline | Week 1 | Week 2 | Week 4 |
|---|---|---|---|---|---|
| Placebo | 99 | 66.6 | 53.5 | 50.4 | 48 |
| Lumiracoxib 50mg BD | 102 | 64.4 | 48.9 | 45.4 | 43.3 |
| Lumiracoxib 100mg BD | 97 | 66.1 | 46 | 43.7 * | 45 |
| Lumiracoxib 200mg BD | 93 | 64.3 | 41.2 * | 39.3 * | 42.9 |
| Lumiracoxib 400mg QD | 87 | 65.8 | 43.7 * | 42.6 * | 41 |
| Diclofenac 75mg BD | 91 | 65.2 | 37 * | 40 * | 40.6 * |

* $p < 0.05$

| | Estimated difference | Upper 95% Confidence limit | p |
|---|---|---|---|
| Lumiracoxib 400QD - Placebo | - 6.5 | 2.4 | 0.1109 |
| Lumiracoxib 200BD – Placebo | - 3.5 | 5.3 | 0.3871 |
| Lumiracoxib 50BD – Placebo | - 2.7 | 5.9 | 0.4813 |
| Lumiracoxib 100BD - Placebo | - 3.0 | 5.7 | 0.4520 |

Mean Patient Global Assessment of disease activity at baseline and at week 4

| | Baseline | Week 4 | P value vs placebo |
|---|---|---|---|
| Placebo | 57.6 | 46.5 | |
| Lumiracoxib 50mg BD | 57.7 | 43.4 | 0.321 |
| Lumiracoxib 100mg BD | 60.6 | 43.6 | 0.199 |
| Lumiracoxib 200mg BD | 57.1 | 40.8 | 0.088 |
| Lumiracoxib 400mg QD | 61.2 | 42.2 | 0.090 |
| Diclofenac 75mg BD | 56.9 | 40.9 | 0.077 |

Mean Physician Global Assessment of disease activity at baseline and week 4

| | Baseline | Week 4 | P value vs placebo |
|---|---|---|---|
| Placebo | 54.3 | 42.4 | |
| Lumiracoxib 50mg BD | 54.8 | 41.6 | 0.695 |
| Lumiracoxib 100mg BD | 55.7 | 41.3 | 0.482 |
| Lumiracoxib 200mg BD | 53.6 | 39.4 | 0.363 |
| Lumiracoxib 400mg QD | 55.4 | 39.1 | 0.217 |
| Diclofenac 75mg BD | 55.4 | 37.1 | **0.024** |

Mean results on total swollen joints at baseline and week 4

| | Baseline | Week 4 | P value vs placebo |
|---|---|---|---|
| Placebo | 10.1 | 7.5 | |
| Lumiracoxib 50mg BD | 10.3 | 8.0 | NS |
| Lumiracoxib 100mg BD | 10.8 | 9.0 | NS |
| Lumiracoxib 200mg BD | 11.2 | 8.7 | NS |
| Lumiracoxib 400mg QD | 10.3 | 8.2 | NS |
| Diclofenac 75mg BD | 11.1 | 8.9 | NS |

Mean results on total tender joints at baseline and week 4

| | Baseline | Week 4 | P value vs placebo |
|---|---|---|---|
| Placebo | 13.0 | 9.1 | |
| Lumiracoxib 50mg BD | 13.0 | 9.6 | NS |
| Lumiracoxib 100mg BD | 13.7 | 9.5 | NS |
| Lumiracoxib 200mg BD | 12.3 | 9.5 | NS |
| Lumiracoxib | 12.5 | 7.8 | NS |

| | | | |
|---|---|---|---|
| 400mg QD | | | |
| Diclofenac 75mg BD | 13.8 | 8.9 | NS |

This study has not found any dose of lumiracoxib to be effective in RA

Study 2312

Double blind, randomised, active comparator-controlled ascending dose, time-lagged study

800mg QD (n = 38), 1200mg QD (n = 41) lumiracoxib
500mg BD naproxen (n = 41)

120 patients with RA of the for at least 3 months
Patients were included if they had RA with symptoms for at least 3 months, functional status class I, II or III and were on NSAIDs or has a history of taking NSAIDs for at least 1 month and had a baseline pain assessment (Likert scale) of moderate, severe or extreme

Dosing for 28 days in RA patients

Primary efficacy endpoint was the RA pain assessment on a 5-pont categorical scale. Other endpoints were the number of swollen joints (28-joint count), the number of tender joints (28-joints count) CRP, Patient and Physician global assessment of disease activity (5-point categorical scale)

Baseline demography

| | Mean age years | M / F (%) | Moderate | Severe | Extreme |
|---|---|---|---|---|---|
| Lumiracoxib 800mg QD | 51.6 | 39.5 / 60.5 | 81.6 % | 15.8 % | 0 |
| Lumiracoxib 1200mg QD | 47.9 | 22.0 / 78.0 | 61.0 % | 31.7 % | 7.3 % |
| Naproxen 500mg BD | 50.8 | 31.7 / 68.3 | 61.0 % | 31.7 % | 7.3 % |

RA pain
There was no significant difference between the three treatments

Patient Global Assessment of disease activity
There was no significant difference between the three treatments

Physician Global Assessment of disease activity
There was no significant difference between the three treatments

CRP levels
There was no significant difference between the three treatments

Swollen joints count
There was no significant difference between the three treatments

Tender joints count
There was no significant difference between the three treatments.

## 7.3 Dose Selection in ACUTE post-dental surgery pain

Two studies have been submitted (0115 and 0103) covering a dose range from 100mg QD to 800mg QD

Study 0115

Double blind, randomised, parallel groups, placebo and active-controlled. Single doses of lumiracoxib 200mg, 400mg and 800mg compared to single dose of rofecoxib 50mg and placebo

Patients

Post-operative dental patients following the removal of 2 or more impacted third molar teeth who are not receiving any other analgesics within 48 hours of surgery.

Efficacy endpoints

Primary endpoints: Sum of Pain Intensity Difference (SPID8) – categorical scale

Other endpoints
Time-specific Pain Intensity Difference (PID – categorical scale
Time-specific Pain Relief (PR)
Time-specific Pain Relief Intensity Difference (PRID)
Time to onset of analgesia up to 12 hours
Pain Intensity Difference (PID) – VAS
Total Pain Relief (TOTPAR8)
Time to taking rescue medication
Patient's global evaluation of treatment.

**Results on efficacy endpoints in Study 0115**

Patient disposition

| | Placebo | L 200 | L 400 | L 800 | Rof 50 |
|---|---|---|---|---|---|
| Randomised | 52 | 52 | 52 | 52 | 51 |
| Completed | 4 | 6 | 17 | 24 | 20 |
| Lost due to insufficient efficacy | 48 | 46 | 35 | 28 | 31 |

SPID8

| | Placebo | L 200 | L 400 | L 800 | Rof 50 |
|---|---|---|---|---|---|
| Mean | - 3.33 | 4.64 | 7.32 | 8.08 | 5.64 |

Statistical analyses of treatments (p values) on primary efficacy variable

| | Placebo | L 200 | L 400 | Rof 50 |
|---|---|---|---|---|
| Placebo | - | - | - | - |
| L 200 | < 0.001 | - | - | - |
| L 400 | < 0.001 | 0.020 | - | NS |
| L 800 | < 0.001 | 0.023 | NS | NS |

Median time (hours) to onset of analgesia

| | Placebo | L 200 | L 400 | L 800 | Rof 50 |
|---|---|---|---|---|---|
| Mean | > 12 | 0.99 | 0.76 | 0.72 | 0.90 |

The differences between placebo and the three lumiracoxib doses were statistically significant. The differences between the active treatments were not statistically significant.

Median time (hours) to rescue medication

| | Placebo | L 200 | L 400 | L 800 | Rof 50 |
|---|---|---|---|---|---|
| Mean | 1.17 | 6.07 | 10.32 | 19.95 | 8.82 |

Percentage patients rating treatment as good or excellent:

Lumiracoxib 400mg 73 %
Lumiracoxib 800mg 71 %
Rofecoxib 50mg 59 %

All the three doses of lumiracoxib were significantly different from placebo.

Lumiracoxib 400mg and 800mg were significantly different from lumiracoxib 200mg. There was no significant difference between 400mg and 800mg doses of lumiracoxib.

The differences between rofecoxib and the three lumiracoxib doses were NOT statistically significant.

Patients' global evaluation revealed no significant difference (a) between lumiracoxib 200mg and placebo or (b) between lumiracoxib 200mg or 400mg and rofecoxib 50mg

The rank order of analgesic effect on primary variable was
- L800 > L400 > R50 > L200 > Pla

**Conclusion:**
Overall, this study supports the use of 400mg lumiracoxib as an effective analgesic agent in post-dental pain model.

Study 0103
Double blind, randomised, parallel groups, placebo and active-controlled

Single doses of lumiracoxib 100mg and 400mg compared to single dose of ibuprofen 400mg and placebo

Patients
Post-operative dental patients following the removal of 2 or more impacted third molar teeth who are not receiving any other analgesics within 48 hours of surgery.

Efficacy endpoints

| | |
|---|---|
| Primary endpoints: | Pain Intensity Difference (PID) to 12 hours – categorical scale |
| | Time-specific Pain Relief (PR) to 12 hours |
| | Time-specific Pain Relief Intensity Difference (PRID) to 12 hours |
| Other endpoints | Time to onset of analgesia |
| | Pain Intensity Difference (PID) – VAS |
| | Total Pain Relief (TOTPAR12) |
| | Sum of Pain Intensity Difference (SPID) |
| | Time to taking rescue medication |

Patient's global evaluation of treatment.

**Results on efficacy endpoints in Study 0103**

Patient disposition

| | Placebo | L 100 | L 400 | Ibu 400 |
|---|---|---|---|---|
| Randomised | 50 | 51 | 50 | 51 |
| Completed | 4 | 12 | 28 | 13 |
| Lost due to insufficient efficacy | 46 | 38 | 22 | 36 |

Lumiracoxib 400mg was consistently superior to lumiracoxib 100mg or placebo with respect to PID, PRID, PR and PID-VAS. Among the 4 treatments, lumiracoxib 400mg had the fasted median time to onset of analgesia.

Lumiracoxib 400mg was generally better than ibuprofen 400mg. It was numerically (but not statistically) superior to ibuprofen 400mg with respect to onset of analgesic effect.

Lumiracoxib 400mg was statistically superior to ibuprofen between 5 and 12 hours with respect to all time-specific measures.

Lumiracoxib 400mg had a significantly longer time to remedication and statistically superior patient global evaluation compared to ibuprofen 400mg.

Lumiracoxib 100mg was statistically superior to placebo, but not from ibuprofen, with respect to all the measures.

**Conclusion:**

This study shows that 100mg lumiracoxib can be effective but 400mg dose may have an optimal efficacy profile as an analgesic agent in post-dental pain model.

## 7.4 Dose Selection in ACUTE pain in primary dysmenorrhoea

No dose-ranging studies have been under taken in this specific pain model.

## 7.5 Dose Selection in ACUTE pain in post-orthopaedic surgery

No dose-ranging studies have been under taken in this specific pain model.

***Assessor's Comments on Dose Selection for Phase III Pivotal Studies***

Osteoarthritis

The programme has essentially failed to distinguish between any of the 4 doses of lumiracoxib.

The programme shows that the lowest dose used, 50mg BD, is effective but it is difficult to see how this can be quantified as the lowest effective dose since there is no information on doses lower than 50mg BD. Among the four doses, 50mg BD is consistently superior to 100mg BD dose. In fact, for some secondary endpoints (HAQ score at 4 weeks, WOMAC physical function score), 100mg BD was statistically no different from placebo.

The only advantage for lumiracoxib 400mg QD is earlier onset of effect compared to lumiracoxib 50mg BD or 100mg BD (week 1 versus week 2). However, this advantage may be more than offset by any dose-

related clinical and laboratory safety (see particularly section 18.1 and 18.2 of the Assessment Report on hepatic and renal safety of lumiracoxib).

| | |
|---|---|
| Rheumatoid arthritis | No dose of lumiracoxib has been found to be effective in RA<br>Although 800mg and 1200mg QD doses did not differ significantly from naproxen 500mg BD, it is difficult to identify a dose of lumiracoxib which is superior to placebo. |
| Primary dysmenorrhoea | No specific study – dose selection extrapolated from studies in acute pain in post-dental surgery patients |
| Acute pain | The model used is acute pain in post-dental surgery patients<br>It is difficult to distinguish clearly between 100mg and 200mg doses of lumiracoxib since the two have not been compared directly. On balance, a dose of 200mg appears better than 100mg dose. When 200mg and 400mg doses are compared, the weight of evidence overall favours the use of 400mg daily dose. <u>However, only additional studies in other models can confirm whether it may be possible to extrapolate this dose to all other pain models.</u> |

**<u>Following Phase III pivotal studies are presented to support efficacy in various indications</u>**

| | Short-term studies | 13-week placebo-controlled studies | 26-39 weeks Long-term efficacy | Endoscopy studies |
|---|---|---|---|---|
| OA | 2319, 2307 | 0109, 0112, 0128 | 0112E | 0126 |
| RA | | 0111, 0114, 0110 | 0111 | 0110 |
| Primary dysmenorrhoea | 0129, 0130 | | | |
| Acute Pain | 0131. 0132 2302 | | | |

## 8. EFFICACY IN OSTEOARTHRITIS (OA)

The following studies are presented to support efficacy of lumiracoxib in osteoarthritis:

**<u>Controlled trials (in osteoarthritis)</u>**

9 large, controlled phase III trials
- 3 adequate and well controlled major efficacy trials [studies 0109, 0112 and 0128]
- 6 supportive trials [studies 0104, 2316, 2319, 2301, 2307 and 0126.
  Study 0126 is also a 13-weeks endoscopy study

**<u>Long-term data</u>**

1 extension of 39 weeks of one of the controlled major efficacy trials [study 0112E]

**I.1.1.1.1.1.1.1 <u>Trials used for combined analysis</u>**

Data from 2 of the placebo controlled major efficacy trials [studies 0109 and 0112] were combined to:
a. provide a better estimate of treatment effect
b. assess the efficacy subgroup analyses (comparison of efficacy and of dosing requirements)
**c.** explore efficacy in joints other than knee and hip

**<u>The Applicant's Summary of Dose Selection Procedure in OA</u>**

The dose and the regimen were chosen based on [study 0104 in osteoarthritis, in which BD and QD regimens were tested and found to be comparable. In addition, CP [study 0122] (multiple dose in rheumatoid arthritis patients with PK measurements in plasma and synovial fluid) and PK analyses from study 0104 supported the use of QD dosing.

The selection of the final dose (200mg QD or 400mg QD) was confirmed in the major efficacy trials and supported by [study 2316], which demonstrated an inferior efficacy with 100mg QD compared to higher doses. The selection of the QD regimen was supported by previous data from CP studies [study 0101] (single rising dose in healthy volunteers), 0104 (including PK analyses), 0122 and on analyses from other phase III trials, particularly [study 2301], which showed effective pain relief over 24 hours from once a day dosing.

**The Assessor's Summary of Optimal Dose in OA**
The programme has essentially failed to distinguish between any of the 4 doses of lumiracoxib. The programme shows that the lowest dose used, 50mg BD, is effective but it is difficult to see how this can be quantified as the lowest effective dose since there is no information on doses lower than 50mg BD.

Among the four doses, 50mg BD is consistently superior to 100mg BD dose. In fact, for some secondary endpoints (HAQ score at 4 weeks, WOMAC physical function score), 100mg BD was statistically no different from placebo.

The only advantage for lumiracoxib 400mg QD is earlier onset of effect compared to lumiracoxib 50mg BD or 100mg BD (week 1 versus week 2).

## 8.1 Study 0109

Objectives and design:
A 13 week, international, multicentre, randomised, double blind, double-dummy, placebo-controlled, parallel group trial assessing the safety and efficacy of 2 doses of lumiracoxib (200mg and 400mg QD) in patients with primary knee osteoarthritis, using celecoxib (200mg QD) as a comparator.

The primary objective was to determine if lumiracoxib (200mg or 400mg QD) is effective in treating osteoarthritis (OA) compared to placebo and celecoxib 200mg QD with respect to: overall OA pain intensity on a 100 mm Visual Analog Scale (VAS); patient global assessment of disease activity; and patient functional status (utilizing the pain sub-scale of the WOMAC LK3.1 questionnaire) after 13 weeks of treatment.

Randomised 1600 patients:
- 462 with lumiracoxib 200mg QD
- 463 with lumiracoxib 400mg QD
- 444 with celecoxib 200mg QD and
- 231 with placebo.

It should be noted that the current EU approved dose of celecoxib is 200mg QD which may be increased to 200mg BD.

**Inclusion/exclusion criteria:**
Patients included were male or female, ≥ 18 years old with symptomatic primary OA of the knee (by American College of Rheumatology criteria) and requiring non-steroidal anti-inflammatory drug (NSAID) therapy. At baseline they had a pain intensity of ≥ 40mm on a VAS. Females capable of child bearing were to be using reliable contraceptive methods. Patients with secondary OA, other diseases of the joint or significant medical problems, or taking prohibited medication were excluded.

**Efficacy:**
Primary efficacy parameters:
- Overall pain intensity in the targeted knee after 13 weeks of treatment using a 100 mm VAS;
- Patient's global assessment of disease activity after 13 weeks of treatment using a 100 mm VAS,
- Patient's functional status after 13 weeks of treatment utilizing the pain sub-scale of the WOMAC 3.1.LK questionnaire;
- WOMAC Total score after 13 weeks of treatment (added at the request of the US FDA at the pre-NDA meeting).

Secondary efficacy parameters:
- Overall pain intensity in the targeted knee (by visit) using a 100 mm VAS
- Physician's global assessment of disease activity (by visit) using a 100 mm VAS
- Patient's global assessment of disease activity (by visit) using a 100 mm VAS
- Patient's functional status utilizing the SF-36 and WOMAC 3.1. LK questionnaires.

Other efficacy parameters:
- Responder rates defined according to the Osteoarthritis Research Society International (OARSI) criterion;
- Standardized area under the curve (AUC) of OA pain in the target joint
- Responder rates defined as ≥ 20 % decrease from baseline in OA pain in the target joint

**Duration of treatment:**
13 weeks

**Results:**
Patient Disposition

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg QD |
|---|---|---|---|---|
| Randomised | 232 | 465 | 465 | 446 |
| Completed | 164 (70.7%) | 369 (79.4%) | 358 (77.0%) | 347 (77.8%) |
| Discontinued | 68 | 96 | 107 | 99 |
| Lack of effect | 35 | 31 | 25 | 33 |
| AE | 17 | 32 | 32 | 33 |

Overall pain intensity (VAS scale) at 13 weeks

| | **N** | **LS Mean** | **Contrast with** | **Estimated difference** | **95% CI** | **p** |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 462 | 37.29 | Lumiracoxib 400mg QD | 1.44 | -1.81 4.70 | 0.385 |
| Lumiracoxib 200mg QD | 462 | 37.29 | Celecoxib 200mg QD | - 1.12 | - 4.42 2.17 | 0.503 |
| Lumiracoxib 200mg QD | 462 | 37.29 | Placebo | - 7.39 | - 11.38 - 3.40 | < 0.001 |
| Lumiracoxib 400mg QD | 463 | 35.84 | Celecoxib 200mg QD | - 2.57 | - 5.86 0.72 | 0.126 |
| Lumiracoxib 400mg QD | 463 | 35.84 | Placebo | - 8.83 | - 12.82 - 4.84 | < 0.001 |
| Celecoxib 200mg QD | 444 | 38.41 | Placebo | - 6.27 | - 10.29 - 2.25 | 0.002 |
| Placebo | 231 | 44.68 | | | | |

Patient Global Assessment of Disease Activity at 13 weeks

| | N | LS Mean | vs | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 462 | 37.41 | Lumiracoxib 400mg QD | 0.87 | - 2.26 4.01 | 0.585 |
| Lumiracoxib 200mg QD | 462 | 37.41 | Celecoxib 200mg QD | - 1.43 | - 4.60 1.74 | 0.377 |
| Lumiracoxib 200mg QD | 462 | 37.41 | Placebo | - 8.55 | - 12.39 - 4.70 | < 0.001 |
| Lumiracoxib 400mg QD | 463 | 36.53 | Celecoxib 200mg QD | - 2.30 | - 5.47 0.87 | 0.155 |
| Lumiracoxib 400mg QD | 463 | 36.53 | Placebo | - 9.42 | - 13.26 - 5.58 | < 0.001 |
| Celecoxib 200mg QD | 444 | 38.84 | Placebo | - 7.12 | - 10.99 - 3.25 | < 0.001 |
| Placebo | 231 | 45.95 | | | | |

WOMAC Pain Sub-scale at 13 weeks

| | N | LS Mean | vs | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 462 | 6.38 | Lumiracoxib 400mg QD | 0.16 | - 0.29 0.66 | 0.454 |
| Lumiracoxib 200mg QD | 462 | 6.38 | Celecoxib 200mg QD | - 0.14 | - 0.63 0.34 | 0.556 |
| Lumiracoxib 200mg QD | 462 | 6.38 | Placebo | - 1.27 | - 1.86 - 0.69 | < 0.001 |
| Lumiracoxib 400mg QD | 463 | 6.20 | Celecoxib 200mg QD | - 0.33 | - 0.81 0.15 | 0.184 |
| Lumiracoxib 400mg QD | 463 | 6.20 | Placebo | - 1.46 | - 2.04 - 0.87 | < 0.01 |
| Celecoxib 200mg QD | 444 | 6.53 | Placebo | - 1.13 | - 1.72 - 0.54 | < 0.001 |
| Placebo | 231 | 7.66 | | | | |

WOMAC Total Score at 13 weeks

| | N | LS Mean | vs | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 459 | 30.51 | Lumiracoxib 400mg QD | 0.10 | - 2.00 2.20 | 0.926 |
| Lumiracoxib 200mg QD | 459 | 30.51 | Celecoxib 200mg QD | - 1.41 | - 3.53 0.70 | 0.190 |
| Lumiracoxib 200mg QD | 459 | 30.51 | Placebo | - 7.38 | - 9.97 - 4.48 | < 0.001 |
| Lumiracoxib 400mg QD | 459 | 30.41 | Celecoxib 200mg QD | - 1.51 | - 3.63 0.60 | 0.161 |
| Lumiracoxib 400mg QD | 459 | 30.41 | Placebo | - 7.48 | - 10.06 - 4.91 | < 0.001 |
| Celecoxib 200mg QD | 442 | 31.92 | Placebo | - 5.97 | - 8.57 - 3.37 | < 0.001 |
| Placebo | 226 | 37.89 | | | | |

These data show that all the three active treatments are significantly superior to placebo

Lumiracoxib 400mg, lumiracoxib 200mg and celecoxib 200mg daily are all equally effective with no significant difference between any two of them.

The following results show that the 400mg dose has no advantages over the 200mg dose:

| | 2 weeks | 4 weeks | 8 weeks | 13 weeks |
|---|---|---|---|---|
| | Overall joint pain intensity – Change from baseline | | | |
| L 200<br>L 400 | -24.7<br>-25.2 | - 25.5<br>- 27.0 | - 27.7<br>- 28.8 | - 28.7<br>- 29.7 |
| | Patient Global Assessment of | | | |
| L 200<br>L 400 | -21.2<br>-22.6 | - 23.1<br>- 23.7 | - 24.7<br>- 25.4 | - 25.3<br>- 25.8 |
| | Response rate (OARSI criterion) | | | |
| L 200<br>L 400 | 53.0 %<br>53.8 % | | | 69.7 %<br>71.5 % |
| | Response rate (reduction of ≥ 20 % in pain intensity) | | | |
| L 200<br>L 400 | 64.7 %<br>66.7 % | 66.7 %<br>70.6 % | 70.1 %<br>69.5 % | 66.9 %<br>68.9 % |

None of the differences between the two treatments are statistically significant

**Applicant's summary of efficacy in study 0109**
Efficacy of both lumiracoxib 200mg QD and 400mg QD for the treatment of OA of the knee was confirmed by positive results for all four primary efficacy variables: i) OA pain in the target knee, ii) patient's global assessment of disease activity, iii) WOMAC pain and iv) WOMAC total scores after 13 weeks.

Lumiracoxib 200mg QD, lumiracoxib 400mg QD and celecoxib 200mg QD were all significantly more effective than placebo after 2, 4, 8 and 13 weeks of treatment for both the patient's and physician's global assessment of disease activity.

Both doses were shown to be non-inferior to celecoxib 200mg with respect to efficacy. Lumiracoxib 200mg QD, lumiracoxib 400mg QD and celecoxib 200mg QD were also significantly more effective than placebo at weeks 2 and 13 for the newly validated Osteoarthritis Research Society International (OARSI) response to treatment criteria.

For area under the curve (AUC) of OA pain and ≥ 20 % decrease from baseline in OA pain intensity, lumiracoxib 200mg QD, lumiracoxib 400mg QD and celecoxib 200mg QD were significantly more effective than placebo at weeks 2, 4, 8 and 13.

Lumiracoxib 400mg QD was significantly better than celecoxib 200mg QD for the OARSI response to treatment criteria and AUC of OA pain over the entire treatment phase. There were no statistically significant differences between the TWO doses of lumiracoxib for any of the efficacy parameters.

## 8.2 Study 0112

Objectives and design:
A 13-week multicentre randomised double blind double dummy placebo-controlled parallel trial in patients with knee primary osteoarthritis using celecoxib as a comparator.

The primary objective of this trial was to determine if lumiracoxib (200 or 400mg QD) was effective in osteoarthritis as compared with placebo. Comparison of efficacy with celecoxib 200mg QD was a secondary objective.

Randomised 1702 patients:

- 487 with lumiracoxib 200mg QD,
- 491 with lumiracoxib 400mg QD,
- 481 with celecoxib 200mg QD and
- 243 with placebo.

It should be noted that the current EU approved dose of celecoxib is 200mg QD which may be increased to 200mg BD.

Inclusion/exclusion criteria:
Patients included were male or female, ≥ 18 years old with symptomatic primary OA of the knee (by American College of Rheumatology criteria) and requiring non-steroidal anti-inflammatory drug (NSAID) therapy. At baseline they had a pain intensity of ≥ 40mm on a VAS. Females capable of child bearing were to be using reliable contraceptive methods. Patients with secondary OA, other diseases of the joint or significant medical problems, or taking prohibited medication were excluded.

Efficacy:
The primary variables were:
- Overall OA joint pain intensity in the target knee after 13 weeks of treatment.
- Patient's global assessment of disease activity after 13 weeks of treatment using a 100mm VAS.
- Patient functional status after 13 weeks of treatment utilizing the Pain sub-scale of the WOMAC LK3.1 questionnaire.
- An additional co-primary variable was WOMAC Total score after 13 weeks of treatment.

The secondary efficacy variables were:
- Overall OA pain intensity in the target joint (by visit)
- Physician's global assessment of disease activity using a 100mm VAS
- Patient functional status after 13 weeks of treatment utilizing the Stiffness and DPDA (difficulty in performing daily activities) sub-scales of the WOMAC LK3.1 questionnaire.
- Patient health status utilizing the SF-36 questionnaire.

Duration of treatment:
13 weeks

**Results:**
Patient Disposition

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg QD |
|---|---|---|---|---|
| Randomised | 243 | 487 | 491 | 481 |
| Completed | 200 (82.3%) | 408 (83.8%) | 414 (84.3%) | 401 (83.4%) |
| Discontinued | 43 | 79 | 77 | 80 |
| Lack of effect | 15 | 13 | 14 | 15 |
| AE | 20 | 41 | 41 | 48 |

Overall pain intensity (VAS scale) at 13 weeks

| | **N** | **LS Mean** | **Contrast with** | **Estimated difference** | **95% CI** | **p** |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 487 | 39.07 | Lumiracoxib 400mg QD | 1.61 | - 1.27 4.49 | 0.273 |
| Lumiracoxib | 487 | 39.07 | Celecoxib | - 0.58 | - 3.47 | 0.694 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 200mg QD | | | 200mg QD | | 2.31 | |
| Lumiracoxib 200mg QD | 487 | 39.07 | Placebo | - 6.33 | - 9.86<br>- 2.80 | < 0.001 |
| Lumiracoxib 400mg QD | 491 | 37.46 | Celecoxib 200mg QD | - 2.19 | - 5.07<br>0.69 | 0.137 |
| Lumiracoxib 400mg QD | 491 | 37.46 | Placebo | - 7.94 | - 11.47<br>- 4.41 | < 0.001 |
| Celecoxib 200mg QD | 481 | 39.65 | Placebo | - 5.75 | - 9.29<br>- 2.21 | 0.001 |
| Placebo | 243 | 45.40 | | | | |

Patient Global Assessment of Disease Activity at 13 weeks

| | **N** | **LS Mean** | **Contrast with** | **Estimated difference** | **95% CI** | **p** |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 487 | 39.67 | Lumiracoxib 400mg QD | 1.11 | - 1.68<br>3.90 | 0.435 |
| Lumiracoxib 200mg QD | 487 | 39.67 | Celecoxib 200mg QD | -1.17 | - 3.98<br>1.63 | 0.413 |
| Lumiracoxib 200mg QD | 487 | 39.67 | Placebo | - 7.62 | - 11.05<br>- 4.20 | < 0.001 |
| Lumiracoxib 400mg QD | 491 | 38.56 | Celecoxib 200mg QD | - 2.28 | - 5.08<br>0.52 | 0.110 |
| Lumiracoxib 400mg QD | 491 | 38.56 | Placebo | - 8.73 | - 12.15<br>- 5.31 | < 0.001 |
| Celecoxib 200mg QD | 481 | 40.84 | Placebo | - 6.45 | - 9.89<br>- 3.02 | 0.002 |
| Placebo | 243 | 47.29 | | | | |

WOMAC Pain Sub-scale at 13 weeks

| | **N** | **LS Mean** | **Contrast with** | **Estimated difference** | **95% CI** | **p** |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 487 | 6.91 | Lumiracoxib 400mg QD | 0.09 | - 0.36<br>0.54 | 0.692 |
| Lumiracoxib 200mg QD | 487 | 6.91 | Celecoxib 200mg QD | - 0.05 | - 0.50<br>0.40 | 0.837 |
| Lumiracoxib 200mg QD | 487 | 6.91 | Placebo | - 0.86 | - 1.41<br>- 0.31 | 0.002 |
| Lumiracoxib 400mg QD | 491 | 6.82 | Celecoxib 200mg QD | - 0.14 | - 0.58<br>0.31 | 0.548 |
| Lumiracoxib 400mg QD | 491 | 6.82 | Placebo | - 0.95 | - 1.49<br>- 0.40 | < 0.001 |
| Celecoxib 200mg QD | 481 | 6.96 | Placebo | - 0.81 | - 1.36<br>- 0.26 | 0.004 |
| Placebo | 243 | 7.77 | | | | |

WOMAC Total Score at 13 weeks

| | **N** | **LS Mean** | **Contrast with** | **Estimated difference** | **95% CI** | **p** |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 484 | 34.48 | Lumiracoxib 400mg QD | 0.37 | - 1.52<br>2.27 | 0.699 |
| Lumiracoxib 200mg QD | 484 | 34.48 | Celecoxib 200mg QD | - 0.44 | - 2.34<br>1.46 | 0.650 |
| Lumiracoxib 200mg QD | 484 | 34.48 | Placebo | - 4.82 | - 7.14<br>- 2.50 | < 0.001 |
| Lumiracoxib 400mg QD | 488 | 34.11 | Celecoxib 200mg QD | - 0.81 | - 2.71<br>1.08 | 0.401 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Lumiracoxib 400mg QD | 488 | 34.11 | Placebo | - 5.19 | - 7.52<br>- 2.87 | < 0.001 |
| Celecoxib 200mg QD | 478 | 34.92 | Placebo | - 4.38 | - 6.71<br>- 2.05 | < 0.001 |
| Placebo | 242 | 39.30 | | | | |

These data show that all the three active treatments are significantly superior to placebo

Lumiracoxib 400mg, lumiracoxib 200mg and celecoxib 200mg daily are all equally effective with no significant difference between any two of them.

The following results show that the 400mg dose has no advantages over the 200mg dose:

| | 2 weeks | 4 weeks | 8 weeks | 13 weeks |
|---|---|---|---|---|
| | Overall joint pain intensity – Change from baseline | | | |
| L 200<br>L 400 | - 19.2<br>- 20.2 | - 21.8<br>- 24.0 | - 25.7<br>- 28.8 | - 26.0<br>- 27.4 |
| | Patient Global Assessment of | | | |
| L 200<br>L 400 | - 14.9<br>- 16.4 | - 19.5<br>- 20.6 | - 21.9<br>- 23.8 | - 23.2<br>- 24.1 |
| | Response rate (OARSI criterion) | | | |
| L 200<br>L 400 | 50.1 %<br>54.2 % | | | 64.3 %<br>69.5 % |
| | Response rate (reduction of ≥ 20 % in pain intensity) | | | |
| L 200<br>L 400 | 56.9 %<br>60.1 % | | | 66.1 %<br>70.7 % |

None of the differences between the two treatments are statistically significant

**Applicant's summary of efficacy in study 0112**
After 13 weeks of treatment lumiracoxib 200mg QD and lumiracoxib 400mg QD were significantly more effective than placebo in terms of overall pain in the target joint and patient's global assessment of disease activity, and WOMAC pain sub-score. In the WOMAC Total score lumiracoxib 200mg QD, lumiracoxib 400mg QD and celecoxib 200mg QD were all significantly more effective than placebo after 13 weeks of treatment.

Both doses were non-inferior to celecoxib 200mg QD with respect to efficacy.

Lumiracoxib 400mg QD was shown to have statistical superiority over celecoxib 200mg QD at weeks 2, 4 and 8 in overall OA joint pain intensity, but the treatment difference, although numerically superior, did not achieve statistical significance at week 13 (i.e. at the primary endpoint).

All active treatments were significantly more effective than placebo in measures of response to treatment (OARSI criteria and □20% reduction from baseline in OA pain intensity) and in terms of AUC of OA pain.

## 8.3 Study 0128

Design and objectives:
This was a 13-week, multicentre, randomised, double blind, double dummy, placebo and active-controlled, parallel group trial of lumiracoxib (400mg QD) in patients with primary osteoarthritis (OA) in the hip using rofecoxib (25mg QD) as a comparator. The planned sample size was 495 patients with a 2:2:1 randomisation.

The primary objective of this trial was to determine if lumiracoxib 400mg QD was effective in treating osteoarthritis of the hip as compared to placebo.

The total number of patients randomised was 513 allocated as follows:
- 207 lumiracoxib 400mg QD (2 of whom did not receive study drug),
- 102 rofecoxib 25mg QD,
- 204 placebo

It should be noted that the current EU approved dose of rofecoxib is 12.5mg QD which may be increased to 25mg QD.

Inclusion/exclusion criteria:
Patients included were male or female, ≥ 18 years old with symptomatic primary OA of the hip, requiring non-steroidal anti-inflammatory drug (NSAID) therapy. At baseline they had a pain intensity of at least 40mm on the VAS. Potential childbearing females were to be using reliable contraceptive methods. Patients with secondary OA, other diseases of the joint or significant medical problems were excluded.

**Efficacy:**
The primary variables were:
- Overall OA pain intensity in the targeted hip after 13 weeks of treatment using a 100mm VAS
- Patient's global assessment of disease activity after 13 weeks of treatment using a 100mm VAS
- Patient's functional status after 13 weeks of treatment utilizing the pain sub-scale of the WOMAC LK3.1 questionnaire
- WOMAC Total score after 13 weeks of treatment

Secondary efficacy parameters:
- Overall OA pain intensity in the targeted hip using a 100mm VAS
- Patient's global assessment of disease activity (by visit) using a 100mm VAS
- Physician's global assessment of disease activity (by visit) using a 100mm VAS
- Patient's functional status after 13 weeks of treatment (visit 6) utilizing the stiffness and difficulty in performing daily activities (DPDA) sub-scales of the WOMAC LK3.1 questionnaire, and
- Patient's health status utilizing the Health Assessment Questionnaire (HAQ Standard Disability Index (SDI) after 13 weeks of treatment.

Other efficacy parameters:
- Responder rates defined according to the Osteoarthritis Research Society International (OARSI) criterion
  Standardized area under the curve (AUC) of OA pain in the target joint
  Responder rates defined as ≥ 20 % decrease from baseline in OA pain in the target joint

**Duration of treatment:**
13 weeks

**Results:**
Patient Disposition

| | Placebo | Lumiracoxib 400mg QD | Rofecoxib 25mg QD |
|---|---|---|---|
| Randomised | 204 | 207 | 102 |
| Completed | 150 (73.5%) | 162 (78.3%) | 82 (80.4%) |
| Discontinued<br>Lack of effect | 54<br>23 | 45<br>12 | 20<br>7 |

| | | | |
|---|---|---|---|
| AE | 17 | 18 | 10 |

Overall pain intensity (VAS scale) at 13 weeks

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 400mg QD | 205 | 41.32 | Placebo | - 6.35 | - 10.94<br>- 1.76 | 0.007 |
| Lumiracoxib 400mg QD | 205 | 41.32 | Rofecoxib 25mg QD | 3.15 | - 2.46<br>8.76 | 0.271 |
| Rofecoxib 25mg QD | 102 | 38.17 | Placebo | - 9.50 | - 15.12<br>- 3.87 | < 0.001 |
| Placebo | 204 | 47.66 | | | | |

Patient Global Assessment of Disease Activity at 13 weeks

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 400mg QD | 205 | 42.47 | Placebo | - 7.04 | - 11.67<br>- 2.41 | 0.003 |
| Lumiracoxib 400mg QD | 205 | 42.47 | Rofecoxib 25mg QD | 3.16 | - 2.52<br>8.85 | 0.275 |
| Rofecoxib 25mg QD | 101 | 39.31 | Placebo | - 10.20 | - 15.90<br>- 4.51 | < 0.001 |
| Placebo | 203 | 49.52 | | | | |

WOMAC Pain Sub-scale at 13 weeks

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 400mg QD | 204 | 7.15 | Placebo | - 0.65 | - 1.37<br>0.07 | 0.077 |
| Lumiracoxib 400mg QD | 204 | 7.15 | Rofecoxib 25mg QD | 0.54 | - 0.35<br>1.42 | 0.234 |
| Rofecoxib 25mg QD | 101 | 6.61 | Placebo | - 1.19 | - 2.07<br>- 0.30 | 0.009 |
| Placebo | 204 | 7.80 | | | | |

WOMAC Total Score at 13 weeks

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 400mg QD | 201 | 35.25 | Placebo | - 3.21 | - 6.21<br>- 0.22 | 0.036 |
| Lumiracoxib 400mg QD | 201 | 35.25 | Rofecoxib 25mg QD | 3.49 | - 0.20<br>7.18 | 0.064 |
| Rofecoxib 25mg QD | 100 | 31.76 | Placebo | - 6.70 | - 10.38<br>- 3.02 | < 0.001 |
| Placebo | 204 | 38.46 | | | | |

Both the active treatments are superior to placebo (except lumiracoxib 400mg QD which is not statistically significantly superior to placebo as far as WOMAC Pain Sub-scale at 13 weeks is concerned.

Rofecoxib 25mg QD is close to achieving a statistically significant difference from lumiracoxib 400mg QD as far as WOMAC Total Score at 13 weeks is concerned.

On balance, rofecoxib 25mg QD is more effective than lumiracoxib 400mg QD.

**Applicant's summary of efficacy in study 0128**
Overall, efficacy of lumiracoxib 400mg QD for the treatment of OA of the hip was confirmed by positive results for 3 out of 4 of the primary efficacy analyses in the domains of OA pain (VAS mm) in the target joint, patient's global assessment of disease activity and functional status measured by WOMAC Total scores after 13 weeks of treatment.

WOMAC pain sub-scale was numerically superior to placebo, but statistical significance was not shown at 13 weeks.

At 2, 4, 8 and 13 weeks of treatment lumiracoxib 400mg QD and rofecoxib 25mg QD were statistically superior to placebo for treatment of OA of the hip with respect to VAS pain intensity in the target joint, and patient's and physician's assessments of disease activity. Both active treatments were statistically significantly more effective than placebo in the additional measure of response to treatment by the OARSI criteria at 2 and 13 weeks, in responder rate analysis of ≥ 20% reduction in baseline OA pain intensity at 4 and 8 weeks and in the analysis of area under the pain curve.

Generally, efficacy of lumiracoxib 400mg QD was comparable to rofecoxib 25mg QD. Non-inferiority to rofecoxib could not be demonstrated in study 0128, the predictive power to do this would be very low (<40%).

## 8.4 Study 2319

This is a 4-week multi-centre, randomised, double blind placebo-controlled parallel groups study of two doses of lumiracoxib in patients with primary osteoarthritis of the hand.

The primary endpoint was overall osteoarthritis pain intensity in the target joint in the previous 24 hours as measured by VAS after 4 weeks of treatment.

Other endpoints were patient global assessment of disease activity (VAS) at 4 weeks and AUSCAN score after 4 weeks. This score combines the scores for pain, stiffness and difficulty performing daily activities.

**Results**

Overall pain intensity (VAS scale) at 4 weeks

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 205 | 41.93 | Lumiracoxib 400mg QD | 0.32 | - 3.74 4.38 | 0.877 |
| Lumiracoxib 200mg QD | 205 | 41.93 | Placebo | - 9.87 | - 13.90 - 5.84 | < 0.001 |
| Lumiracoxib 400mg QD | 193 | 41.61 | Placebo | - 10.19 | - 14.27 - 6.11 | < 0.001 |
| Placebo | 196 | 51.80 | | | | |

Patient Global Assessment of Disease Activity (VAS) at 4 weeks

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 205 | 43.94 | Lumiracoxib 400mg QD | 2.28 | - 1.54 6.10 | 0.242 |
| Lumiracoxib 200mg QD | 205 | 43.94 | Placebo | - 8.34 | - 12.13 - 4.55 | < 0.001 |
| Lumiracoxib 400mg QD | 193 | 41.66 | Placebo | - 10.62 | - 14.45 - 6.79 | < 0.001 |
| Placebo | 196 | 52.28 | | | | |

AUSCAN Total Score after 4 weeks

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 201 | 26.02 | Lumiracoxib 400mg QD | 1.46 | - 0.57<br>3.50 | 0.158 |
| Lumiracoxib 200mg QD | 201 | 26.02 | Placebo | - 3.09 | - 5.12<br>- 1.06 | 0.003 |
| Lumiracoxib 400mg QD | 191 | 24.56 | Placebo | - 4.55 | - 6.59<br>- 2.51 | < 0.001 |
| Placebo | 191 | 29.11 | | | | |

The data show that lumiracoxib is effective in the treatment of primary osteoarthritis of the hand and that the two doses are equally effective. 400mg daily dose had no superiority over 200mg dose in any parameter at any time point (week 2 or week 4).

## 8.5 Long-term efficacy - Study 0112E

This is a 39-week active-controlled extension to the 13-week placebo-controlled study 0112 which compared two doses of lumiracoxib with one dose of celecoxib.

Those patients who had been randomised to placebo were converted in a double blind 1:1:1 randomised manner to the three active treatments.

Ex-placebo patients were randomised to:
Lumiracoxib 200mg QD 56
Lumiracoxib 400mg QD 59
Celecoxib 200mg QD 56

| | Placebo | L 200mg | L 400mg | C 200mg |
|---|---|---|---|---|
| **Study 0112** | | | | |
| Randomised | 243 | 487 | 491 | 481 |
| Completed | 200 | 408 | 414 | 401 |
| Consented to Extension | 171 | 355<br>+56 | 360<br>+59 | 349<br>+56 |
| **Study 0112E** | | | | |
| Randomised | | 411 | 419 | 405 |
| Completed | | 308 (74.9%) | 328 (78.3%) | 325 (80.2%) |
| Discontinued | | 103 | 91 | 80 |
| Unsatisfactory efficacy | | 25 (6.1 %) | 13 (3.1%) | 31 (7.7%) |
| Adverse events | | 42 (10.2%) | 41 (9.8%) | 23 (5.7%) |

The primary variables were:
- Overall OA pain intensity in the targeted joint (VAS)
- Patient's global assessment of disease activity (VAS)
- WOMAC Pain subscale score
- WOMAC Total score

**Results:**

Osteoarthritis Pain Intensity in the target joint (VAS)

| | **Original randomised group** | | | **Original randomised group plus ex-placebo patients** | | |
|---|---|---|---|---|---|---|
| | **L 200** | **L 400** | **C 200** | **L 200** | **L 400** | **C 200** |
| | **352** | **358** | **348** | **408** | **417** | **404** |
| Baseline | 66.5 | 65.6 | 64.8 | 62.8 | 62.1 | 61.5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Change at month 3 | - 30.1 | - 31.5 | - 28.5 | - 26.5 | - 28.0 | - 25.4 |
| Change at month 6 | - 30.0 | - 30.7 | - 28.4 | - 27.0 | - 27.5 | - 24.5 |
| Change at month 9 | - 29.8 | - 30.6 | - 29.4 | - 26.2 | - 27.1 | - 26.0 |
| Change at month 12 | - 28.1 | - 28.7 | - 28.3 | - 28.1 | - 28.7 | - 28.3 |

The two doses of lumiracoxib were no different at any time point.

Patient Global Assessment of Disease Activity (VAS)

| | **Original randomised group** | | | **Original randomised group plus ex-placebo patients** | | |
|---|---|---|---|---|---|---|
| | **L 200** | **L 400** | **C 200** | **L 200** | **L 400** | **C 200** |
| | **352** | **358** | **348** | **408** | **417** | **404** |
| Baseline | 64.5 | 63.0 | 63.1 | 61.2 | 59.9 | 60.9 |
| Change at month 3 | - 28.1 | - 28.3 | - 25.4 | - 25.2 | - 25.4 | - 23.1 |
| Change at month 6 | - 27.6 | - 26.6 | - 25.6 | - 25.0 | - 24.3 | - 22.8 |
| Change at month 9 | - 26.8 | - 26.4 | - 26.5 | - 23.8 | - 23.5 | - 24.1 |
| Change at month 12 | - 25.2 | - 24.6 | - 26.1 | - 25.2 | - 24.6 | - 26.1 |

The two doses of lumiracoxib were no different at any time point.

WOMAC Pain Subscale Score

| | **Original randomised group** | | | **Original randomised group plus ex-placebo patients** | | |
|---|---|---|---|---|---|---|
| | **L 200** | **L 400** | **C 200** | **L 200** | **L 400** | **C 200** |
| | **352** | **358** | **348** | **408** | **417** | **404** |
| Baseline | 10.4 | 10.1 | 10.1 | 10.0 | 9.7 | 9.7 |
| Change at month 3 | - 3.8 | - 3.7 | - 3.5 | - 3.4 | - 3.4 | - 3.2 |
| Change at month 6 | - 3.9 | - 3.9 | - 3.7 | - 3.9 | - 3.9 | - 3.7 |
| Change at month 12 | - 3.6 | - 3.7 | - 3.4 | - 3.6 | - 3.7 | - 3.4 |

The two doses of lumiracoxib were no different at any time point.

WOMAC Total Score

| | **Original randomised group** | | | **Original randomised group plus ex-placebo patients** | | |
|---|---|---|---|---|---|---|
| | **L 200** | **L 400** | **C 200** | **L 200** | **L 400** | **C 200** |
| | **352** | **358** | **348** | **408** | **417** | **404** |
| Baseline | 50.4 | 49.1 | 48.4 | 48.6 | 47.1 | 47.1 |
| Change at month 3 | - 16.8 | - 16.6 | - 15.8 | - 15.1 | - 15.0 | - 14.3 |
| Change at month 6 | - 17.3 | - 17.0 | - 15.6 | - 17.3 | - 17.0 | - 15.6 |
| Change at month 12 | - 16.1 | - 16.4 | - 15.5 | - 16.1 | - 16.4 | - 15.5 |

The two doses of lumiracoxib were no different at any time point.

The data show that the efficacy of lumiracoxib is maintained over at least 52 weeks.

**Applicant's Overall Summary of Efficacy in OA**

The data from adequate and well-controlled trials demonstrate that lumiracoxib is efficacious in osteoarthritis patients, showing consistent superiority compared to placebo, and at least comparable, and in some cases superior, efficacy to active therapy with celecoxib over the 13 week treatment period.

The 200mg QD and 400mg QD doses of lumiracoxib were chosen using dose selection studies [0104 and 2316], which demonstrated that efficacy of lumiracoxib was maintained using a once a day regimen.

Lumiracoxib at doses of 200mg and 400mg, taken once a day in the morning for 13 weeks, was found to be significantly superior to placebo for treatment of OA of the knee [studies 0109 and 0112] and hip [study 0128].

While a dose of 200mg QD was efficacious for treatment of knee OA, 400mg QD gave a generally greater reduction of OA pain and disease activity, as well as better improvement of patient function.

Lumiracoxib 400mg QD showed statistical superiority over celecoxib 200mg QD in the analysis of OA pain in the knee joint in studies 0109 and 0112, at weeks 2 and 4.

When the data from the two studies were pooled, superiority of lumiracoxib 400mg QD over celecoxib 200mg QD was also observed through 13 weeks.

Reduction of OA knee joint pain was maintained for the whole of the 52 week treatment period of study 0112 and its extension [study 0112E

In the hip joint (study 0128), percentage reduction in mean pain from baseline was slightly less than in the knee joint for lumiracoxib 400mg QD and rofecoxib 25mg QD. In the placebo groups, reduction in mean pain at 13 weeks was higher in the knee joint than in the hip joint.

A post-hoc analysis of study 0104 showed no clinically relevant difference in treatment outcomes between knee and hip OA. In hand OA, lumiracoxib 200mg QD and 400mg QD were superior to placebo for reduction of pain and disease activity, and improvement of patient function (AUSCAN scores) [study 2319].

Lumiracoxib demonstrated an early analgesic effect. In studies 0109 and 0112 lumiracoxib was superior to celecoxib 200mg QD at week 2. In study 2301, lumiracoxib was superior to placebo at 3 hours from dosing while celecoxib was not.

Study 2301 provided evidence of a sustained 24-hour relief of pain, since evening WOMAC pain assessments were lower in the lumiracoxib group than in placebo. Knee joint (pain intensity difference) PID values did not fluctuate between the am and pm measurement with lumiracoxib 400mg QD, unlike those for celecoxib 200mg BD.

Using the pooled dataset, the 400mg QD lumiracoxib dose was statistically significantly better than celecoxib more often at study endpoints for efficacy outcomes (OA pain intensity, patient global assessment, AUC of overall OA pain intensity, response to treatment using both OARSI criteria and ≥ 20 % reduction from baseline in overall OA pain), but both treatments were consistently better than placebo in all measured outcomes. The data from the other supportive trials reinforce these conclusions.

Data pooling for subgroup analysis showed no clinically relevant differences in efficacy or dose requirements according to severity or duration of disease, age, sex, race or BMI.

These results provide conclusive evidence of efficacy of lumiracoxib in knee, hip and hand OA. The majority of OA patients will respond favourably to lumiracoxib at a dose of 200mg given once daily. Some patients may derive additional benefit from 400mg once daily.

***Assessor's Comments on Efficacy of lumiracoxib in osteoarthritis:***

It is concluded that:

- Lumiracoxib 200mg and 400mg QD are effective in relieving pain in osteoarthritis of knee. 400mg QD is effective in relieving pain in osteoarthritis of the hip joints. There are no reasons to believe that 200mg QD dose will not be effective at the hip joints.
- Lumiracoxib 200mg and 400mg QD are effective in relieving pain in osteoarthritis of knee or hip joints.
- Both doses are as effective as celecoxib 200mg QD and rofecoxib 25mg QD
- It should be noted that the current EU approved dose of celecoxib is 200mg QD which may be increased to 200mg BD while the current EU approved dose of rofecoxib is 12.5mg QD which may be increased to 25mg QD.
- The data show that the efficacy of lumiracoxib is maintained over at least 52 weeks. The two doses – 200mg and 400mg daily – are equally effective in this regard with no different at any time point.
- The data show that lumiracoxib is effective in the treatment of primary osteoarthritis of the hand and that the two doses are equally effective. 400mg daily dose had no superiority over 200mg dose in any parameter at any time point (week 2 or week 4).
- There is no difference between 200mg and 400mg QD doses of lumiracoxib.
- This observation should be examined in the context of phase II programme which has essentially failed to distinguish between any of the 4 doses of lumiracoxib ranging from 50mg BD to 400mg QD.
- The phase II programme shows that the lowest dose used, 50mg BD, is effective but it is difficult to see how this can be quantified as the lowest effective dose since there is no information on doses lower than 50mg BD.
- Among the four doses, 50mg BD is consistently superior to 100mg BD dose. In fact, for some secondary endpoints (HAQ score at 4 weeks, WOMAC physical function score), 100mg BD was statistically no different from placebo. The only advantage for lumiracoxib 400mg QD is earlier onset of effect compared to lumiracoxib 50mg BD or 100mg BD (week 1 versus week 2). However, this advantage has not been confirmed in pivotal phase III studies.
- The risk/benefit ratio for a 400mg dose is unfavourable (dose-related clinical and laboratory safety, particularly the gastro-intestinal, hepatic and renal safety of lumiracoxib - please see sections 13, 14, 16 and 18 of this Assessment Report).

## 9. EFFICACY IN RHEUMATOID ARTHRITIS (RA)

There are a total of 3 studies (0110, 0111, 0114) with one of them (0111) providing 26-weeks long-term efficacy data. In addition, study 0110 provided 13-weeks endoscopy data.

**Controlled trials in rheumatoid arthritis**

3 large, controlled phase III trials:
- 2 major efficacy trials [0111 and 0114]
- 1 supportive trial [0110] that was primarily a safety study but also measuring efficacy
  Study 0110 also provided 13-weeks endoscopy data.

**Trials used for combined analysis**

Data from the 2 placebo-controlled major efficacy trials [0111 and 0114] were combined to:
a. provide a better estimate of treatment effect
b. assess the efficacy in subgroup analyses (comparison of efficacy and of dosing requirements)

**The Applicant's Summary of Dose Selection Procedure in RA**

The data from two adequate and well-controlled trials [0111 and 0114] show that lumiracoxib is effective for treating the signs and symptoms of active RA. The 200mg and 400mg QD doses of lumiracoxib are chosen based on the results of the dose-finding study 0105 and the dose selection information provided by the major efficacy studies 0111 and 0114, which also demonstrated that efficacy of lumiracoxib was maintained using a once a day regimen.

**The Assessor's Summary of Optimal Dose in RA**

No dose of lumiracoxib has been found to be effective in RA during the Phase II programme (studies 0105 and 2312.

Although 800mg and 1200mg QD doses did not differ significantly from naproxen 500mg BD, it is difficult to identify a dose of lumiracoxib which is superior to placebo.

### 9.1 Study 0114

Objectives and design:
A 13-week, international, multicentre, randomised, double blind, double-dummy, placebo-controlled, parallel group trial of 2 doses of lumiracoxib (200mg and 400mg QD) in patients with rheumatoid arthritis (RA) using celecoxib (200mg BD) as a comparator

To determine if lumiracoxib (200 or 400mg QD versus placebo was effective in treating RA with respect to the percentage of responders to the ACR20 criteria after 13 weeks of treatment.

The planned sample size was 1100 patients, 275 per treatment group but over 300 patients were ultimately recruited per group. At screening, patients included were male or female, ≥ 18 years old with RA requiring NSAID therapy, and with active disease. After a 3 to 14 day NSAID/analgesic washout period, at baseline, randomised patients were to have evidence of an RA flare defined by specific increases since screening, in RA pain and in the number of tender and/or swollen joints.

The numbers of patients randomised were:
- 315 in lumiracoxib 200mg QD group
- 313 in lumiracoxib 400mg QD group
- 302 in celecoxib 200mg BD group
- 309 in placebo group.

Inclusion/exclusion criteria:
Patients included were male or female, ≥18 years old with symptomatic RA (as defined by the American College of Rheumatology (ACR) criteria for the classification of RA) and requiring non-steroidal anti-inflammatory drug (NSAID) therapy. At baseline they were to have a pain intensity of at least 40mm on the visual analog scale (VAS) and increased disease activity. Females of childbearing potential were to be using reliable contraceptive methods. Patients gave written informed consent before any study procedures were performed and were treated as outpatients. Patients with adult juvenile chronic arthritis, other rheumatic diseases or significant medical problems were excluded.

**Efficacy:**
The primary efficacy variable in this study is percentage of responders according to the ACR20 criteria after 13 weeks of treatment with lumiracoxib 200mg or 400mg QD compared with placebo, in the ITT population.

The ACR20 components are secondary efficacy variables and include swollen 66-joint and tender 68-joint (includes hips) counts, patient's overall assessment of RA pain, patient's and physician's global assessment of disease activity, CRP level and HAQ standard disability index (SDI) score.

Further secondary variables are percentage of responders to ACR50 criteria, time to first response to ACR20, time to discontinuation due to unsatisfactory effect, physical and mental component summary measures from the SF-36.

**Duration of treatment:**
13 weeks

**Results:**
Patient Disposition

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg BD |
|---|---|---|---|---|
| Randomised | 309 | 315 | 313 | 302 |
| Completed | 192 (62.1%) | 213 (67.6%) | 215 (68.7%) | 218 (72.2%) |
| Discontinued | 117 | 102 | 98 | 84 |
| Lack of effect | 82 | 66 | 56 | 42 |
| AE | 13 | 15 | 18 | 21 |

Percentage of responders (according to ACR20 criteria) at 13 weeks

| | **N** | **% responders** | **Contrast with** | **Odds ratio** | **95% CI** | **p** |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 315 | 46.0 | Placebo | 1.20 | 0.87 1.66 | 0.262 |
| Lumiracoxib 400mg QD | 312 | 46.5 | Placebo | 1.69 | 0.88 1.69 | 0.225 |
| Celecoxib 200mg BD | 302 | 52.0 | Placebo | 1.51 | 1.09 2.09 | 0.013 |
| Placebo | 308 | 41.9 | | | | |

Overall RA pain intensity (VAS): Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg BD |
|---|---|---|---|---|
| N | 309 | 315 | 313 | 302 |
| Baseline | 69.6 | 69.2 | 70.9 | 70.8 |

| | | | | |
|---|---|---|---|---|
| Week 2 | - 13.6 | - 19.8 *** | - 22.4 *** | - 26.9 *** |
| Week 4 | - 18.9 | - 22.7 * | - 26.1 *** | - 28.8 *** |
| Week 8 | - 19.9 | - 23.7 * | - 26.5 ** | - 29.4 *** |
| Week 13 | - 20.3 | - 22.9 | - 25.6 * | - 28.7 *** |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

Patient's Assessment of Disease Activity (VAS): Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg BD |
|---|---|---|---|---|
| N | 309 | 315 | 313 | 302 |
| Baseline | 63.7 | 63.3 | 63.4 | 63.9 |
| Week 2 | - 9.2 | - 14.7 *** | - 16.6 *** | - 20.5 *** |
| Week 4 | - 13.9 | - 17.8 * | - 19.8 *** | - 22.1 *** |
| Week 8 | - 13.0 | - 16.4 * | - 19.9 *** | - 22.4 *** |
| Week 13 | - 14.9 | - 16.1 | - 19.5 * | - 22.3 *** |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

Physician's Assessment of Disease Activity (VAS): Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg BD |
|---|---|---|---|---|
| N | 309 | 315 | 313 | 302 |
| Baseline | 61.2 | 61.9 | 60.0 | 61.5 |
| Week 2 | - 14.5 | - 18.5 * | - 18.3 ** | - 25.0 *** |
| Week 4 | - 18.1 | - 21.9 * | - 21.8 ** | - 26.7 *** |
| Week 8 | - 20.2 | - 21.5 | - 22.8 * | - 26.0 ** |
| Week 13 | - 20.1 | - 20.8 | - 22.2 | - 26.3 ** |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

Swollen 66-joint Count: Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg BD |
|---|---|---|---|---|
| N | 308 | 315 | 312 | 302 |
| Baseline | 17.2 | 18.4 | 17.9 | 17.6 |
| Week 2 | - 6.1 | - 6.8 | - 7.0 | - 7.4 * |
| Week 4 | - 7.0 | - 7.7 | - 7.9 | - 8.2 |
| Week 8 | - 7.3 | - 8.0 | - 8.3 | - 8.0 |
| Week 13 | - 7.2 | - 7.5 | - 8.0 | - 8.2 |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

Tender 68-joint Count: Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg BD |
|---|---|---|---|---|
| N | 308 | 315 | 312 | 302 |
| Baseline | 27.8 | 28.7 | 28.5 | 27.3 |
| Week 2 | - 8.7 | - 9.4 | - 10.7 * | - 10.7 ** |
| Week 4 | - 9.9 | - 10.9 | - 11.4 | - 12.6 ** |
| Week 8 | - 10.8 | - 11.1 | - 12.8 | - 12.6 * |
| Week 13 | - 11.3 | - 11.1 | - 11.8 | - 13.4 * |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

**Conclusion:**
This study does NOT show lumiracoxib to be effective in RA.

**Applicant's summary of efficacy in study 0114**

The primary efficacy variable was response to treatment according to ACR20 criteria at 13 weeks. The ACR20 criteria were adjusted by re-classifying responders as non-responders those who took more than 5 grams of rescue medication in any 7-day period after the week-2 visit and were discontinued for unsatisfactory therapeutic effect at that visit. Main secondary efficacy parameters included response to treatment according to ACR20 criteria by visit and the individual components of the ACR20 composite variable.

At the primary endpoint of 13 weeks, the ACR20 response rates were not superior to placebo for either dose of lumiracoxib, although both doses were superior to placebo from week 2 to week 8. At week 13, numerical differences in favour of lumiracoxib 200mg and 400mg were observed with 46-47% of patients on lumiracoxib responding by ACR20 criteria versus 42% of placebo patients and 52% of patients taking celecoxib 200mg BD.

## 9.2 Study 0111

Objectives and design:
A 26-week multicentre, international, randomised, double blind, double-dummy, placebo controlled, parallel group study of 2 doses of lumiracoxib (200 and 400mg QD) in patients with rheumatoid arthritis using naproxen (500mg BD) as comparator.

The primary objective was to determine if lumiracoxib (200mg QD or 400mg QD) is effective in rheumatoid arthritis (RA) as compared to placebo with respect to the responder rate to the ACR20 criteria at 13 weeks.

The patient numbers were very similar in each treatment group:
- 280 in 200mg lumiracoxib group
- 281 in 400mg lumiracoxib group
- 279 in naproxen patients and
- 284 in placebo.

Inclusion/exclusion criteria:
Patients were males and females ≥18 years of age with a diagnosis of rheumatoid arthritis with symptoms for at least 3 months. Rheumatoid arthritis functional status was between I and III of the revised ACR criteria, and patients required regular non-steroidal anti-inflammatory drug (NSAID) therapy. At baseline, patients should have had (i) a minimum of 3 swollen joints and an increase of either 2 or 20% in the number of swollen joints since screening (whichever was greater), (ii) a minimum of 6 tender/painful joints and an increase of either 2 or 20% in the number of tender/ painful joints since screening (whichever was greater) and (iii) pain intensity of at least 40 mm on the visual analog scale (0-100mm VAS) during the previous 24 hours and an increase of either ≥20% or 10 mm in pain intensity since screening (whichever was greater).

**Efficacy:**
Primary efficacy parameters:
Response to treatment according to the ACR20 criteria at 13 weeks (changed from 26 weeks after a protocol amendment) with lumiracoxib 200mg QD or 400mg QD compared with placebo, in the ITT population.

*Note: The primary endpoint was changed from 26 weeks to 13 weeks during a protocol amendment in October 2001 because the first phase of the above study 0114 had an unexpectedly high placebo response rate over 13 weeks, possibly due to aggressive use of concomitant medications. It was thought that this would be even more marked over 26 weeks.*

Secondary efficacy parameters:

The individual ACR20 components were secondary efficacy variables and include swollen 66-joint and tender 68-joint (tender includes hips) counts, patient's overall assessment of rheumatoid arthritis pain, patient's and physician's global assessment of disease activity, CRP level and HAQ standard disability index (SDI) score.

Further secondary variables were time to first response to treatment according to the ACR20 criteria, sustained response to treatment according to the ACR20 criteria, response to treatment according to the modified ACR50 criteria, time to discontinuation due to unsatisfactory effect, rescue medication use and RAQoL Rheumatoid Arthritis Quality of Life questionnaire.

**Duration of treatment:**
26 weeks

**Results:**
Patient Disposition

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|---|
| Randomised | 284 | 280 | 281 | 279 |
| Completed | 158 (55.6%) | 194 (69.3%) | 181 (64.4%) | 192 (68.8%) |
| Discontinued | 126 | 86 | 100 | 87 |
| Lack of effect | 93 | 49 | 52 | 42 |
| AE | 20 | 20 | 28 | 30 |

Percentage of responders (according to ACR20 criteria) at 13 weeks

| | **N** | **% responders** | **Contrast with** | **Odds ratio** | **95% CI** | **p** |
|---|---|---|---|---|---|---|
| **Lumiracoxib 200mg QD** | 280 | 41.1 % | **Lumiracoxib 400mg QD** | 0.94 | 0.66 1.32 | **0.703** |
| Lumiracoxib 200mg QD | 280 | 41.1 % | Naproxen 500mg BD | 1.08 | 0.76 1.53 | 0.654 |
| **Lumiracoxib 200mg QD** | 280 | 41.1 % | **Placebo** | 1.48 | 1.04 2.11 | **0.031** |
| Lumiracoxib 400mg QD | 281 | 42.7 % | Naproxen 500mg BD | 1.16 | 0.82 1.64 | 0.407 |
| **Lumiracoxib 400mg QD** | 281 | 42.7 % | **Placebo** | 1.58 | 1.11 2.25 | **0.011** |
| Naproxen 500mg BD | 279 | 39.1 % | Placebo | 1.36 | 0.96 1.95 | 0.087 |
| Placebo | 284 | 32.4 % | | | | |

Percentage of responders (according to ACR20 criteria): Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|---|
| N | 284 | 280 | 281 | 279 |
| Week 2 | 20.1 | 31.8 ** | 34.5 *** | 31.2 ** |
| Week 4 | 27.1 | 36.1 * | 42.7 *** | 41.6 *** |
| Week 13 | 32.4 | 41.1 * | 42.7 * | 39.1 |
| Week 20 | 31.3 | 39.3 * | 38.1 | 35.8 |
| Week 26 | 31.0 | 43.2 ** | 36.7 | 40.1 * |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

Percentage of responders (according to ACR20 criteria) at 26 weeks
*This is pre-amendment to protocol analysis.*

| | N | % responders | Contrast with | Odds ratio | 95% CI | p |
|---|---|---|---|---|---|---|
| **Lumiracoxib 200mg QD** | 280 | 47.1 | **Lumiracoxib 400mg QD** | 1.30 | 0.66 1.32 | **0.133** |
| Lumiracoxib 200mg QD | 280 | 47.1 | Naproxen 500mg BD | 1.25 | 0.76 1.53 | 0.204 |
| **Lumiracoxib 200mg QD** | 280 | 47.1 | **Placebo** | 1.90 | 1.04 2.11 | **< 0.001** |
| Lumiracoxib 400mg QD | 281 | 40.9 | Naproxen 500mg BD | 0.96 | 0.82 1.64 | 0.818 |
| **Lumiracoxib 400mg QD** | 281 | 40.9 | **Placebo** | 1.46 | 1.11 2.25 | **0.037** |
| Naproxen 500mg BD | 279 | 41.6 | Placebo | 1.52 | 0.96 1.95 | 0.021 |
| Placebo | 284 | 32.4 | | | | |

Overall RA pain intensity (VAS): Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|---|
| N | 283 | 279 | 281 | 279 |
| Baseline | 68.2 | 67.3 | 67.7 | 67.9 |
| Week 2 | 51.16 | 45.41 *** | 44.86 *** | 44.91 *** |
| Week 4 | 48.47 | 41.89 *** | 41.01 *** | 42.43 *** |
| Week 13 | 47.43 | 41.05 ** | 42.21 ** | 43.21 * |
| Week 20 | 48.32 | 40.44 *** | 41.75 *** | 42.80 ** |
| Week 26 | 48.01 | 39.73 *** | 42.35 ** | 42.61 ** |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

Patient's Assessment of Disease Activity (VAS): Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|---|
| N | 282 | 279 | 280 | 279 |
| Baseline | 60.5 | 61.1 | 61.4 | 62.7 |
| Week 2 | 53.71 | 45.26 *** | 44.92 *** | 45.24 *** |
| Week 4 | 49.76 | 41.89 *** | 41.44 *** | 41.81 *** |
| Week 13 | 48.68 | 42.32 *** | 43.04 ** | 43.10 ** |
| Week 20 | 49.07 | 41.83 *** | 42.94 *** | 42.11 *** |
| Week 26 | 48.81 | 41.18 *** | 43.42 ** | 42.49 *** |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

Physician's Assessment of Disease Activity (VAS): Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|---|
| N | 284 | 280 | 279 | 279 |
| Baseline | 56.1 | 55.8 | 56.3 | 56.8 |
| Week 2 | 45.39 | 41.40 ** | 39.32 *** | 38.77 *** |
| Week 4 | 42.62 | 37.77 *** | 37.15 *** | 36.30 *** |
| Week 13 | 41.42 | 38.00 * | 37.01 ** | 36.44 ** |
| Week 20 | 42.59 | 37.74 ** | 36.37 *** | 36.13 *** |
| Week 26 | 41.93 | 37.03 ** | 37.91 * | 35.74 *** |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

Swollen 66-joint Count: Change over time

| | Placebo | Lumiracoxib | Lumiracoxib | Naproxen |
|---|---|---|---|---|

| | | 200mg QD | 400mg QD | 500mg BD |
|---|---|---|---|---|
| N | 284 | 280 | 281 | 279 |
| Baseline | 15.0 | 15.3 | 15.5 | 14.9 |
| Week 2 | 9.87 | 8.14 *** | 8.43 ** | 8.46 ** |
| Week 4 | 9.22 | 7.04 *** | 7.49 *** | 7.68 ** |
| Week 13 | 8.43 | 6.79 ** | 7.09 * | 7.85 |
| Week 20 | 8.72 | 6.57 *** | 6.57 *** | 7.54 * |
| Week 26 | 8.90 | 6.86 *** | 7.19 ** | 7.44 ** |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

Tender 68-joint Count: Change over time

| | Placebo | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|---|
| N | 284 | 280 | 281 | 279 |
| Baseline | 25.7 | 25.8 | 26.2 | 25.7 |
| Week 2 | 18.56 | 16.11 *** | 16.28 *** | 15.63 *** |
| Week 4 | 17.49 | 14.14 *** | 14.84 *** | 14.27 *** |
| Week 13 | 16.28 | 13.39 *** | 14.26 * | 14.36 * |
| Week 20 | 16.60 | 12.82 *** | 13.87 ** | 13.97 ** |
| Week 26 | 17.01 | 13.14 *** | 14.04 *** | 13.97 *** |

p versus placebo: * < 0.05. ** < 0.01 and *** < 0.001

**Conclusions:**
For the primary endpoint of efficacy at 13 weeks, both doses of lumiracoxib were significantly superior to placebo with no difference between the two doses (200mg QD and 400mg QD). The responder rate was numerically superior for 400mg dose (42.7% versus 41.1%). At 26 weeks, however, the responder arte was numerically superior for 200mg dose (43.2% versus 36.7%).

When the primary efficacy endpoint is considered according to the originally defined ACR criteria, the response rate was still numerically superior for 200mg dose (47.1% versus 40.9%).

For most of the other endpoints, 200mg is numerically superior to 400mg dose.

**Applicant's summary of efficacy in study 0111**
The primary efficacy variable was response to treatment according to ACR20 criteria at 13 weeks. The ACR20 criteria were adjusted by re-classifying as non-responders those who took more than 5 grams of rescue medication in any 7-day period after the week-2 visit, discontinued due to insufficient efficacy before or at the week-13 visit, or who started or raised the dose of 1 or more medications expected to influence their ACR20 assessment. Main secondary efficacy parameters included response to treatment according to ACR20 criteria at other time points and the components of the ACR20 composite variable.

At 13 weeks the ACR20 response rates were superior to placebo for both doses of lumiracoxib but not for naproxen. The superiority of lumiracoxib to placebo was seen from week 2 to week 13, was maintained with 200mg lumiracoxib until 26 weeks but statistical (not numerical) superiority was lost after week 13 with 400mg lumiracoxib, due to a small decrease in response rates after week 13.

## 9.3 Study 0110

This is primarily a gastrointestinal safety study.
Its duration was 13-weeks.

The primary efficacy results are summarised below.

| | Lumiracoxib **400mg** QD | Lumiracoxib **800mg** QD | Celecoxib 200mg BD | Ibuprofen 800mh TDS |
|---|---|---|---|---|
| N | 227 | 227 | 223 | 216 |
| | **Patient Joint Pain Intensity** | | | |
| % Improved | 23.8 | 18.9 | 27.8 | 25.5 |
| p vs ibuprofen | 0.683 | 0.100 | 0.580 | |
| p vs celecoxib | 0.332 | **0.027** | | |
| p vs L 800mg | 0.210 | | | |
| | **Patient Global Assessment** | | | |
| % Improved | 20.7 | 26.0 | 30.0 | 25.0 |
| p vs ibuprofen | 0.283 | 0.811 | 0.239 | |
| p vs celecoxib | **0.024** | 0.340 | | |
| p vs L 800mg | 0.185 | | | |
| | **Physician Global Assessment** | | | |
| % Improved | 21.1 | 18.1 | 22.0 | 23.1 |
| p vs ibuprofen | 0.613 | 0.187 | 0.769 | |
| p vs celecoxib | 0.831 | 0.301 | | |
| p vs L 800mg | 0.409 | | | |

| | Lumiracoxib **400mg** QD | Lumiracoxib **800mg** QD | Celecoxib 200mg BD | Ibuprofen 800mh TDS |
|---|---|---|---|---|
| N | 227 | 227 | 223 | 216 |
| | **Swollen 28-joint count** | | | |
| Baseline | 8.9 | 9.7 | 9.4 | 9.5 |
| End of study | 6.0 | 6.9 | 5.8 | 6.5 |
| **Change** | **- 2.9** | **- 2.8** | **- 3.6** | **- 3.0** |
| | **Tender 28-joint count** | | | |
| Baseline | 12.3 | 12.6 | 12.5 | 13.5 |
| End of study | 8.2 | 8.4 | 7.5 | 8.8 |
| Change | **- 4.1** | **- 4.1** | **- 5.0** | **- 4.7** |

The study was powered only for comparison between lumiracoxib and ibuprofen in respect of cumulative incidence of endoscopically detected gastroduodenal ulcers up to the end of the study.

It is noted that although this study was not powered to evaluate efficacy differences between the three drugs, it has thrown up statistically significant differences between:

- Celecoxib and 400mg lumiracoxib, in favour of celecoxib
- Celecoxib and 800mg lumiracoxib, in favour of celecoxib

In terms of joint counts, celecoxib and ibuprofen was consistently superior numerically to either doses of lumiracoxib.

**Conclusion:**
This study casts further questions on the efficacy of lumiracoxib in RA with no evidence of any dose-response relationship between the two doses.

## Applicant's Overall Summary of Efficacy in RA

All studies, both short-term and long-term, both supportive and major, showed efficacy.

In study 0111, lumiracoxib 200mg and 400mg, taken once a day in the morning were both found to be statistically significantly superior to placebo for treatment of RA according to response to treatment by ACR20 criteria at 2, 4, and 13 weeks. Both doses significantly reduced RA pain at 2, 4 and 13 weeks and significantly improved HAQ SDI at 4 weeks. Only the 400mg dose achieved significant improvement of HAQ SDI at 13 weeks.

In study 0114, lumiracoxib 200mg and 400mg, taken once a day in the morning, were found to be statistically significantly superior to placebo with respect to response to treatment by ACR20 criteria at 2 and 4 weeks but not at 13 weeks. Both doses statistically significantly reduced RA pain at 2, 4 and 8 weeks but only the 400mg dose produced significant RA pain relief at 13 weeks. With respect to HAQ SDI, lumiracoxib 400mg achieved statistically significant reductions in scores at 2, 4, 8 and 13 weeks, whereas the 200mg dose produced only marginally significant reductions at weeks 2 and 4.

The combined efficacy analyses on the pooled 0111 and 0114 dataset provide conclusive evidence that lumiracoxib 200mg QD and 400mg QD are effective at 2, 4 and 13 weeks for treating the signs and symptoms of RA in terms of ACR20 response to treatment, RA pain, and HAQ SDI (not significant for 200mg QD at 13 weeks). The higher dose of 400mg QD provides some additional benefit especially at the beginning of therapy (2 to 4 weeks). However, at later time points there are no relevant differences between the two doses.

ACR20 response rates, reduction of RA pain, improvement in patient's physical function (from HAQ SDI scores) and reduction of patient's disease activity were maintained for the whole of the 26 weeks of treatment with lumiracoxib 200mg QD in study 0111.

Lumiracoxib 200mg and 400mg QD tended to reduced joint tenderness and/or swelling and significantly improved patient's and physician's global assessments of disease activity over 13 weeks.

Lumiracoxib doses of 200mg QD and 400mg QD were comparable to naproxen 500mg BD (study 0111) and ibuprofen 800mg TID [study 0110] but somewhat less effective than celecoxib 200mg BD [study 0114, study 0110].

Subgroup analysis using the pooled dataset showed that efficacy of lumiracoxib with respect to placebo was not affected by age group, or BMI category, or disease duration. In general, greater efficacy was seen in patients with a high baseline disease severity.

Statistically significant treatment effects were seen in terms of RA pain (200mg QD and 400mg QD) and HAQ SDI (200mg QD) in both males and females. With respect to ACR20 response to treatment, clear treatment effects were seen in males (200mg QD and 400mg QD) but efficacy was reduced in females especially in female Hispanics.

There were no clear trends in the size of treatment differences between the subgroups in the analysis by concomitant use of methotrexate and/or corticosteroids.

No additional efficacy was obtained from lumiracoxib doses of 800mg QD and 1200mg QD compared with 400mg QD [studies 0110 and 2312].

### *Assessor's Comments on Efficacy of lumiracoxib in Rheumatoid arthritis:*

It is concluded that:

- The efficacy of lumiracoxib in RA is questionable – there is no consistent evidence of efficacy or its durability.

- The dose selection studies (0105 and 2312) had investigated doses ranging from 50mg BD to 1200mg QD. No dose of lumiracoxib has been found to be effective in RA. Although 800mg and 1200mg QD doses did not differ significantly from naproxen

500mg BD, it is difficult to identify a dose of lumiracoxib which is superior to placebo.

- In the two major well-controlled studies, one failed to produce any evidence of efficacy (0114) while the other showed that the lower dose (200mg QD) was more effective than the higher dose of 400mg QD.

- When the data from the two major well-controlled studies are combined, the pooled results are statistically significant for the primary endpoint but the findings are driven by one (smaller) study and show the lack of consistency between the two studies. Even the combined results show lack of statistical significance for 4 secondary parameters on 200mg dose and 1 secondary parameter on 400mg dose.

At 13 weeks

| | Study 0111 | Study 0114 | Studies 0111 + 0114 |
|---|---|---|---|
| | **Lumiracoxib 200mg QD** | | |
| N = | 280 | 315 | 595 |
| ACR20 | SS | NOT S | SS |
| RA Pain | SS | NOT S | SS |
| HAQ-SDI | NOT S | NOT S | NOT S |
| Tender joint count | SS | NOT S | NOT S |
| Swollen joint count | SS | NOT S | NOT S |
| Patient Global Ass-t | SS | NOT S | SS |
| Physician Global Ass-t | SS | NOT S | NOT S |
| | **Lumiracoxib 400mg QD** | | |
| N = | 281 | 312 | 593 |
| ACR20 | SS | NOT S | SS |
| RA Pain | SS | SS | SS |
| HAQ-SDI | SS | SS | SS |
| Tender joint count | SS | NOT S | NOT S |
| Swollen joint count | SS | NOT S | SS |
| Patient Global Ass-t | SS | SS | SS |
| Physician Global Ass-t | SS | NOT S | SS |

SS = Statistically significant NOT S = Not statistically significant

## 10. EFFICACY IN PRIMARY DYSMENORRHOEA

There are a total of 2 studies (0129, 0130) investigating the efficacy of lumiracoxib in primary dysmenorrhoea.

**Controlled trials in primary dysmenorrhoea**

2 large, controlled phase III trials:
- 2 major efficacy trials [0129 and 0130]

### 10.1 Study 0129

Objectives and design:
A multicentre, randomised, double blind, double-dummy, placebo-controlled, complete-block crossover trial assessing the analgesic effects of lumiracoxib in women with primary dysmenorrhoea using rofecoxib as a comparator

The primary objective was to determine whether a single dose of lumiracoxib 400mg is effective in treating moderate to severe menstrual pain in women with primary dysmenorrhoea. The secondary objectives were (a) to compare the efficacy of a single dose of lumiracoxib 400mg with a single dose of rofecoxib 50mg for the treatment of moderate to severe menstrual pain in women with primary dysmenorrhoea (b) to compare the efficacy of

lumiracoxib 400mg QD with rofecoxib 50mg QD and with placebo, when administered from the onset of moderate to severe menstrual pain for up to 3 days in women with primary dysmenorrhoea;

Patients were randomised to one of six treatment sequences of lumiracoxib, rofecoxib and placebo, thus receiving the three treatments in three different menstrual periods.

Study medication was administered for up to 3 days starting at the onset of moderate to severe menstrual pain. Rescue medication (acetaminophen 500mg) was allowed, but not until at least one hour (after the 60 minute pain assessment) after the first dose of study medication in each treatment period. Pain assessments were collected up to 12 hours after the first dose on the first day of each treatment period. Thereafter, patients were allowed to take study medication for up to 3 days (24 and/or 48 hours), if needed. A patient global assessment of treatment was performed 72 hours (3 days) after the initial dose in each treatment period.

Inclusion/exclusion criteria:
Females ≥ 18 years with self-reported history of moderate to severe primary dysmenorrhoea; no evidence by gynaecologic examination of other cause of dysmenorrhoea within 1 year prior to entry; healthy based on medical history, examination, and laboratory tests.

**Efficacy:**
The primary efficacy variable was the Summed (time-weighted) Pain Intensity Difference (SPID8) calculated over the 0 to 8 hour time period on Day 1 of a treatment period.

Secondary efficacy variables were:
- SPID12 calculated over 0 to 12 hours on Day 1 of a treatment period
- Time-specific pain intensity difference (PID) based on the categorical scale at time points up to 12 hours after dosing on Day 1 of a treatment period
- Time-specific pain relief (PR) based on the categorical scale at time points up to 12 hours after dosing on Day 1 of a treatment period
- Time-specific pain relief intensity difference (PRID) based on the categorical scale at time points up to 12 hours after dosing on Day 1 of a treatment period
- Time-specific PID based on the visual analog scale (VAS) at time points up to 12 hours after dosing on Day 1 of a treatment period
- Total (time-weighted) pain relief from 0 to 8 hours (TOTPAR-8) and from 0 to 12 hours (TOTPAR-12) on Day 1 of a treatment period
- Time-to-rescue medication use (measured up to 12 hours on Day 1 of a treatment period)
- Patient global evaluation (measured at the end of Day 3 of a treatment period)
- Time-to-onset of analgesia (defined as the earliest time point at which PID (VAS) was statistically significantly different from placebo)

**Duration of treatment:**
Patients took the study medication in each of the 3 cycles, starting at the onset of moderate to severe dysmenorrhoea. After the first dose, patients were permitted to take a dose for a total of 3 days.

**Results:**
Patient Disposition L=lumiracoxib; R=rofecoxib; P=placebo

| **Sequence →** | L/R/P | L/P/R | R/L/P | R/P/L | P/L/R | P/R/L |
|---|---|---|---|---|---|---|
| Randomised | 16 | 15 | 13 | 13 | 14 | 15 |
| Completed | 14 | 14 | 12 | 10 | 13 | 14 |
| Discontinued | 2 | 1 | 1 | 3 | 1 | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Lack of effect | - | - | - | - | - | - |
| AE | - | - | 1 | - | - | - |

SPID8 (ITT population)

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 400mg QD | 78 | 11.32 | Placebo | 4.66 | 2.81<br>6.51 | < 0.001 |
| Rofecoxib 50mg QD | 80 | 11.31 | Lumiracoxib 400mg QD | 0.01 | - 1.82<br>1.85 | 0.988 |
| Placebo | 78 | 6.66 | Rofecoxib 50mg QD | 4.65 | 2.81<br>6.48 | < 0.001 |

Mean Time-specific PID based on the visual analog scale (VAS) at time points up to 12 hours after dosing on Day 1 of a treatment period (ITT population, LOCF)

| | Assessment Time Points (hrs) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 12 |
| Lumiracoxib 400mg QD | 6.0 | 15.1 | 23.6 * | 32.0 * | 43.1 * | 47.9 * | 51.4 * | 52.6 * | 51.0 * | 50.6 * | 43.2 * |
| Rofecoxib 50mg QD | 6.0 | 17.9 ** | 26.5 * | 34.6 * | 39.8 * | 43.4 * | 45.9 * | 48.0 * | 48.8 * | 49.2 * | 47.5 * |
| Placebo | 5.0 | 11.7 | 16.7 | 19.5 | 22.7 | 25.1 | 26.2 | 27.4 | 27.0 | 27.4 | 26.4 |

* $p < 0.05$ vs placebo but NOT versus each other ** $p < 0.05$ vs placebo

Time-to-rescue medication use (measured up to 12 hours on Day 1 of a treatment period)

| ITT population | Placebo | Lumiracoxib 400mg QD | Rofecoxib 50mg QD |
|---|---|---|---|
| N = | 79 | 80 | 82 |
| N taking rescue medication | 32 (40.5 %) | 15 (18.8 %) | 10 (12.2 %) |
| Median time to rescue medication | > 12 hours | > 12 hours | > 12 hours |

Patient global evaluation (measured at the end of Day 3 of a treatment period)

| ITT population | Placebo | Lumiracoxib 400mg QD | Rofecoxib 50mg QD |
|---|---|---|---|
| Poor | 34.2 % | 2.5 % | 3.7 % |
| Fair | 15.2 % | 11.3 % | 9.8 % |
| Good | 16.5 % | 30.0 % | 14.6 % |
| Excellent | 8.9 % | 30.0 % | 46.3 % |
| Not done | 25.3 % | 26.3 % | 25.6 % |
| p vs rofecoxib | | 0.510 | |
| p vs placebo | | < 0.001 | < 0.001 |

**Conclusion:**
A single 400mg dose of lumiracoxib is effective in treating the symptoms of primary dysmenorrhoea.

Lumiracoxib 400mg QD was found to be equivalent to rofecoxib 50mg QD, and superior to placebo, with regard to all other endpoints.

## 10.2 Study 0130

Objectives and design:
A multicentre, randomised, double blind, double-dummy, placebo-controlled, complete-block crossover trial assessing the analgesic effects of lumiracoxib in women with primary dysmenorrhoea using naproxen as a comparator

The primary objective was to determine whether a single dose of lumiracoxib 400mg is effective in treating moderate to severe menstrual pain in women with primary dysmenorrhoea. The secondary objectives were (a) to compare the efficacy of a single dose of lumiracoxib 400mg with naproxen 500mg BD for the treatment of moderate to severe menstrual pain in women with primary dysmenorrhoea (b) to compare the efficacy of lumiracoxib 400mg QD with naproxen 500mg BD. and with placebo, when administered from the onset of moderate to severe menstrual pain for up to 3 days in women with primary dysmenorrhoea;

Patients were randomised to one of six treatment sequences of lumiracoxib, naproxen and placebo, thus receiving the three treatments in three different menstrual periods.

Study medication was administered for up to 3 days starting at the onset of moderate to severe menstrual pain. Rescue medication (acetaminophen 500mg) was allowed, but not until at least one hour (after the 60 minute pain assessment) after the first dose of study medication in each treatment period. Pain assessments were collected up to 12 hours after the first dose on the first day of each treatment period. Thereafter, patients were allowed to take study medication for up to 3 days (24 and/or 48 hours), if needed. A patient global assessment of treatment was performed 72 hours (3 days) after the initial dose in each treatment period.

Inclusion/exclusion criteria:
Females ≥ 18 years with self-reported history of moderate to severe primary dysmenorrhoea; no evidence by gynaecologic examination of other cause of dysmenorrhoea within 1 year prior to entry; healthy based on medical history, examination, and laboratory tests.

**Efficacy:**
The primary efficacy variable was the Summed (time-weighted) Pain Intensity Difference (SPID8) calculated over the 0 to 8 hour time period on Day 1 of a treatment period.

Secondary efficacy variables were:
- SPID12 calculated over 0 to 12 hours on Day 1 of a treatment period
- Time-specific pain intensity difference (PID) based on the categorical scale at time points up to 12 hours after dosing on Day 1 of a treatment period
- Time-specific pain relief (PR) based on the categorical scale at time points up to 12 hours after dosing on Day 1 of a treatment period
- Time-specific pain relief intensity difference (PRID) based on the categorical scale at time points up to 12 hours after dosing on Day 1 of a treatment period
- Time-specific PID based on the visual analog scale (VAS) at time points up to 12 hours after dosing on Day 1 of a treatment period
- Total (time-weighted) pain relief from 0 to 8 hours (TOTPAR-8) and from 0 to 12 hours (TOTPAR-12) on Day 1 of a treatment period
- Time-to-rescue medication use (measured up to 12 hours on Day 1 of a treatment period)
- Patient global evaluation (measured at the end of Day 3 of a treatment period)
- Time-to-onset of analgesia (defined as the earliest time point at which PID (VAS) was statistically significantly different from placebo)

**Duration of treatment:**

Patients took the study medication in each of the 3 cycles, starting at the onset of moderate to severe dysmenorrhoea. After the first dose, patients were permitted to take a dose for a total of 3 days.

**Results:**

Patient Disposition L=lumiracoxib; N=naproxen; P=placebo

| **Sequence →** | L/N/P | L/P/N | N/L/P | N/P/L | P/L/N | P/N/L |
|---|---|---|---|---|---|---|
| Randomised | 20 | 16 | 18 | 18 | 19 | 18 |
| Completed | 14 | 11 | 12 | 13 | 15 | 10 |
| Discontinued | 6 | 5 | 6 | 5 | 4 | 8 |

SPID8 (ITT population)

| | **N** | **LS Mean** | **Contrast with** | **Estimated difference** | **95% CI** | **p** |
|---|---|---|---|---|---|---|
| Lumiracoxib 400mg QD | 81 | 9.86 | Placebo | 3.38 | 1.73<br>5.04 | < 0.001 |
| Naproxen 500mg BD | 88 | 11.04 | Lumiracoxib 400mg QD | - 1.18 | - 2.83<br>0.47 | 0.159 |
| Placebo | 88 | 6.47 | Naproxen 500mg BD | 4.57 | 2.95<br>6.18 | < 0.001 |

Mean Time-specific PID based on the visual analog scale (VAS) at time points up to 12 hours after dosing on Day 1 of a treatment period (ITT population, LOCF)

| | Assessment Time Points (hrs) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 12 |
| Lumiracoxib 400mg QD | 4.5<br>A | 14.4<br>AB | 21.4<br>B | 25.0<br>B | 32.3<br>AB | 36.9<br>A | 36.1<br>A | 37.2<br>A | 37.0<br>A | 36.3<br>A | 32.4<br>A |
| Naproxen 500mg BD | 7.3<br>A | 20.3<br>A | 29.9<br>A | 37.1<br>A | 40.0<br>A | 41.4<br>A | 41.7<br>A | 42.8<br>A | 41.7<br>A | 41.6<br>A | 35.1<br>A |
| Placebo | 3.8<br>A | 9.7<br>B | 15.7<br>B | 16.6<br>C | 20.7<br>C | 21.8<br>B | 23.0<br>B | 22.9<br>B | 22.1<br>B | 21.9<br>B | 19.7<br>B |

At each time point, the two treatments carrying the same letter are NOT significantly different from each other at $p < 0.05$.

Time-to-rescue medication use (measured up to 12 hours on Day 1 of a treatment period)

| ITT population | Placebo | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|
| N = | 88 | 83 | 89 |
| N taking rescue medication | 34 (38.6 %) | 19 (22.9 %) | 15 (16.9 %) |
| Median time to rescue medication | > 12 hours | > 12 hours | > 12 hours |

Patient global evaluation (measured at the end of Day 3 of a treatment period)

| ITT population | Placebo | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|
| Poor | 26.1 % | 14.5 % | 15.7 % |
| Fair | 23.9 % | 22.9 % | 18.0 % |
| Good | 22.7 % | 25.3 % | 21.3 % |
| Excellent | 3.4 % | 19.3 % | 25.8 % |
| Not done | 23.9 % | 18.1 % | 19.1 % |
| p vs naproxen | | 0.363 | |
| p vs placebo | | 0.003 | < 0.001 |

**Conclusion:**
A single 400mg dose of lumiracoxib is effective in treating the symptoms of primary dysmenorrhoea.

Lumiracoxib 400mg QD was found to be statistically equivalent to naproxen 500mg BD, and superior to placebo, with regard to all other endpoints. However, naproxen was numerically superior to lumiracoxib.

***Assessor's Comments on Efficacy of lumiracoxib in Primary dysmenorrhoea:***
A single 400mg dose of lumiracoxib is effective in treating the symptoms of primary dysmenorrhoea.

Lumiracoxib 400mg QD was found to be statistically equivalent to rofecoxib 50mg QD or naproxen 500mg BD, and superior to placebo, with regard to all other endpoints. However, naproxen was numerically superior to lumiracoxib.

The indication should be restricted to the population studied (that is, patients with moderate to severe primary dysmenorrhoea).

## 11. EFFICACY IN ACUTE PAIN

There are a total of 5 studies (0115, 2302, 0131, 0132 and 0103) investigating the efficacy of lumiracoxib in acute pain, using two models – post dental surgery and post-orthopaedic surgery.

**Controlled trials in acute pain**

5 large, controlled phase III trials:
- 2 major efficacy trials [0115 and 2302] in post-dental surgery pain
- 1 supportive efficacy trial [0103] in post-dental surgery pain
- 2 major efficacy trials [0131 and 0132] in post-orthopaedic surgery pain

**Please note:**
Studies 0115 and 0103 have been discussed earlier in sections 7.3 of this Assessment Report.

The remaining 3 studies – 2302 in post-dental surgery pain patients and 0131 and 0132 in post-orthopaedic surgery pain patients will be discussed here.

### 11.1 Study 2302 in post-dental surgery pain

Objectives and design:
A double blind, randomised, double-dummy, parallel group, single centre trial comparing the analgesic effects of a single dose of lumiracoxib, rofecoxib, celecoxib, and placebo in the treatment of postoperative dental pain.

The primary objective of this study was to determine if a single dose of lumiracoxib 400mg, when administered following the removal of 2 or more impacted third molar teeth, was effective in relieving pain when compared to placebo with respect to Summed (time-weighted) Pain Intensity Difference based on the categorical scale calculated over the 0-8 hour time period (SPID-8).

A total of 355 patients were randomised:
101 to lumiracoxib,

102 to rofecoxib,
101 to celecoxib, and
51 to placebo.

In order to have a sufficient number of patients for the comparison between the COX189 and rofecoxib groups for the primary efficacy analysis, the pooled ITT population from studies 0115 and 2302 was used.

Inclusion/exclusion criteria:
Patients were males or non-pregnant, non-lactating females 17 years of age or older who required an analgesic due to moderate to severe pain from extraction of 2 or more impacted (partial or full) third molars (1 had to be mandibular), and who had not received any analgesic medication from 48 hours prior to surgery until the patient completed the study.

Efficacy:
Primary efficacy was assessed by the Summed (time-weighted) Pain Intensity Difference calculated over the 0-8 hour time period (SPID-8).

Secondary efficacy measures included:
- time-specific Pain Intensity Difference (PID), Pain Relief (PR) and PRID (combined PR and PID) based on categorical scales and time-specific PID based on the visual analog scale (VAS) at time points up to 24 hours after dosing, and total (time-weighted) PR from 0-8 hours (TOTPAR-8).
- time-to-onset of analgesia,
- time-to-rescue medication intake, and
- patient global evaluation were also assessed.

**Duration of treatment:**
Patients received one dose of study medication on Day 0 of Visit 2.

**Results:**
Patient Disposition

| | Placebo | Lumiracoxib 400mg | Rofecoxib 50mg | Celecoxib 200mg |
|---|---|---|---|---|
| Randomised | 51 | 101 | 102 | 101 |
| Completed | 0 | 16 | 24 | 13 |
| Discontinued | 51 | 85 | 78 | 88 |

SPID8 (ITT population)

| | Placebo | Lumiracoxib 400mg | Rofecoxib 50mg | Celecoxib 200mg |
|---|---|---|---|---|
| | **Study 2302** | | | |
| Mean | - 3.85 | 6.04 | 4.86 | 1.36 |
| p vs Placebo | | < 0.001 | | |
| p vs rofecoxib | | 0.048 | | |
| p vs celecoxib | | < 0.001 | | |
| | **Studies 2302 + 0115** | | | |
| Mean | - 3.59 | 6.47 | 5.12 | |

Time to onset of analgesia

| | N | Median time (h) | 95 % CI |
|---|---|---|---|
| Placebo | 51 | > 12 | |
| Lumiracoxib 400mg | 101 | 0.66 | 0.513, 0.899 |
| Rofecoxib 50mg | 102 | 0.85 | 0.717, >12 |

| | | | |
|---|---|---|---|
| Celecoxib 200mg | 101 | > 12 | 1.016, >12 |

TOTPAR8

| | N | LS Mean | p value for comparison | |
|---|---|---|---|---|
| Placebo | 51 | 2.43 | | |
| Lumiracoxib 400mg | 101 | 15.32 | 0.074<br>< 0.001<br>< 0.001 | vs rofecoxib<br>vs celecoxib<br>vs placebo |
| Rofecoxib 50mg | 102 | 12.96 | 0.004<br>< 0.001 | vs celecoxib<br>vs placebo |
| Celecoxib 200mg | 101 | 9.12 | < 0.001 | vs placebo |

Time to rescue medication

| | N | Median time (h) | 95 % CI |
|---|---|---|---|
| Placebo | 51 | 1.25 | 1.17, 11.38 |
| Lumiracoxib 400mg | 101 | 7.15 | 6.23, 8.57 |
| Rofecoxib 50mg | 102 | 3.80 | 2.37, 9.18 |
| Celecoxib 200mg | 101 | 2.04 | 1.48, 3.37 |

Patient Global Assessment (%)

| | Placebo | Lumiracoxib 400mg | Rofecoxib 50mg | Celecoxib 200mg |
|---|---|---|---|---|
| Randomised | 51 | 101 | 102 | 101 |
| Poor | 78.4 | 20.8 | 26.5 | 48.5 |
| Fair | 15.7 | 19.8 | 20.6 | 18.8 |
| Good | 2.0 | 27.7 | 26.5 | 18.8 |
| Excellent | 2.0 | 31.7 | 25.5 | 13.9 |
| N/A | 2.0 | 0 | 1.0 | 0 |

The data show that a single dose of lumiracoxib 400mg provides an effective analgesia in post-dental surgery pain.

## 11.2 Study 0131 in post-orthopaedic surgery pain

Objectives and design:
A multicentre, randomised, double blind, double-dummy, active-comparator (naproxen), placebo-controlled, parallel group trial assessing the analgesic effect of lumiracoxib 400mg QD in the treatment of post-surgical pain following total knee or hip arthroplasty.

The primary objective was t to determine whether a single oral dose of lumiracoxib 400mg QD is effective in patients with moderate to severe post-surgical pain following total knee or hip arthroplasty.

Secondary objectives were to assess the efficacy of multiple doses of lumiracoxib 400mg QD in comparison to naproxen 500mg BD and placebo in patients with post-surgical pain following total knee or hip arthroplasty for up to five days.

This was a double blind, randomised, double-dummy, active-comparator, placebo-controlled study consisting of 2 phases: a 12-hour single-dose analgesic evaluation followed by a multiple-dose analgesic evaluation over 5 days (or until discontinuation). Following total primary unilateral knee or hip arthroplasty, patient controlled analgesia (PCA) was stopped within 48 hours after surgery and eligible patients were randomised to receive either lumiracoxib 400mg QD, naproxen 500mg BD or matching placebo.

The study enrolled 180 randomised patients (60 per treatment group).

Inclusion/exclusion criteria:
Male and female patients aged 18-80 years, and weighing >100 lbs. (45.4 kg) who had undergone total knee or hip arthroplasty.

Key inclusion criteria: Physical status PS 1-3 (ASA Physical status classification system), moderate to severe baseline post-operative pain (≥ 2 on 0-3 point scale) within 6 hours after the last PCA dose and within 48 hours after surgery.

Key exclusion criteria:
A history or presence of nasal polyps, bronchospasm or angioedema induced by NSAIDS, known hypersensitivity to naproxen, aspirin, acetaminophen, hydrocodone, morphine or antipyretics or with allergies manifested by attacks of asthma, urticaria or acute rhinitis following treatment with agents with cyclo-oxygenase-inhibiting activity. A current history of severe or uncontrolled renal, hepatic, endocrine, pulmonary, cardiac, neurologic or cerebral disease, blood coagulation disorders or anaemia.

ECG abnormalities during screening including ventricular tachycardia, evidence of myocardial infarction or ischaemia, and 2nd or 3rd degree heart block.

Patients with upper GI ulcer or significant GI complaints within the past 6 months and peptic ulcer disease or significant GI disease or bleeding within the past year were also excluded.

Efficacy:
The primary efficacy parameter was the summed (time-weighted) pain intensity difference from 0 to 8 hours (SPID-8) after the first dose of study medication on Day 0.

Secondary efficacy parameters were the time-specific pain intensity difference (PID) based on the categorical scale and visual analog scale (VAS), and the summed (time-weighted) pain intensity difference from 0 to 12 hours (SPID-12) after the first dose of study medication on Day 0. Also, the time-specific pain relief (PR) and time-specific pain relief intensity difference (PRID) based on categorical scales, the time to perceptible pain relief and time to meaningful pain relief, total (time-weighted) pain relief from 0-8 hours (TOTPAR-8) and from 0-12 hours (TOTPAR-12) after the first dose of study medication on Day 0, time to rescue medication intake (measured up to 12 hours on Day 0), and the patient global evaluation (at the end of the single and multiple dose phases).

**Duration of treatment:**
The study consisted of a 2-week screening period which included surgery followed by patient controlled analgesia (PCA) for up to 48 hours.
Randomised patients then entered a single-dose 12-hour analgesic evaluation phase followed by a multiple- dose analgesic evaluation over the course of five days (or until discontinuation).

**Results:**
Patient Disposition

| | Placebo | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|
| Randomised | 60 | 60 | 60 |
| Completed | 37 | 32 | 28 |
| Discontinued<br>Lack of effect | 23<br>0 | 28<br>1 | 32<br>1 |

| | | | |
|---|---|---|---|
| AE | 4 | 7 | 6 |

SPID8

| | Placebo | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|
| Mean | 1.3 | 4.6 | 6.0 |
| P vs placebo | | 0.009 | |
| P vs naproxen | | 0.164 | |

TOTPAR8

| | Placebo | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|
| Mean | 6.25 | 10.34 | 11.55 |
| P vs placebo | | 0.010 | < 0.001 |
| P vs naproxen | | 0.448 | |

Kaplan Meier estimate of time to onset of analgesia

| | N | Median time (h) | 95% CI |
|---|---|---|---|
| Placebo | 60 | > 12 | |
| Lumiracoxib 400mg QD | 60 | 1.54 | 0.8, >12 |
| Naproxen 500mg BD | 60 | 1.03 | 0.53, >12 |

Kaplan Meier estimate of time to first rescue medication during single dose phase

| | N | Median time (h) | 95% CI |
|---|---|---|---|
| Placebo | 60 | 2.00 | 1.57, 2.82 |
| Lumiracoxib 400mg QD | 60 | 3.88 | 1.63, 6.20 |
| Naproxen 500mg BD | 60 | 3.90 | 2.77, 6.03 |

Patient Global Assessment (%)

| | Placebo | Lumiracoxib 400mg QD | Naproxen 500mg BD |
|---|---|---|---|
| | End of single dose phase | | |
| Poor | 28.2 | 26.7 | 23.3 |
| Fair | 38.3 | 21.7 | 16.7 |
| Good | **26.7** | **21.7** | **41.7** |
| Excellent | **1.7** | **26.7** | **16.7** |
| N/A | 5.0 | 3.3 | 1.7 |
| | End of multiple dose phase | | |
| Poor | 5.0 | 1.7 | 1.7 |
| Fair | 16.7 | 8.3 | 10.0 |
| Good | **41.7** | **38.3** | **45.0** |
| Excellent | **18.3** | **30.0** | **18.3** |
| N/A | 18.3 | 21.7 | 25.0 |

These results support the efficacy of lumiracoxib 400mg QD as an effective analgesic in post-orthopaedic patients. It is statistically superior to placebo. It is statistically equivalent to, but numerically not as good as, naproxen.

## 11.3 Study 0132 in post-orthopaedic surgery pain

This study was similar to study 0131 except that the comparator was controlled release oxycodone and used two doses of lumiracoxib (400mg QD and 800mg QD).

This was a double blind, randomised, double-dummy, active-comparator, placebo-controlled study consisting of 2 phases: a 12-hour single-dose analgesic evaluation followed by a multiple-dose analgesic evaluation occurring over 5 days (or until discharge from hospital) on an inpatient basis, and then up to 2 weeks on an outpatient basis. Following total primary unilateral knee or hip arthroplasty, patient-controlled analgesia (PCA) or scheduled IV or IM opiate injections were stopped approximately 24 hours after surgery and eligible patients were randomised to receive either
lumiracoxib 400mg QD, lumiracoxib 800mg QD, CR oxycodone 20mg BD or matching placebo.

At the end of the inpatient portion of the multiple-dose phase patients randomised to placebo or lumiracoxib 800mg QD were switched to lumiracoxib 400mg QD for the 2-week outpatient portion. Patients who previously received CR oxycodone 20mg BD or lumiracoxib 400mg QD continued with the same treatment.

**Results:**

Patient Disposition

| | Placebo | Lumiracoxib 400mg | Lumiracoxib 800mg | Oxycodone 20mg |
|---|---|---|---|---|
| | In-patient phase | | | |
| Randomised | 60 | 60 | 61 | 59 |
| Completed | 5 | 6 | 2 | 2 |
| Discontinued | 55 | 54 | 59 | 57 |
| | Out-patient multiple dose phase | | | |
| | Lumiracoxib 400mg | Lumiracoxib 400mg | Lumiracoxib 400mg | Oxycodone 20mg |
| Randomised | 27 | 41 | 39 | 27 |
| Completed | 16 | 20 | 16 | 12 |
| Discontinued | 11 | 21 | 23 | 15 |

SPID8 (ITT population)

| | Placebo | Lumiracoxib 400mg | Lumiracoxib 800mg | Oxycodone 20mg |
|---|---|---|---|---|
| N = | 60 | 60 | 61 | 59 |
| Mean | 3.1 | 5.7 | 5.6 | 3.1 |
| Median | 1.0 | 7.3 | 7.0 | 2.5 |
| | p values for the difference | | | |
| Lumiracoxib 400mg | 0.013 | | | |
| Lumiracoxib 800mg | 0.014 | 0.977 | | |
| Oxycodone 20mg | 0.990 | 0.014 | 0.015 | |

TOTPAR8 (ITT population)

| | Placebo | Lumiracoxib 400mg | Lumiracoxib 800mg | Oxycodone 20mg |
|---|---|---|---|---|
| N = | 60 | 60 | 61 | 59 |
| LS Mean | 9.17 | 13.02 | 12.97 | 9.67 |
| | p values for the difference | | | |
| Lumiracoxib | 0.011 | | | |

| | | | | |
|---|---|---|---|---|
| 400mg | | | | |
| Lumiracoxib 800mg | 0.011 | 0.972 | | |
| Oxycodone 20mg | 0.742 | 0.027 | 0.028 | |

Patient Global Assessment (%) (ITT population)

| | Placebo | Lumiracoxib 400mg | Lumiracoxib 800mg | Oxycodone 20mg |
|---|---|---|---|---|
| | End of single dose phase | | | |
| Poor | 33.3 | 20.0 | 19.7 | 25.4 |
| Fair | 28.3 | 16.7 | 19.7 | 25.4 |
| Good | **25.0** | **38.3** | **24.6** | **37.3** |
| Excellent | **11.7** | **23.3** | **34.4** | **8.5** |
| N/A | 1.7 | 1.7 | 1.6 | 3.4 |
| | End of in-patient multiple dose phase | | | |
| Poor | 3.3 | 1.7 | 4.9 | 8.5 |
| Fair | 6.7 | 5.0 | 4.9 | 11.9 |
| Good | **35.0** | **35.0** | **39.3** | **49.2** |
| Excellent | **18.3** | **46.7** | **37.7** | **10.2** |
| N/A | 36.7 | 11.7 | 13.1 | 20.3 |

Statistical analysis of Patient Global Assessment

| | At the end of single dose phase | At the end of in-patient multiple dose phase |
|---|---|---|
| Lumiracoxib 400mg vs lumiracoxib 800mg | p = 0.690 | p = 0.493 |
| Lumiracoxib 400mg vs oxycodone 20mg | p = 0.132 | p = 0.037 |
| **Lumiracoxib 400mg vs placebo** | **p = 0.016** | **p = 0.345** |
| Lumiracoxib 800mg vs oxycodone 20mg | p = 0.060 | p = 0.158 |
| **Lumiracoxib 800mg vs placebo** | **p = 0.004** | **p = 0.146** |
| Oxycodone 20mg vs placebo | p = 0.374 | p = 0.010 |

These data suggest that the analgesic effect of lumiracoxib may be short-term only.

***Assessor's Comments on Efficacy of lumiracoxib in Acute Pain:***
It is concluded that lumiracoxib 400mg QD is an effective analgesic for very short-term use.

The indication should be restricted to the population studied (that is, patients with moderate to severe pain following dental or orthopaedic surgery).

## 12. STATISTICAL ASSESSMENT OF EFFICACY

This assessment considers the evidence of efficacy of lumiracoxib in osteoarthritis, rheumatoid arthritis, acute pain and primary dysmenorrhoea. In addition to a description of each pertinent trial and a critique of the trial methodology, the statistical assessor's opinion is summarised in italics at the end of each section.

### 12.1 Osteoarthritis (OA)

#### 12.1.1 Dose-Finding

The recommended dose is 200mg QD. It is proposed that some patients may receive additional benefit from short-term use of 400mg QD.

Trials 0104, 2316 and 2301 were used to determine the doses and regimen of lumiracoxib tested in Phase III. A once-daily regimen was chosen of the basis of the clinical pharmacology, the PK and trial 0104, the only trial that tested multiple regimens of

lumiracoxib (50, 100 and 200mg BD plus 400mg QD). Efficacy on 200mg BD and 400mg QD is described as 'comparable', though this was not based on a formal test of equivalence. Therefore the clinical trial evidence for preferring once daily to twice daily dosing is weak. There are no further data comparing 200mg QD with 400mg QD in Phase II, only in Phase III. Therefore, further comments on the proposed posology will be made below.

12.1.2 Pivotal Studies of Efficacy

There were three pivotal trials in OA (0109, 0112 and 0128). In addition, data from trials 0109 and 0112 have been presented in a combined analysis. Trial 2319 assessed OA of the hand.

The three pivotal studies were all randomised, double-blind (double-dummy), parallel-group, multiple-dose (13 weeks), placebo-controlled studies. Trials 0109 (n=1608) and 0112 (n=1702) were in OA of the knee and compared lumiracoxib 200mg QD and lumiracoxib 400mg QD with celecoxib 200mg QD. Trial 0112 included a 39-week extension phase. Trial 0128 (n=511) was conducted in OA of the hip and compared lumiracoxib 400mg QD with rofecoxib 25mg QD and placebo.

The primary efficacy parameters used in each of the three trials were (i) overall pain intensity (measured by VAS), (ii) patient's global assessment of disease (VAS) (iii) pain subscale of WOMAC and (iv) WOMAC total score. The primary analyses were based on the ITT population using ANCOVA with the relevant baseline as covariate. The model also included a term for centre and the presence of treatment by centre interaction was assessed. Missing data were imputed using LOCF. Sensitivity analyses were performed via an ITT analysis without LOCF, a completers analysis and a per-protocol analysis.

The trials aimed to demonstrate superiority to placebo and non-inferiority to the active control. A hierarchical testing strategy was implemented such that non-inferiority was only assessed if superiority to placebo had been demonstrated. The pre-specified margins of non-inferiority were 5mm for endpoints (i) and (ii) respectively, and 0.6 points for endpoint (iii). A non-inferiority margin was not pre-specified for (iv) as this endpoint was added retrospectively at the request of the FDA.

The rates of discontinuation were approximately 22%, 16% and 23% in trials 0109, 0112 and 0128 respectively. The two main reasons for withdrawal were adverse events and lack of efficacy. The proportions of patients withdrawing due to AE's were similar across the treatment groups and the proportions withdrawing due to lack of efficacy were similar across the active treatment groups but greater in the placebo group. By treatment group, between 32%-42%, 23%-26% and 28%-38% of patients were excluded from the per-protocol population in trials 0109, 0112 and 0128 respectively, primarily due to the administration of prohibited medication or an exposure to trial medication of less than 68 days.

There was no evidence of a treatment by centre interaction in any of the pivotal efficacy studies. All active treatments demonstrated highly statistically significant superiority to placebo on all endpoints (with the exception of lumiracoxib 400mg on WOMAC pain sub-scale in trial 0128, p=0.077). A significantly greater proportion of patients in the placebo group took rescue medication during the course of the studies. Criteria for non-inferiority were met between both doses of lumiracoxib and celecoxib, but lumiracoxib 400mg was not shown to be non-inferior to rofecoxib. In trials 0109 and 0112 there were no significant differences between the two doses of lumiracoxib, though the 400mg dose showed marginally greater effects than the 200mg dose across all four primary endpoints. In the pooled analysis of the two studies in OA of the knee the 400mg dose was superior to celecoxib on VAS pain scores.

The extension to trial 0112 included 1235 of the 1423 patients who completed trial 0112. Of these 171 had received placebo in the original study. The primary endpoints, analysis methods and non-inferiority margins were as per the original study. Both doses of lumiracoxib met the pre-specified criteria for non-inferiority compared with celecoxib.

Trial 2319 was a multi-centre, randomised, double-blind (double-dummy), placebo-controlled, parallel-group trial of lumiracoxib 200mg QD and lumiracoxib 400mg QD in patients with primary OA of the hand. The primary endpoint was the overall OA pain intensity after 4 weeks of treatment, measured by VAS. AUSCAN total score was also measured. Both doses of lumiracoxib demonstrated statistically significantly superior effects to placebo.

12.1.3 Comments on Methodology

There were four primary endpoints in each study. Three were pre-specified in the trial protocols and one, WOMAC total score, was added at the request of the FDA. As lumiracoxib was superior to placebo on (virtually) all endpoints, the absence of any adjustment for multiplicity is not a concern. The borderline evidence of statistical significance for lumiracoxib 400mg QD on the WOMAC pain sub-scale in trial 0128 is not considered to be of major importance given results on other endpoints and in the other pivotal trials.

A secondary objective of each trial was to demonstrate non-inferiority to the respective active control. Non-inferiority margins of 5mm and 0.6 points were used on the VAS and the WOMAC pain score respectively. These were derived using estimated effects of lumiracoxib treatment versus placebo from 0104 and published data on placebo comparisons with celecoxib. The choices for delta seem reasonable. (NB: In trial 0112, $\Delta$=3mm was pre-specified for the VAS endpoints and was retrospectively changed to 5mm for interpretation of the trial results. This would generally be unacceptable, but the rationale for choosing 5mm seems reasonable and the demonstration of superiority to placebo is of greater relevance. Furthermore, the confidence intervals comparing lumiracoxib with celecoxib met the pre-specified criteria of 3mm for the core trial, though not the 39-week extension, and the change appears to have been purely to promote consistency across the trial programme).

To avoid multiplicity comparisons with the active controls were only performed if both doses of lumiracoxib had proved to be superior to placebo on all primary endpoints. Non-inferiority compared with celecoxib was established, but, even excepting the lack of statistical significance versus placebo on the WOMAC pain sub-scale in trial 0128, lumiracoxib 400mg failed to demonstrate non-inferiority to rofecoxib in OA of the hip. The applicant describes these results as showing 'no statistically significant differences between lumiracoxib and rofecoxib'. This is a weak interpretation of analyses designed to show non-inferiority. Indeed, it is noted that there was borderline evidence of a smaller effect for lumiracoxib than for rofecoxib (WOMAC total score, p=0.064). This was probably not a chance finding as results on other primary and some secondary endpoints also showed borderline statistical significance in favour of rofecoxib.

Clinical judgement will be required to determine whether the effects demonstrated for lumiracoxib 200mg QD in trials 0109 and 0112 can be generalised to OA of the hip, where (trial 0128) only 400mg QD was tested. It should be borne in mind that the effect sizes for 400mg QD in trial 0128 were smaller relative to placebo (less than half in the case of the WOMAC scales) than the effects in 0109 or 0112. If, as the applicant claims, there is a dose-response for lumiracoxib then the clinical relevance of the effects that might have been seen with 200mg QD should be considered. The applicant claims (Page 24 of the Clinical

Overview) that a subgroup analysis of trial 0104 evidenced similar estimates of treatment effect for patients with hip OA compared with patients with knee OA. However, the groups would have been too small for this conclusion to be drawn with any great certainty.

No patients in any of the pivotal trials experienced both the 400mg and 200mg doses Therefore the proposal that some patients may receive additional benefit from short-term use of 400mg QD following initial treatment with 200mg QD has not actually been tested. It is not clear that a dose increase would confer additional benefit for a given patient. Evidence for the proposed posology can therefore only be based on the non-significant increases in effect observed with 400mg and the biological plausibility of an increased effect at a higher dose. This is not strong evidence and the proposed posology should be carefully considered.

The conduct of a pooled analysis is considered reasonable. However, it adds little in this case as superiority to placebo and non-inferiority compared with celecoxib had already been established. Estimates of treatment effect from the pooled analysis are considered preferable to those from trials 0109 or 0112 as they will be more precise.

A randomised withdrawal study might have been a preferable way of demonstrating long-term efficacy. As not all patients initially randomised to 0112 (n=1702) entered the extension phase (n=1423), the extension phase compares populations that are not fully randomised. It is possible therefore that there exists systematic differences other than treatment received between the groups of patients continuing on lumiracoxib 200mg, lumiracoxib 400mg and celecoxib. However, reasons for withdrawal and timing of withdrawal were similar in each treatment group in 0112 therefore this is probably not a great concern. There is no concurrent placebo group in the extension phase, but given the results of the original study, it is likely that the assay sensitivity of the extension phase was good. The results demonstrated non-inferiority according to the retrospective non-inferiority margin, but not the protocolled margin (see above). There is no evidence to support long-term dosing with the 400mg dose of lumiracoxib, but this has not been proposed.

### 12.1.4 Summary of evidence of efficacy in OA

The dose finding work is not thorough. In particular the decision to administer lumiracoxib QD rather than bd is based on weak statistical evidence. The choice of 200mg or 400mg QD is best made from the pivotal trials.

The pivotal trials are of good quality. There is good evidence of short-term efficacy relative to placebo in both hip and knee OA. Non-inferiority of both lumiracoxib 200mg QD and 400mg QD was established compared with celecoxib 200mg QD in OA of the knee but not compared with rofecoxib in OA of the hip.

Clinical judgement is required for the following concerns:

- *Lumiracoxib 200mg has not been tested in OA of the hip. Can it be assumed that efficacy of lumiracoxib 200mg in OA of the hip would be statistically significant and clinically relevant bearing in mind that the estimates of treatment effect for lumiracoxib 400mg QD in trial 0128 were less impressive that the effects of lumiracoxib 400mg QD in trials 0109 and 0112?*
- *No patients in any of the pivotal trials experienced both the 400mg and 200mg doses. There was no clear evidence that 400mg was superior to 200mg. It is not clear that a dose increase would confer additional benefit for a given patient. This is supported by results in the 0112 extension phase. Is there sufficient evidence, based on the non-significant increases in short-term effect observed with 400mg and the biological plausibility of an increased effect at a higher dose, to support the proposed posology?*

- *The evidence of longer-term efficacy (>3 months) is less impressive as it is not based on fully randomised patient populations and the protocolled criteria for non-inferiority were not met. A randomised withdrawal study might have been more appropriate. However, effects of lumiracoxib 200mg QD and 400mg QD appear similar to those of celecoxib 200mg QD and this is probably adequate.*

## 12.2 Acute pain and primary dysmenorrhoea

### 12.2.1 Dose-Finding

The recommended dose is 400mg QD. Dose selection for the acute pain and primary dysmenorrhoea indications are based on the results of 2 studies, one of which (study 0115) is also one of the major efficacy studies in post-surgical dental pain, and study 0103 which is also a supportive study in post-surgical dental pain. In light of this, the data from these studies are discussed below.

### 12.2.2 Pivotal Studies of Efficacy

Post-dental pain:

Four studies were conducted in post-dental surgery pain (0103, 0115, 2302 and 2329). Three had a similar design. The exception was trial 2329 which tested 400mg QD versus 2 x 200mg QD. This trial was stopped prematurely because the FDA indicated that they already considered the two regimens to be equivalent. It provides no useful evidence of efficacy or inefficacy and so will not be discussed further.

The completed studies were randomised, double-blind, placebo and active controlled studies in patients following the removal of two or more impacted third molar teeth. The doses of lumiracoxib tested were 100 and 400mg QD (trial 0103), 200, 400 and 800mg QD (trial 0115) and 400mg QD (trial 2302). The active comparators were ibuprofen 400mg (trial 0103), rofecoxib 50mg (trial 0115) and rofecoxib 50mg and celecoxib 200mg (trial 2302).

The primary endpoint in the pivotal study (2302) was the summed (time-weighted) pain intensity differences calculated over the 0-8 hour time period (SPID-8). Secondary variables included the time-specific PID, pain-relief (PR), PID measured by VAS, total time-weighted PR from 0-8 hours (TOTPAR 0-8) and time to onset of analgesia. The primary analysis was based on ANCOVA including terms for treatment, number of teeth removed and baseline pain intensity. LOCF was used for data missing due to use of rescue medication. The other two studies employed similar endpoints and analysis methods.

The number of patients withdrawn from the study due to insufficient efficacy is shown in the table below.

| Trial | Treatment | Total randomised | Total withdrawn | Withdrawals due to lack of efficacy |
|---|---|---|---|---|
| 0103 | Lumiracoxib 100mg | 51 | 39 | 38 |
| | Lumiracoxib 400mg | 50 | 22 | 22 |
| | Ibuprofen 400mg | 51 | 36 | 36 |
| | Placebo | 50 | 46 | 46 |
| 0115 | Lumiracoxib 200mg | 52 | 46 | 46 |
| | Lumiracoxib 400mg | 52 | 35 | 35 |
| | Lumiracoxib 800mg | 52 | 28 | 28 |
| | Rofecoxib 50mg | 51 | 31 | 31 |
| | Placebo | 52 | 48 | 48 |
| 2302 | Lumiracoxib 400mg | 101 | 85 | 85 |
| | Rofecoxib 50mg | 102 | 78 | 78 |
| | Celecoxib 200mg | 101 | 88 | 88 |
| | Placebo | 51 | 51 | 51 |

Lumiracoxib was superior to placebo at all doses across all three studies. The 400mg QD dose was superior to the 100mg (trial 0103) and 200mg doses (trial 0115) and not inferior to the 800mg dose (trial 0115). The efficacy of lumiracoxib was comparable to each active comparator.

12.2.3 Comments on Methodology (post-dental pain)

Because these are single dose studies of short duration, they are relatively simple from a methodological point of view. The one complication is the large number of withdrawals due to use of rescue medication. However, this has been handled through LOCF imputation, which is reasonable. Indeed the use of rescue medication itself gives some notion of the efficacy of lumiracoxib. The endpoints, analysis populations and statistical analyses appear to be appropriate and the results are considered reliable.

There is clear evidence of efficacy relative to placebo in dental pain and a dose of 400mg seems reasonable from an efficacy point of view as it is superior to lower doses of lumiracoxib and not inferior to the higher doses tested.
There was no formal investigation of non-inferiority. However, such a conclusion seems reasonable as the efficacy of lumiracoxib appears to be at least comparable to each active controls and is statistically significantly superior on some endpoints - though clinical judgement should verify that the chosen doses of the active controls were appropriate.

12.2.4 Primary Dysmenorrhea:

Trials 0129 (n=86) and 0130 (n=109) were multicentre, randomised, double-blind, double-dummy, placebo- and active-controlled, complete-block, 3-period crossover trials in women with a self-reported history of primary dysmenorrhoea. Patients received lumiracoxib 400 mg, active control (rofecoxib 50mg in 0129 or naproxen 500mg in 0130), or placebo for up to 3 days (if needed) from the onset of moderate to severe menstrual pain, in each of 3 menstrual cycles. Patients were randomised to 6 different treatment sequences which determined the order in which the 3 treatments were administered.

Efficacy was assessed using SPID-8 as the primary variable. Secondary variables were also similar to those used in the post-dental pain studies. If rescue medication was taken in the first 12 hours of treatment, no further efficacy measures were taken, though a global assessment of efficacy was still taken after day 3. Missing values for pain intensity and pain relief for SPID8 were imputed using LOCF or BOCF (baseline observation carried forward) as appropriate. The primary analysis was based on the ITT population and used ANCOVA, including terms for treatment and period as fixed effects, patient as a random effect and pain intensity at baseline as a covariate. A closed testing strategy was used in order to account for multiple testing: first lumiracoxib was compared with placebo, then, if significant, it was compared with rofecoxib / naproxen.

The table below shows the number of premature discontinuations and the use of rescue medication within the first 12 hours of treatment:

| Trial | Treatment | Withdrawn * | Use of rescue medication |
|---|---|---|---|
| 0129 (n=86) | Lumiracoxib | 0 | 18.8% |
| | Rofecoxib | 5 | 12.2% |
| | Placebo | 2 | 40.5% |
| 0130 (n=109) | Lumiracoxib | 5 | 22.9% |
| | Naproxen | 9 | 16.9% |
| | Placebo | 10 | 38.6% |

* The most common reasons for discontinuation were withdrawal of consent and loss to follow-up. The majority of withdrawals occurred after the 3-day treatment period during the washout period, they are attributed to last treatment received. Two patients in 0129 and 10 patients in 0130 never received study medication.

Each of the active treatment groups in both trials was statistically significantly more effective than placebo for SPID-8 and the majority of secondary endpoints. There was no statistically significant difference between lumiracoxib 400 mg and either active control.

Comments on Methodology (primary dysmenorrhoea):
The proposed posology for the treatment of pain from primary dysmenorrhoea was derived from the dental pain model. Clinical judgement should decide whether this is reasonable. Unlike other pain models, lumiracoxib 400mg was the only dose tested in primary dysmenorrhoea and it is not clear whether a dose lower than 400mg might have been effective relative to placebo.

It is unusual to see crossover trials used to demonstrate pivotal evidence of efficacy. Crossover trials have the advantage that treatment comparisons can be made 'within-patient'. This usually reduces variability and thus the number of patients required to confirm a particular size of treatment effect. The desirable trial design features for obtaining reliable data from a crossover trial are as follows: that the treated condition should be ongoing and chronic (so that the patient returns to a 'baseline' state at the start of each treatment period), that the duration of the trial is sufficiently short to avoid large numbers of patient dropouts (single dose trials are usually preferable to multiple dose trials), that there is only negligible potential for differential carryover (i.e. effects from one period persisting into a later period). These conditions appear to be fulfilled for the two pivotal studies under consideration.

The pivotal trials are consistent in design with previous trials designed to test efficacy in this pain model. In particular the endpoints and methods of statistical analysis are appropriate. Crucial issues with this type of study are the number of patient withdrawals and the handling of missing data, particularly for data missing due to use of rescue medication.

The contribution to the efficacy analysis of patients who withdrew during the course of the trial depends on the number of treatment periods completed. A patient completing only two periods will contribute (within-patient) only to the comparison between the two treatments received. A patient completing only one period can offer no within-patient information. This 'loss of information' is to be expected in crossover trials and there is no imputation for this type of missing data, which is appropriate.

Efficacy data has not been collected following administration of rescue medication. Instead LOCF is applied which will reflect the 'failure' of the treatment received. This is appropriate. The use of rescue medication within the first 12 hours gives some indication itself of efficacy. More patients have used additional medication on placebo than on either active treatment.

In the conclusions to both trial reports and in the expert summaries the applicant claims 'similar' efficacy for lumiracoxib and the active controls, naproxen and rofecoxib. This is an over-interpretation of the efficacy data. While it is true that no statistically significant differences were observed between the treatments, no a priori margins for non-inferiority were pre-specified and efficacy was, in general, slightly less impressive on lumiracoxib. While this does not affect the robust evidence versus placebo, claims of comparable efficacy to other active treatments are not supported.

As for the trials in post-orthopaedic pain, a closed testing strategy was implemented to avoid concerns over multiplicity.

In trial 0130 trial medication was wrongly dispensed for two patients. This will mean that results according to a strict definition of the ITT population will differ from results by treatment received, though the levels of statistical significance are so extreme as to make this a very minor concern.

12.2.5 Post-orthopaedic pain

Two studies were conducted in post-orthopaedic surgery pain (0131and 0132). These were randomised, double-blind, placebo and active controlled studies in the treatment of moderate to severe post-surgical pain following total knee or hip arthroplasty. The doses of lumiracoxib tested in each trial were 400mg QD and 400 and 800mg QD respectively. The active comparators were naproxen 500mg BD (trial 0131) and controlled release oxycodone every 12 hours (trial 0132). Both studies were conducted in two phases, a single dose 12-hour evaluation followed by a multiple dose evaluation over 5 days (or until discontinuation).

The primary endpoint in both studies was the summed (time-weighted) pain intensity differences calculated over the 0-8 hour time period (SPID-8) following the first dose of study medication on Day 0. Secondary variables were also similar to those used in the post-dental pain studies. If rescue medication was taken in the first 12 hours of treatment, no further efficacy measures were taken until the multiple dose phase. Missing values for pain intensity and pain relief were imputed using LOCF or BOCF as appropriate. The primary analysis was based on the ITT population and used ANCOVA, including terms for centre, treatment, baseline pain intensity and surgery type. A closed testing strategy was used in order to account for multiple testing: the 400mg QD dose of lumiracoxib was first compared with placebo, and then with naproxen provided that superiority to placebo had been established.

Unlike the post-dental pain trials, few patients were withdrawn due to lack of efficacy. Lumiracoxib 400mg QD and 800mg QD were superior to placebo in both studies and were superior, at both doses, to oxycodone, which showed negligible evidence of efficacy compared with placebo. There was no statistically significant difference between lumiracoxib and naproxen on the primary endpoint, though naproxen was marginally more effective on other endpoints, reaching statistical significance on occasion. There was no advantage for lumiracoxib 800mg compared with lumiracoxib 400mg. An effect of lumiracoxib was also observed in the multiple dose phase of the study. The 400mg QD dose was superior to the 100mg and 200mg doses and not inferior to the 800mg dose.

Comments on Methodology (post-orthopaedic pain):

The proposed posology for the treatment of post-orthopaedic surgery pain was derived from the dental pain model. Clinical judgement should decide whether this is reasonable.

The trial designs are comparable to those generally accepted as standard in this pain model. In particular the endpoints and methods of statistical analysis are relatively straightforward. Crucial issues with this type of study are the number of patient withdrawals and the handling of missing data, particularly for data missing due to use of rescue medication. However, these appear to have been handled appropriately.

There would usually be concern over the number of statistical analyses conducted in a trial with more than two treatments. However, the applicant has accounted for potential multiplicity in an appropriate fashion: a closed testing strategy was implemented such that comparisons with active-controls were only conducted when placebo-controlled comparisons had demonstrated significance. In trial 0132 the primary analyses were conducted only on the 400mg QD dose not the 800mg QD dose. However, as the primary analyses were statistically significant certain latitude can be granted for interpreting results on secondary analyses and endpoints.

### 12.2.6 Summary of efficacy in Acute Pain and Primary Dysmenorrhoea

*The dose finding work for the indications of acute pain and primary dysmenorrhoea is based on results from the dental pain model. A dose of 400mg has been selected which is reasonable, based on efficacy, for the dental pain model.*

*Clinical judgement should consider whether extrapolation of this dose for use in post-orthopaedic surgery and primary dysmenorrhoea is appropriate.*

*Doses lower than 400mg were not tested in these two pain models and might have been efficacious relative to placebo (though perhaps not compared with the active controls which were, generally, marginally more effective than lumiracoxib 400mg).*

*The pivotal trials are consistent with previous trials designed to test efficacy in these pain models. They are relatively straightforward and the quality of the statistical input is high. The efficacy of lumiracoxib 400mg versus placebo has been clearly established in dental pain, primary dysmenorrhoea and post-orthopaedic surgery pain.*

*The applicant has concentrated on demonstrating efficacy relative to placebo, which is considered reasonable. No attempt was made to establish non-inferiority between lumiracoxib 400mg and the chosen active controls and therefore claims of 'similar' efficacy are, in general, weak evidence of efficacy.*

## 12.3 Rheumatoid arthritis (RA)

12.3.1 Dose-Finding

The recommended dose is 200mg QD. It is proposed that some patients may receive additional benefit from short-term use of 400mg once daily.

Trials 0105 and 2312 were used to determine the doses and regimen of lumiracoxib tested in Phase III. Trial 2312 tested 2 doses of lumiracoxib, both of which were greater than those proposed in the posology. Trial 0105 tested multiple regimens of lumiracoxib (50, 100 and 200mg BD plus 400mg QD) against placebo and diclofenac 75mg BD. Efficacy of efficacy relative to placebo was negligible for all lumiracoxib doses and a linear trend test for dose response was not significant. Based on secondary timepoints and secondary endpoints it was concluded that lumiracoxib 200mg BD and 400mg QD were 'comparable' to diclofenac. This was not based on a formal test of equivalence. There is no data comparing 200mg QD with 400mg QD in Phase II, only in Phase III. Therefore, further comments on the proposed posology will be made below.

12.3.2 Pivotal Studies of Efficacy

There were two pivotal trials in RA (0111 and 0114). A pooled analysis of data from these trials has also been presented.

The pivotal studies were both randomised, double-blind (double-dummy), parallel-group, multiple-dose (26 weeks for 0111, 13 weeks for 0114), placebo-controlled studies. Trial 0111 (n=1124) compared lumiracoxib 200mg QD and 400mg QD with naproxen 500mg BD and placebo. Trial 0114 (n=1239) compared lumiracoxib 200mg QD and 400mg QD with celecoxib 200mg BD and placebo.

The primary efficacy parameter in both trials was response to treatment according to ACR20 at 13 weeks (a protocol amendment had changed the primary timepoint from 26 weeks in trial 0111 and the precise definition of responder had also been changed). Secondary variables included the individual components of ACR20. The primary analyses, based on the ITT

population, used a multiple logistic regression model (with country, treatment, swollen 66-joint count at baseline and tender 68 joint count at baseline as main effects) to derive odds ratios and associated confidence intervals. Components of the ACR20 criteria were analysed using ANCOVA with centre and treatment as main effects. For primary and secondary analyses missing data on each component of ACR20 were imputed using LOCF. Sensitivity analyses were performed via an ITT analysis without LOCF, a completers analysis and a per-protocol analysis.

The primary aim of the trials was to demonstrate superiority to placebo. The trials were not designed to demonstrate non-inferiority with the active controls.

*The rates of discontinuation were approximately 36% and 32% in trials 0111 and 0114 respectively. The two main reasons for withdrawal were adverse events and lack of efficacy. The proportion withdrawing due to AE's were similar across the treatment groups and the proportion withdrawing due to lack of efficacy was similar across the active treatment groups (albeit a little higher in the lumiracoxib 200mg QD group in trial 0114) but greater in the placebo group. By treatment group, between 37%-53% and 42%-52% of patients were excluded from the per-protocol population in trials 0111 and 0114 respectively, primarily due to the administration of excess rescue medication or an exposure to trial medication of less than 68 days.*

In trial 0111 both doses of lumiracoxib were significantly superior to placebo on ACR20 at week 13. Naproxen demonstrated effects of borderline statistical significance (p=0.087). Both doses of lumiracoxib and naproxen demonstrated statistical significance compared with placebo on the majority of components of ACR20 (see table below). A notable exception was C-reactive protein (CRP) level, where significance was in favour of placebo against both doses of lumiracoxib at weeks 2, 4, 13 and 20, though not at week 26 (NS). Statistical significance for lumiracoxib 200mg QD was not observed on HAQ score at week 13. At week 26 the statistical significance of the higher dose of lumiracoxib depended on which definition of ACR response was used (see comment below). The 200mg QD dose and naproxen were significantly different to placebo. There were no statistically significant differences between naproxen and lumiracoxib. Both the 200mg QD dose and the 400mg QD dose were statistically superior to placebo on RA pain, but neither demonstrated statistical significance on HAQ.

In trial 0114 neither dose of lumiracoxib was significantly superior to placebo on ACR20 at week 13. Celecoxib was significantly superior to placebo. At least one retrospective subgroup analysis was conducted to explore these equivocal findings. Statistically significant advantages (mostly borderline) over placebo were observed sporadically on the secondary endpoints at week 13 for lumiracoxib 400mg QD vs placebo, including RA pain, patient's but not physician's assessment of disease activity and HAQ score. Celecoxib was consistently superior to placebo.

In the pooled analysis of the two studies both doses of lumiracoxib were significantly superior to placebo on ACR20 at week 13 (when using the pre-amendment definition of response). Statistically significant differences to placebo at week 13 were observed on other endpoints as described in the table below. The applicant has chosen not to present CRP levels in the pooled analysis. No differences were observed between the two doses of lumiracoxib.

| | Study 0111 | | Study 0114 | | Pooled studies ** 0111+ 0114 | |
|---|---|---|---|---|---|---|
| | Lum 200mg | Lum 400mg | Lum 200mg | Lum 400mg | Lum 200mg | Lum 400mg |
| ACR20 (primary) * | **1.48 (1.04, 2.11)** | **1.58 (1.11, 2.25)** | 1.20 (0.87, 1.66) | 1.22 (0.88, 1.69) | **1.36 (1.08, 1.72) p=0.009** | **1.38 (1.09, 1.74) p=0.007** |

| | | | | | | |
|---|---|---|---|---|---|---|
| RA pain (VAS) | **-6.38 (-10.18,-2.57)** | **-5.22 (-9.02, -1.43)** | -2.90 (-6.96, 1.16) | **-4.72 (-8.79, -0.66)** | **-4.56 (-7.42, -1.69) p=0.002** | **-5.00 (-7.86, -2.13) p<0.001** |
| HAQ SDI | -0.07 (-0.15, 0.02) | **-0.09 (-0.18, -0.01)** | -0.04 (-0.13, 0.05) | **-0.13 (-0.22, -0.04)** | -0.05 (-0.11, 0.01) p=0.105 | **-0.11 (-0.17, -0.05) p<0.001** |
| Tender joint count | **-2.90 (-4.56, -1.23)** | **-2.02 (-3.69, -0.35)** | 0.59 (-1.39, 2.56) | -0.23 (-2.21, 1.75) | -1.09 (-2.45, 0.27) p=0.118 | -1.08 (-2.44, 0.28) p=0.120 |
| Swollen joint count | **-1.64 (-2.70, -0.58)** | **-1.34 (-2.39, -0.28)** | 0.26 (-0.97, 1.49) | -0.51 (-1.74, 0.72) | -0.65 (-1.50, 0.21) p=0.140 | **-0.90 (-1.76, -0.05) p=0.039** |
| Patient's GA (VAS) | **-6.36 (-9.90, -2.82)** | **-5.65 (-9.18, -2.11)** | -1.55 (-5.57, 2.47) | **-4.92 (-8.95, -0.90)** | **-3.72 (-6.49, -0.94) p=0.009** | **-5.17 (-7.94, -2.39) p<0.001** |
| Physician's GA (VAS) | **-3.42 (-6.47, -0.36)** | **-4.40 (-7.46, -1.35)** | -0.33 (-4.04, 3.39) | -3.02 (-6.75, 0.70) | -1.74 (-4.26, 0.77) p=0.174 | **-3.61 (-6.13, -1.09) p=0.005** |
| CRP level | *3.74 (0.83, 6.65)* | *3.67 (0.75, 6.58)* | 2.39 (-0.44, 5.23) | 1.90 (-0.94, 4.74) | | |

Lum – lumiracoxib. GA – global assessment. Multiplicity has not been taken into account. * Pooled analysis definition of ACR20 responder is the pre-amendment definition in protocol 0111. ** ACR20 results as odds ratios, 95% confidence intervals and p-values (numbers > 1 indicate an advantage for lumiracoxib). Other results as estimates of effect, 95% confidence intervals and p-values for the pooled analysis (negative numbers indicate an advantage for lumiracoxib). VAS measured in mm. Significant results favouring lumiracoxib are in bold. Significant results favouring placebo are in italics. A meta-analysis of CRP levels was not conducted.

### 12.3.3 Comments on Methodology

There are methodological concerns with both studies. Trial 0114 failed to achieve its primary objective. The applicant concludes that despite a lack of statistical significance on ACR20 at the primary timepoint, 'the numerical differences suggest that lumiracoxib is effective in RA'. This is a poor interpretation of the clinical trial data and is clearly insufficient evidence of efficacy. The post hoc subgroup analyses attempting to explain the results do not aid the evidence of efficacy for lumiracoxib and results on secondary endpoints should be treated with caution given the lack of statistical significance on the primary endpoints.

The major concern in trial 0111 relates to the protocol amendments (which changed the primary timepoint and the definition of ACR20 responder) and the evidence for longer-term efficacy, also to the lack of effect in the naproxen arm at week 13. This might be a chance observation. However, when the active control fails to demonstrate an expected effect it is wise to verify that the trial has been designed in such a way as to provide a fair comparison. For example, is the patient population appropriate? It is not clear that confirmatory evidence of efficacy is available from these two pivotal studies alone and the pooled analysis is considered highly relevant.

The CPMP Points to Consider on medicinal products in rheumatoid arthritis recommends that pain (e.g. RA pain as measured by VAS) and physical function (e.g. HAQ) are assessed as primary endpoints. The use of ACR20 is acceptable but the effects on the composite endpoints should be mirrored on the relevant components (see table above). This guidance should be borne in mind when interpreting the results from the individual trials and the pooled analysis.

The pooled analysis is generally considered reasonable as a means to further investigate the effects on lumiracoxib as the two studies were similar and one trial (0111) was positive at the primary timepoint. In the pooled analysis, based on the pre-amendment definition of 'responder' there is a clear effect for both lumiracoxib 200mg QD and lumiracoxib 400mg QD compared with placebo on ACR20. However, this analysis is complicated by the fact that a protocol amendment in trial 0111 changed the definition of 'responder'. As trial 0111 was conducted after trial 0114 the amended version of the definition was, at the time, clearly thought to be more appropriate. However, it has not been used for the pooled analysis. It is not clear that the results of the pooled analysis would be significant if the amended version of the definition were employed. This is discussed further in the paragraphs below.

The interpretation of the ACR20 data in the two trials individually and in the pooled analysis is complicated by changes to the definition of 'responder' and 'non-responder'. An ACR20 response was defined as a 20% improvement in swollen joint count, tender joint count and in at least 3 of the following 5 measures: overall RA pain intensity; patient's / physician's global assessment of disease, CRP, HAQ score.

In trial 0114, patients were classified as non-responders, regardless of ACR20 data, if they took >5 grams of rescue medication in any 7-day period and were discontinued for unsatisfactory response at that visit. Twelve patients were re-classified in this way.

In trial 0111 patients were initially classified as non-responders, regardless of ACR20 data, if they took >5 grams of rescue medication in any 7-day period. In fact no patient in study 0111 needed to be reclassified from responder to non-responder using the pre-amendment definition and no patient would have been reclassified because of discontinuation due to unsatisfactory therapeutic effect.

The definitions used in the protocol 0114 and the original protocol 0111 were therefore equivalent.

By protocol amendment the definition of responder in 0111 was extended by additionally re-classifying responders as non-responders for the further duration of the study if they discontinued from the study due to unsatisfactory response or if they increased the dose of or started new concomitant treatment which might have affected ACR20. Therefore the 0114 definition and the amended 0111 definition are different.

In the pooled efficacy analysis on the combined 0111 and 0114 datasets, the definition of response to treatment used in study 0111 (pre-amendment) and in study 0114 was applied. The applicant states that the post-amendment definition in study 0111 could not have been applied post-hoc to study 0114 because the necessary data (name of, dose of and reason for rescue medication) had not been collected in study 0114. Therefore sensitivity analyses on this point cannot be conducted.

The applicant has presented the results of trial 0111 using both definitions of responder. This raises concerns over multiplicity as the applicant might choose to focus on the more favourable results. It is considered that the amended version should be considered as the primary analysis. This does not materially affect the results at the primary week 13 timepoint. However, at 26 weeks 10.4%, 8.3%, 3.4% and 4.3%, of responders were reclassified as non-responders in the lumiracoxib 400 mg QD and 200 mg QD dose groups, the naproxen group and the placebo group respectively. Lumiracoxib 400 mg QD group was not shown to be superior to placebo.

The applicant considers that the adjustment to the definition of response to treatment due to prohibited use of concomitant medication was too conservative. However, this seems to be a post hoc argument attempting to explain disappointing results. Another perfectly tenable hypothesis is that the new definition of responder is more appropriate and that the difference between 400mg QD and placebo was simply too small to detect at 26 weeks. The lumiracoxib 200mg QD group retains its statistical significance compared with placebo. However, under the spirit of the hierarchical testing strategy this statistical test should only have been conducted if lumiracoxib 400mg QD had demonstrated significant superiority to placebo. It is not clear that robust evidence of efficacy has been provided at 26 weeks. A second source of evidence (i.e. a second 26 week trial) would have been useful.

In the pooled analysis lumiracoxib 400mg QD demonstrates statistical significance over placebo more consistently than the 200mg QD dose. However, there is no clinical trial evidence that a given patient will benefit from an increased dose. For example, there is no evidence of statistically significant superiority for 400mg QD compared with 200mg QD on any endpoint and there is no evidence of a consistent dose-response on the primary endpoints. In particular, the results from trial 0111, where 200mg QD appears to be at least as effective as 400mg QD at 26 weeks, do not support the proposed posology.

A large number of patients withdrew from the study and have been excluded from the sensitivity analyses. Furthermore, there were a large number of major protocol violations. This will result in potentially biased and underpowered statistical comparisons in the sensitivity analyses and the applicant's choice of primary analysis population (ITT with LOCF) is considered reasonable for a trial aiming to demonstrate superiority to placebo.

12.3.4 Summary of efficacy in RA

The dose finding work is not thorough. In particular the decision to administer lumiracoxib QD rather than bd is based on weak statistical evidence. There is insufficient evidence of efficacy relative to placebo or diclofenac in the dose finding study and in one of the two pivotal efficacy studies.

Conducting a pooled analysis of the pivotal studies is considered reasonable. However, the demonstration of statistical significance on ACR20 is complicated by the definition of responder. The applicant states that the definition of responder used in trial 0111 cannot be applied retrospectively to trial 0114 (and consequently to the pooled analysis) as the appropriate data was not collected. Therefore sensitivity analyses on this point cannot be requested. There remains a concern that the results of the pooled analysis and the results at week 26 are not robust to the definition of responder.

Based on the pooled data there the efficacy of the 200mg dose seems marginal. The evidence of efficacy for the 400mg dose is more convincing statistically, but the magnitude of the effects are very similar to those observed at the lower dose, leading also to concerns over the proposed posology.

Clinical judgement is required for the following concerns:

- *Despite the efficacy on lumiracoxib 200mg QD and 400mg QD appearing 'comparable', the lower dose has not showed an effect on HAQ,, neither in the individual studies nor the pooled analysis (as discussed in the CPMP guidance). Is there adequate evidence of efficacy at the lower dose?*

- *No patients in any of the pivotal trials experienced both the 400mg and 200mg doses and it is not clear that a dose increase will confer additional benefit for a given patient. This concern is supported by results of trial 0111 (the only positive trial) and the pooled analysis. Is there sufficient evidence to support the proposed posology?*

- *Clinical judgement should verify that population recruited to trial 0111 was appropriate as the active control, naproxen, did not show a significant effect compared with placebo.*

# 13. CLINICAL SAFETY

## 13.1 Overview of Dataset

The Applicant has divided the data into nine different sets depending on indication and duration of the studies.

13.1.1 Source

| Dataset | Population | Studies supplying the patients |
|---|---|---|
| 1 | Short-term OA studies (≤ 13 weeks data) | 0104, 0109, 0112, 0126, 0128, 2301, 2307, 2316, 2319 |
| 2 | Long term OA studies (≤ 1 year data) | 0112, 0112E |
| 3 | OA and RA studies (≤ 13 weeks data) | 0104, 0105, 0109, 0110, 0112, 0114, 0126, 0128, 2301, 2307, 2312, 2316, 2319 |
| 4 | Post-surgical dental pain | 0103, 0115, 2302, 2329 |
| 5 | Post orthopaedic surgery pain | 0131, 0132 |
| 6 | Primary dysmenorrhoea | 0129, 0130 |
| 7 | Short-term RA studies (≤ 13 weeks data) | 0105, 0110, 0111, 0114, 2312 |
| 8 | Endoscopy studies | 0110, 0126 |
| 9 | All OA and RA studies (excluding acute pain studies) | 0104, 0105, 0109, 0110, 0111, 0112, 0112E, 0114, 0126, 0128, 2301, 2307, 2312, 2316, 2319 |
| | **Datasets modified for Special Expert Evaluation Reports (SPERs)** | |
| 3-modified | Dataset 3 + Study O111 to 13 weeks | 0104, 0105, 0109, 0110 (up to 13 weeks), 0112, 0114, 0126, 0128, 2301, 2307, 2312, 2316, 2319 |
| 7-modified | All RA studies (≤ 13 weeks data) | 0105, 0110, 0114, 2312, 0111 (≤ 13 weeks data) |
| 7a | RA studies (long-term alone) | 0111 |
| 9-modified | All non-acute pain studies (ie OA and RA studies ≥ 13 weeks | 0109, 0110, 0111, 0112, 0112E, 0114, 0126, 0128 |

| Dataset | All lumiracoxib patients-years | Dataset | All lumiracoxib patients-years |
|---|---|---|---|
| **1** | 677.6 | **2** | 531.2 |
| **3** | 934.6 | **4** | 1.5 |
| **5** | 1.6 | **6** | 11.5 |
| **7** | 476.4 | **8** | 218.8 |
| **9** | 1685.2 | | |

It is evident that dataset 9 captures the most comprehensive patient population. Dataset 3 represents all short-term studies in OA and RA and is the next most comprehensive dataset

13.1.2 Exposure (number of patients)

Exposure to lumiracoxib by dose and duration in this total population was as follows:

| | 100mg BD | 200mg QD | 200mg BD | 400mg QD | Placebo |
|---|---|---|---|---|---|
| ≤ 3 months | 193 | 594 | 193 | 1155 | 970 |
| > 3 months | 0 | 924 | 0 | 1271 | 732 |
| > 6 months | 0 | 295 | 0 | 277 | 158 |
| > 12 months | 0 | 256 | 0 | 273 | 0 |
| **Total** | **193** | **2069** | **193** | **2976** | **1860** |
| **Patient-years** | **14.6** | **719.7** | **14.1** | **872.9** | **234.1** |

13.1.3 Exposure (mean number of days)

Exposure by indication to lumiracoxib by dose and duration in this total population was as follows:

| | 200mg QD | 400mg QD | Placebo |
|---|---|---|---|
| OA and RA studies (≤ 13 weeks data) | 73.8 | 66.2 | 55.6 |
| All OA and RA studies | 127.0 | 105.4 | 65.9 |
| Post-dental pain | - | 1.0 | 1.0 |
| Post-orthopaedic pain | - | 3.6 | 3.5 |
| Primary dysmenorrhoea | - | 25.8 | 25.3 |

13.1.4 Exposure (patient-years)

Exposure by indication to lumiracoxib by dose and duration in this total population was as follows:

| | 100mg BD | 200mg QD | 200mg BD | 400mg QD | Placebo |
|---|---|---|---|---|---|
| OA studies | 7.4 | 546.4 | 7.1 | 631.2 | 174.5 |
| RA studies | 7.2 | 173.2 | 7.0 | 227.8 | 161.0 |
| Pain | 0 | 0.1 | 0 | 13.9 | 13.2 |
| **Patient-years** | **14.6** | **719.7** | **14.1** | **872.9** | **234.1** |

13.1.5 Exposure (by demography)

| | 100mg BD | 200mg QD | 200mg BD | 400mg QD | Placebo |
|---|---|---|---|---|---|
| N | 193 | 2069 | 193 | 2976 | 1860 |
| <65 years | 141 | 1324 | 130 | 1932 | 1197 |
| 65-75 years | 47 | 541 | 58 | 757 | 477 |
| 75+ years | 5 | 204 | 5 | 287 | 186 |
| Males | 57 | 524 | 44 | 887 | 501 |
| Females | 136 | 1545 | 149 | 2089 | 1359 |
| Caucasians | 177 | 1817 | 176 | 2585 | 1638 |
| Hispanics | 0 | 181 | 0 | 226 | 151 |
| Blacks | 6 | 45 | 10 | 93 | 40 |
| Asians | 0 | 13 | 1 | 23 | 8 |
| Others | 10 | 13 | 6 | 49 | 23 |
| Impaired renal function | 5 | 42 | 5 | 69 | 59 |
| Low dose aspirin | 10 | 209 | 16 | 264 | 166 |
| High CV risk | 76 | 1030 | 74 | 1447 | 889 |

A detailed breakdown of the adverse events suspected to be drug related in dataset 9 is presented in Table 4.2-5.9 attached to module 2.7.4 Summary of Clinical Safety (pages 11588-11614 of CTD)

Since datasets 1 and 7 represent all short-term studies in OA and RA respectively, these will be used to discuss the short-term safety of lumiracoxib.

Dataset 2 is used to discuss the long-term safety.

## 13.2 Short-term Clinical Safety in Osteoarthritis (Dataset 1)

**Patient Disposition in OA:**

| Treatment group | Total | Total discontinued | | Discontinued due to | | |
|---|---|---|---|---|---|---|
| | | | | Adverse events | | Deaths |
| Lum 50 BD | 98 | 8 | 8.2% | 3 | 3.1% | 0 |
| Lum 100 QD | 122 | 6 | 4.9% | 2 | 1.6% | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Lum 100 BD | 96 | 7 | 7.3% | 3 | 3.1% | 0 |
| Lum 200 QD | 1421 | 221 | 15.6% | 96 | 6.8% | 0 |
| Lum 200 BD | 99 | 15 | 15.2% | 4 | 4.0% | 0 |
| Lum 400 QD | 2013 | 293 | 14.6% | 123 | 6.1% | 1 |
| Rof 25 QD | 257 | 31 | 12.1% | 17 | 6.6% | 0 |
| Cel 200 QD | 1185 | 208 | 17.6% | 97 | 8.2% | 0 |
| Cel 200 BD | 145 | 1 | 0.7% | 0 | 0% | 0 |
| Dic 75 BD | 94 | 16 | 17.0% | 13 | 13.8% | 0 |
| Ibu 800 TDS | 260 | 56 | 21.5% | 34 | 13.1% | 1 |
| Placebo | 1169 | 203 | 17.4% | 63 | 5.4% | 0 |

**All adverse events considered drug-related (%) in OA dataset 1**

| | **Lum 200 QD (n = 1418)** | **Lum 400 QD (n = 2009)** | **Rof 25 QD (n = 257)** | **Cel 200 QD (n = 1183)** | **Ibu 800 TDS (n = 260)** | **Placebo (n = 1168)** |
|---|---|---|---|---|---|---|
| Palpitation | 0.1 | 0.1 | 0 | 0.6 | 0 | 0.1 |
| Dyspepsia | 9.2 | 9.0 | 14.8 | 8.5 | 26.5 | 2.8 |
| Upper abdo pain | 4.9 | 4.8 | 4.7 | 5.2 | 21.2 | 1.8 |
| Diarrhoea | 3.9 | 4.2 | 4.7 | 3.5 | 1.9 | 2.6 |
| Nausea | 3.7 | 3.0 | 6.2 | 3.1 | 5.4 | 1.5 |
| Constipation | 1.8 | 2.0 | 1.2 | 1.9 | 1.5 | 1.2 |
| Abdo pain NOS | 1.3 | 2.2 | 4.3 | 1.5 | 3.5 | 0.7 |
| Flatulence | 1.3 | 1.1 | 1.2 | 1.2 | 2.3 | 0.8 |
| Vomiting | 1.3 | 1.0 | 2.3 | 1.2 | 2.7 | 0.9 |
| Loose stools | 0.8 | 0.9 | 0.4 | 0.6 | 0.4 | 1.0 |
| Epigastric discomfort | 0.8 | 0.6 | 0 | 0.5 | 3.1 | 0.1 |
| Abdo distention | 0.8 | 0.3 | 1.9 | 0.7 | 0.8 | 0.4 |
| Peri oedema | 1.3 | 1.3 | 3.5 | 1.6 | 1.9 | 1.1 |
| Fatigue | 0.9 | 1.3 | 1.9 | 0.8 | 0 | 0.8 |
| Fall | 0.5 | 0.1 | 0.8 | 0.6 | 0.4 | 0.6 |
| Oedema NOS | 0.2 | 0.1 | 0.4 | 0.2 | 0 | 0.1 |
| Influenza | 2.8 | 2.9 | 2.3 | 2.3 | 6.9 | 1.6 |
| Upper resp infection | 2.0 | 1.9 | 0.4 | 2.2 | 4.2 | 1.5 |
| Urinary infection | 1.8 | 0.9 | 0.8 | 1.2 | 3.1 | 0.7 |
| Weight increased | 1.0 | 0.3 | 0.8 | 0.3 | 0.8 | 0.5 |
| Creatinine increased | 0.1 | 0.2 | 0 | 0 | 0.8 | 0.1 |
| Joint swelling | 0.3 | 0.2 | 0 | 0.5 | 0.8 | 0.3 |
| Headache | 8.3 | 8.1 | 6.6 | 9.6 | 15.0 | 6.9 |
| Dizziness | 1.7 | 2.1 | 2.3 | 1.5 | 0 | 0.9 |
| Insomnia | 0.7 | 1.1 | 0.4 | 0.8 | 1.5 | 0.5 |
| Cough | 1.4 | 1.1 | 0.8 | 0.9 | 0.4 | 1.0 |
| Pruritus | 0.7 | 0.5 | 1.6 | 0.7 | 0 | 0.3 |
| Rash | 0.3 | 0 | 0.4 | 0.3 | 0.4 | 0.1 |
| Hypertension NOS | 1.5 | 1.9 | 1.2 | 1.3 | 3.1 | 1.0 |
| Hypertension aggrav | 0.8 | 0.6 | 0 | 1.0 | 3.1 | 0.3 |

**Serious adverse events regardless of causality in OA**

| | **Lum 200 QD (n = 1418)** | **Lum 400 QD (n = 2009)** | **Rof 25 QD (n = 257)** | **Cel 200 QD (n = 1183)** | **Ibu 800 TDS (n = 260)** | **Placebo (n = 1168)** |
|---|---|---|---|---|---|---|
| **Any event in** | **25 (1.8%)** | **26 (1.3%)** | **2 (0.8%)** | **20 (1.7%)** | **9 (3.5%)** | **11 (1.1%)** |
| | | | | | | |
| Anaemia NOS | 1 | | | | 1 | |
| Acute myo infarction | | 1 | | | | |
| Angina pectoris | | | | | | 1 |
| Angina aggravated | | | | 1 | | |
| Unstable angina | | | | | | 1 |
| Atrial fibrillation | | 1 | | 2 | | 1 |
| Atrial flutter | | | | | | 1 |
| Cardiac failure NOS | | | | 1 | | |

| | Lum 200 QD (n = 1418) | Lum 400 QD (n = 2009) | Rof 25 QD (n = 257) | Cel 200 QD (n = 1183) | Ibu 800 TDS (n = 260) | Placebo (n = 1168) |
|---|---|---|---|---|---|---|
| **Any event in** | **25 (1.8%)** | **26 (1.3%)** | **2 (0.8%)** | **20 (1.7%)** | **9 (3.5%)** | **11 (1.1%)** |
| Coro art disease | | | | 1 | | |
| Coro art occlusion | | | | | 1 | |
| Myocardial infarction | 1 | 2 | 1 | | 1 | |
| Pericard haemorrhage | | | | | 1 | |
| Valvular heart disease | | | | | | 1 |
| Deafness | | | | | | 1 |
| Vertigo | | | | 1 | | |
| Retinal detachment | 1 | | | | | |
| Abdominal pain | 1 | 1 | | 1 | | |
| Colitis | | | | 1 | | |
| Constipation | | | | 1 | | |
| DU haemorrhage | | | | | 1 | |
| Duodenitis | 1 | | | | | |
| Dysphagia | 1 | | | | | |
| Faeces discoloured | 1 | | | | | |
| Gastric ulcer | 1 | | | 1 | 2 | |
| GU haemorrhage | 1 | | | | | |
| GI haemorrhage | | 2 | | | | |
| Nausea | | 1 | | | | |
| Oesophageal ulcer | | 1 | | | | |
| Pancreatitis | | 1 | | | | |
| Rectal haemorrhage | | | | 1 | | |
| Reflux oesophagitis | | 1 | | | | |
| Peri oedema | | | | | 1 | |
| Weakness | | 1 | | | | |
| Biliary colic | | | | 1 | | |
| Cholecystitis | 1 | | | 1 | | |
| Cholelithiasis | | 1 | | | | |
| Hepatitis | 1 | | | | | |
| BP decreased | | | | 1 | | |
| ST depression (ECG) | | | | | 1 | |
| Diabetes | 1 | | | | | |
| Arthralgia | | | | | 1 | |
| CVA | 1 | | | | | 1 |
| Dystonia | 1 | | | | | |
| paraesthesia | | 1 | | | | |
| Syncope / TIA | | | | 1 | | 1 |
| Vertebral insuffi-y | | 1 | | | | |
| Mental disorder NOS | | | | 1 | | |
| Urinary calculus | | | | 1 | | |
| Renal colic | | | | | 1 | |
| Renal failure NOS | 1 | | | | | |
| Vaginal haemorrhage | | | 1 | | | |
| Asthma NOS | | 1 | | | | |
| Bronchospasm | | | | | | 1 |
| Pulm embolism | 1 | | | 1 | | |
| Angioneurotic oedema | | 1 | | | | |
| Purpura | | | | 1 | | |
| Arteritis | | 1 | | | | |
| Arterial occlusion | | | | | | 1 |
| DVT | 1 | | | | | |
| Hypertension | 1 | | | 1 | | |
| Hypertension aggrav | | | | | 1 | |

**Serious adverse events leading to discontinuation in OA**

| | Lum 200 QD (n = 1418) | Lum 400 QD (n = 2009) | Rof 25 QD (n = 257) | Cel 200 QD (n = 1183) | Ibu 800 TDS (n = 260) | Placebo (n = 1168) |
|---|---|---|---|---|---|---|
| **Any event in** | **13 (0.9%)** | **16 (0.8%)** | **1 (0.4%)** | **9 (0.8%)** | **2 (0.6%)** | **10 (0.9%)** |
| | | | | | | |
| Atrial fibrillation | | 1 | | 1 | | 1 |
| Atrial flutter | | | | | | 1 |
| Cardiac failure NOS | | | | 1 | | |
| Coro art disease | | | | 1 | | |
| Coro art occlusion | | | | | 1 | |
| Myocardial infarction | 1 | 1 | 1 | | 1 | |
| Pericard haemorrhage | | | | | 1 | |
| Valvular heart disease | | | | | | 1 |
| Deafness | | | | | | 1 |
| Retinal detachment | 1 | | | | | |
| Abdominal pain | | 1 | | 1 | | |
| DU haemorrhage | | | | | 1 | |
| Duodenitis | 1 | | | | | |
| Faeces discoloured | 1 | | | | | |
| Gastric ulcer | 1 | | | 1 | | |
| GU haemorrhage | 1 | | | | | |
| GI haemorrhage | | 2 | | | | |
| Oesophageal ulcer | | 1 | | | | |
| Pancreatitis | | 1 | | | | |
| Reflux oesophagitis | | 1 | | | | |
| Weakness | | 1 | | | | |
| Cholecystitis | 1 | | | | | |
| Diabetes | 1 | | | | | |
| CVA | 1 | | | | | 1 |
| Renal failure | 1 | | | | | |
| Renal failure acute | 1 | | | | | |
| Urinary retention | | 1 | | | | |
| Asthma | | 1 | | | | |
| Bronchospasm | | | | | | 1 |
| Pulm embolism | 1 | | | | | |
| Purpura | | | | 1 | | |
| Arteritis | | 1 | | | | |
| Arterial occlusion | | | | | | 1 |
| DVT | 1 | | | | | |
| Hypertension | | | | 1 | | |

With regard to any non-serious adverse event leading to discontinuation of the study drug, gastrointestinal tract events accounted for the majority of these:

| | Lum 200 QD (n = 1418) | Lum 400 QD (n = 2009) | Rof 25 QD (n = 257) | Cel 200 QD (n = 1183) | Ibu 800 TDS (n = 260) | Placebo (n = 1168) |
|---|---|---|---|---|---|---|
| **Any event in** | **86 (6.1%)** | **114 (5.7%)** | **16 (6.2%)** | **88 (7.4%)** | **33 (12.7%)** | **55 (4.7%)** |
| | | | | | | |
| GI tract | 47 (3.3%) | 64 (3.2%) | 11 (4.3%) | 40 (3.4%) | 26 (10.0% | 19 (1.6%) |
| Nervous system | 10 | 14 | 1 | 9 | 0 | 2 |
| Musculo-skeletal | 8 | 13 | 1 | 17 | 2 | 28 |
| Skin | 6 | 9 | 1 | 13 | 1 | 1 |
| Vascular | 6 | 4 | 0 | 2 | 2 | 1 |

**Deaths by treatment groups in short-term OA studies**

In the entire lumiracoxib programme, there were 18 deaths. Two patients had not been treated. Of the 16 deaths, 11 were within 14-days window of the last dose and 5 were outside this

window. Of the 11 within the window, 7 (0.1%) were on lumiracoxib, 3 (0.1%) on active comparators [2 on celecoxib and 1 on ibuprofen] and 1 (< 0.1%) on placebo.

Of the 16 deaths, 3 were reported in short-term OA studies.

| | **Lum 200 QD (n = 1418)** | **Lum 400 QD (n = 2009)** | **Rof 25 QD (n = 257)** | **Cel 200 QD (n = 1183)** | **Ibu 800 TDS (n = 260)** | **Placebo (n = 1168)** |
|---|---|---|---|---|---|---|
| Myocardial infarction | 1 | 1 | | | | |
| Sudden death | | 1 | | | | |

These data on deaths in short-term studies in OA are abstracted from table 4-11 in Summary of Clinical Safety (p 90 of 274).

## 13.3 Short-term Clinical Safety in Rheumatoid arthritis (Dataset 7)

**Patient Disposition in RA:**

| Treatment group | Total | Total discontinued | | Discontinued due to | | |
|---|---|---|---|---|---|---|
| | | | | Adverse events | | Deaths |
| Lum 50 BD | 102 | 13 | 12.7% | 9 | 8.8% | 0 |
| Lum 100 BD | 98 | 12 | 12.2% | 6 | 6.1% | 0 |
| Lum 200 QD | 595 | 188 | 31.6% | 35 | 5.9% | 1 |
| Lum 200 BD | 94 | 11 | 11.7% | 6 | 6.4% | 0 |
| Lum 400 QD | 908 | 253 | 27.9% | 71 | 7.8% | 1 |
| Lum 800 QD | 265 | 63 | 23.8% | 20 | 7.5% | 0 |
| Lum 1200 QD | 41 | 3 | 7.3% | 1 | 2.4% | 0 |
| Cel 200 BD | 525 | 117 | 22.3% | 39 | 7.4% | 1 |
| Dic 75 BD | 91 | 16 | 17.6% | 13 | 14.3% | 0 |
| Nap 500 BD | 320 | 88 | 27.5% | 31 | 9.7% | 0 |
| Ibu 800 TDS | 216 | 65 | 30.1% | 27 | 12.5% | 1 |
| Placebo | 692 | 260 | 37.6% | 43 | 6.2% | 1 |

**All adverse events considered drug-related (%) in RA**

| | **Lum 200 QD (n = 595)** | **Lum 400 QD (n = 908)** | **Lum 800 QD (n = 265)** | **Cel 200 BD (n = 525)** | **Nap 500 BD (n = 320)** | **Placebo (n = 692)** |
|---|---|---|---|---|---|---|
| Dyspepsia | 4.4 | 10.6 | 24.9 | 14.3 | 4.7 | 3.8 |
| Upper abdo pain | 4.0 | 3.2 | 9.1 | 5.1 | 8.1 | 2.7 |
| Diarrhoea | 2.5 | 3.7 | 7.2 | 4.6 | 3.4 | 2.0 |
| Nausea | 3.0 | 4.6 | 8.3 | 5.1 | 2.8 | 3.5 |
| Constipation | 0.7 | 1.1 | 0.8 | 1.9 | 1.6 | 1.6 |
| Abdo pain NOS | 2.4 | 1.8 | 2.3 | 1.5 | 1.9 | 0.9 |
| Frequent bowels | 0.3 | 0.2 | 0.4 | 0 | 0 | 0.3 |
| Vomiting | 1.5 | 1.8 | 2.3 | 2.3 | 1.6 | 1.0 |
| Loose stools | 0.8 | 1.0 | 1.5 | 0.4 | 0.6 | 1.0 |
| Epigastric discomfort | 0 | 0.8 | 1.9 | 0.8 | 0 | 0.1 |
| Abdo distention | 0.2 | 0.4 | 1.9 | 1.3 | 0.3 | 0.3 |
| Fatigue | 1.0 | 1.4 | 1.9 | 1.5 | 0.9 | 1.2 |
| Appetite decreased | 0.2 | 0.2 | 0 | 0 | 0 | 0.1 |
| Fluid retention | 0 | 0 | 0 | 0 | 0.3 | 0.1 |
| Peri oedema | 0.5 | 1.2 | 2.6 | 2.1 | 1.3 | 1.4 |
| Hypertension NOS | 0.5 | 1.8 | 1.1 | 1.1 | 2.2 | 0.9 |
| Urinary infection | 1.0 | 1.8 | 3.0 | 1.7 | 2.2 | 1.4 |
| Arthralgia | 0.7 | 1.1 | 1.1 | 0.8 | 0.9 | 0.9 |
| Pruritus | 1.3 | 0.8 | 1.5 | 1.7 | 0.3 | 0.7 |
| Rash | 0.3 | 1.0 | 1.5 | 1.0 | 0.9 | 0.6 |
| Herpes simplex | 0.5 | 0.7 | 1.5 | 0.2 | 0 | 0.3 |
| Tinnitus | 0.2 | 0.6 | 0.4 | 0.4 | 0.6 | 0.4 |
| Dizziness | 1.3 | 1.1 | 2.3 | 1.9 | 0.6 | 2.2 |
| Headache | 7.2 | 11.5 | 14.7 | 14.9 | 5.6 | 6.8 |
| Anxiety | 0.2 | 0.6 | 0.4 | 0.2 | 0.6 | 0.6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Paraesthesia | 0.5 | 0.9 | 0.4 | 0.4 | 0.6 | 0.3 |
| Hypoaesthesia | 0.2 | 0.6 | 0.4 | 0.4 | 0.3 | 0.3 |
| Cough | 1.0 | 1.3 | 1.9 | 1.7 | 0.6 | 1.2 |
| Dyspnoea NOS | 0.3 | 0.3 | 0.8 | 1.2 | 0.6 | 0.7 |
| Sinus congestion | 0.2 | 0.6 | 2.3 | 1.0 | 0 | 0.3 |
| Nasal congestion | 0.2 | 0.3 | 1.5 | 0.6 | 0 | 0.3 |
| Pharyngitis | 1.5 | 1.3 | 1.9 | 1.9 | 1.9 | 1.2 |
| Upper resp infection | 2.4 | 2.6 | 3.0 | 4.2 | 1.3 | 0.6 |

**Serious adverse events regardless of causality in RA**

| | **Lum 200 QD (n = 595)** | **Lum 400 QD (n = 908)** | **Lum 800 QD (n = 265)** | **Cel 200 BD (n = 525)** | **Nap 500 BD (n = 320)** | **Placebo (n = 692)** |
|---|---|---|---|---|---|---|
| **Total** | **17 (2.9%)** | **33 (3.6%)** | **4 (1.5%)** | **11 (2.1%)** | **5 (1.6%)** | **9 (1.3%)** |
| | | | | | | |
| Leucopenia NOS | | 1 | | | | |
| Lymphopenia | | 1 | | | | |
| Neutropenia | | 1 | | | | |
| Pancytopenia | 1 | | | | | |
| Acute myo infarction | | 1 | 2 | | | |
| Angina pectoris | 1 | 1 | | | | |
| Unstable angina | | 2 | | | | |
| Atrial fibrillation | 1 | | | 1 | | 1 |
| Cardiopulm arrest | | 1 | | | | |
| Supravent tachycardia | 1 | | | | | |
| Vent tachycardia | | | | 1 | | |
| Retinal art embolism | 1 | | | | | |
| Abdo pain | | 2 | | 1 | | 1 |
| Constipation | 1 | | | | | |
| Duodenal ulcer | | 1 | | | | |
| Gastric ulcer | | 2 | | | | |
| Nausea | | 1 | | | | |
| Vomiting | | 1 | | | | |
| Asthenia | 1 | | | | | |
| Pyrexia | | 2 | | 1 | | |
| Sudden death | | | | 1 | | |
| Abnormal liver funct | | 1 | | | | |
| Diabetes | | 1 | | 1 | | |
| CVA | | 2 | | | | 1 |
| Ischaemic stroke | 1 | | | | | |
| Paraesthesia | | 1 | | | | |
| Speech disorder | | 1 | | | | |
| Syncope | | | | 1 | | |
| TIA | | 2 | | | | |
| Depression | 1 | | | | | |
| Dyspnoea | | 1 | | | | |
| Pharyngitis | | 1 | | | | |
| Pulm Embolism | | 1 | | | | |
| Vesicular rash | | | | 1 | | |
| Skin eruption | | 1 | | | | |
| DVT | 1 | 2 | | | | 2 |
| Haematoma NOS | | 1 | | | 1 | |
| Hypertension NOS | | 1 | 1 | | | |
| Hypertensive crisis | | | | | 1 | |

**Serious adverse events leading to discontinuation in RA**

| | Lum 200 QD (n = 595) | Lum 400 QD (n = 908) | Lum 800 QD (n = 265) | Cel 200 BD (n = 525) | Nap 500 BD (n = 320) | Placebo (n = 692) |
|---|---|---|---|---|---|---|
| **Total** | **7 (1.2%)** | **17 (1.9%)** | **1 (0.4%)** | **5 (1.0%)** | **1 (0.3%)** | **6 (0.9%)** |
| | | | | | | |
| Leucopenia NOS | | 1 | | | | |
| Lymphopenia | | 1 | | | | |
| Neutropenia | | 1 | | | | |
| Pancytopenia | 1 | | | | | |
| Acute myo infarction | | 1 | 1 | | | |
| Angina pectoris | | 1 | | | | |
| Unstable angina | | 1 | | | | |
| Atrial fibrillation | | | | 1 | | |
| Supravent tachycardia | 1 | | | | | |
| Retinal art embolism | 1 | | | | | |
| Abdo pain | | 2 | | 1 | | 1 |
| Duodenal ulcer | | 1 | | | | |
| Gastric ulcer | | 2 | | | | |
| Nausea | | 1 | | | | |
| Vomiting | | 1 | | | | |
| Pyrexia | | | | 1 | | |
| Abnormal liver funct | | 1 | | | | |
| Increased creatinine | | 1 | | | | |
| CVA | | 1 | | | | |
| Speech disorder | | 1 | | | | |
| TIA | | 2 | | | | |
| Depression | 1 | | | | | |
| DVT | 1 | 1 | | | | 2 |
| Haematoma NOS | | | | | 1 | |
| Embolism | | | | | | 1 |

With regard to any non-serious adverse event leading to discontinuation of the study drug, gastrointestinal tract events accounted for the majority of these:

| | Lum 200 QD (n = 595) | Lum 400 QD (n = 908) | Lum 800 QD (n = 265) | Cel 200 BD (n = 525) | Nap 500 BD (n = 320) | Placebo (n = 692) |
|---|---|---|---|---|---|---|
| | | | | | | |
| Total discontinued | 41 (6.9%) | 68 (7.5%) | 18 (6.8%) | 37 (7.0%) | 31 (9.7%) | 45 (6.5%) |
| | | | | | | |
| GI tract events | 17 (2.9%) | 24 (2.6%) | 9 (3.4%) | 14 (2.7%) | 20 (6.3%) | 13 (1.9%) |
| Musculo-skeletal events | 10 (1.7%) | 12 (1.3%) | 2 (0.8%) | 8 (1.5%) | 1 (0.3%) | 13 (1.9%) |

**Deaths by treatment groups in short-term RA studies**

In the entire lumiracoxib programme, there were 18 deaths. Two patients had not been treated. Of the 16 deaths, 11 were within 14-days window of the last dose and 5 were outside this window.

Of the 11 within the window, 7 (0.1%) were on lumiracoxib, 3 (0.1%) on active comparators [2 on celecoxib and 1 on ibuprofen] and 1 (< 0.1%)on placebo.

Of the 16 deaths, 8 were reported in short-term RA studies.

| | Lum 200 QD (n = 595) | Lum 400 QD (n = 908) | Lum 800 QD (n = 265) | Cel 200 BD (n = 525) | Ibu 800 TDS (n = 216) | Placebo (n = 692) |
|---|---|---|---|---|---|---|
| Gastric haematoma | | 1 * | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Myocardial infarction | 1 | | | | | |
| Stroke | | 1 | | | | |
| Sudden death | | | | 1 | | |
| Acute pulm embolism | | 1 | | | | 1 |
| Lung cancer | 1 | | | | | |
| Faecal peritonitis | | | | | 1 | |

These data on deaths in short-term studies in OA are abstracted from table 4-11 in Summary of Clinical Safety (p 90 of 274)
* suspected to be drug-related

## 13.4 Long-term Clinical Safety in Osteoarthritis (Dataset 2)

**Adverse Clinical Experiences by SOC**

| | **Lumiracoxib 200mg QD** | **Lumiracoxib 400mg QD** | **Celecoxib 200mg QD** |
|---|---|---|---|
| **Total Patients (N)** | **543** | **550** | **537** |
| **Any event in n=** | **390 (71.8%)** | **394 (71.6%)** | **368 (68.5%)** |
| Infections/infestations | 148 | 150 | 132 |
| Digestive System | 145 | 161 | 139 |
| Musculo-skeletal | 105 | 127 | 109 |
| Nervous system | 76 | 92 | 78 |
| Investigations | 54 | 45 | 25 |
| General | 50 | 59 | 58 |
| Respiratory System | 44 | 65 | 43 |
| Skin And Skin Appendages | 41 | 38 | 47 |
| Injury, poisoning and procedures | 37 | 30 | 29 |
| Psychiatric system | 31 | 27 | 21 |
| Vascular | 30 | 49 | 41 |
| Cardiac | 18 | 20 | 20 |
| Metabolism and nutrition | 17 | 20 | 12 |
| Renal | 17 | 9 | 7 |
| Ears and labyrinth | 16 | 12 | 18 |
| Eyes | 12 | 12 | 18 |
| Haemopoietic | 8 | 7 | 4 |
| Reproductive | 8 | 7 | 11 |
| Neoplasms | 8 | 4 | 9 |
| Endocrine | 4 | 1 | 4 |
| Immune system | 2 | 6 | 4 |
| Hepatobiliary | 1 | 2 | 2 |
| Congenital, familial | 0 | 0 | 1 |
| Others | 6 | 7 | 4 |

The most frequently reported events (at least 10 patients with the 2 lumiracoxib groups combined) were as follows:

| **Infections** | **Digestive System** | **Musculo-skeletal** | **Nervous system** | **Other events** |
|---|---|---|---|---|
| Nasopharyngitis | Abdominal pain | Arthralgia | Headache | Vertigo |
| Bronchitis | Dyspepsia | Back pain | Dizziness | Peri oedema |
| Cystitis | Constipation | Muscle cramps | Migraine | Depression |
| Gastroenteritis | Diarrhoea | | Paraesthesia | Insomnia |
| Influenza | Flatulence | | | Cough |
| Sinusitis | Loose stools | | | Dyspnoea |
| URTI | Nausea | | | Pruritus NOS |
| Rhinitis | Vomiting | | | Hypertension |
| UTI | | | | Hypertension aggravated |

**Serious adverse clinical experiences**

| | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg QD |
|---|---|---|---|
| **Total Patients (N)** | **543** | **550** | **537** |
| **Any serious event in n=** | **39 (7.2%)** | **46 (8.4%)** | **35 (6.5%)** |
| Anaemia | 1 | 0 | 0 |
| Angina pectoris aggravated | 0 | 0 | 1 |
| Unstable angina | 1 | 0 | 0 |
| Atrial fibrillation | 0 | 1 | 2 |
| Complete AV block | 0 | 1 | 0 |
| Cardiac failure | 1 | 0 | 1 |
| Coronary artery disease | 0 | 0 | 1 |
| Myocardial infarction | 2 | 3 | 0 |
| Myocardial ischaemia | 1 | 0 | 0 |
| Vertigo | 0 | 0 | 1 |
| Cataract | 1 | 0 | 0 |
| Abdominal pain | 1 | 3 | 1 |
| Constipation | 0 | 0 | 1 |
| Diarrhoea | 1 | 0 | 0 |
| Duodenitis | 1 | 0 | 0 |
| Gastric ulcer | 1 | 0 | 0 |
| Gastric ulcer haemorrhage | 1 | 0 | 0 |
| Gastrointestinal haemorrhage | 0 | 2 | 0 |
| Malaena | 0 | 1 | 0 |
| Oesophageal ulcer haemorrhage | 0 | 1 | 0 |
| Acute pancreatitis | 1 | 0 | 0 |
| Rectal haemorrhage | 0 | 0 | 1 |
| Reflux oesophagitis | 0 | 1 | 0 |
| Vomiting | 0 | 1 | 0 |
| Sudden cardiac death | 0 | 1 | 0 |
| Toxic hepatitis | 1 | 0 | 0 |
| Diabetes mellitus | 1 | 0 | 0 |
| Arthralgia | 1 | 1 | 0 |
| CVA | 3 | 0 | 1 |
| Dizziness | 0 | 1 | 0 |
| Paraesthesia | 0 | 1 | 0 |
| TIA | 1 | 2 | 1 |
| Vertebrobasilar insufficiency | 0 | 1 | 0 |
| Asthma | 0 | 1 | 0 |
| Pulmonary embolism | 2 | 0 | 1 |
| Urticaria | 0 | 1 | 0 |
| DVT | 1 | 0 | 0 |
| Hypertension | 0 | 0 | 2 |

**Non-serious adverse events leading to drug withdrawal by SOC**

| | Lumiracoxib 200mg QD | Lumiracoxib 400mg QD | Celecoxib 200mg QD |
|---|---|---|---|
| **Total Patients (N)** | **543** | **550** | **537** |
| **Any event in n=** | **72 (13.3%)** | **68 (12.4%)** | **64 (11.9%)** |
| Infections/infestations | 5 | 3 | 0 |
| Digestive System | 25 | 29 | 27 |
| Musculo-skeletal | 6 | 9 | 8 |
| Nervous system | 8 | 8 | 11 |
| Investigations | 14 | 13 | 6 |
| General | 5 | 6 | 5 |
| Respiratory System | 2 | 3 | 2 |
| Skin And Skin Appendages | 5 | 3 | 8 |
| Injury, poisoning and procedures | 4 | 0 | 0 |
| Psychiatric system | 1 | 2 | 3 |
| Vascular | 5 | 5 | 3 |
| Cardiac | 1 | 1 | 6 |
| Metabolism and nutrition | 2 | 0 | 0 |
| Renal | 2 | 1 | 0 |
| Ears and labyrinth | 1 | 1 | 5 |
| Eyes | 1 | 0 | 0 |
| Haemopoietic | 2 | 0 | 0 |
| Reproductive | 0 | 1 | 0 |
| Neoplasms | 0 | 0 | 0 |
| Endocrine | 1 | 0 | 0 |
| Immune system | 0 | 1 | 1 |
| Hepatobiliary | 0 | 0 | 0 |
| Congenital, familial | 0 | 0 | 0 |
| Others | 0 | 0 | 0 |

**Deaths by treatment groups in long-term OA study**

In the entire lumiracoxib programme, there were 18 deaths. Two patients had not been treated. Of the 16 deaths, 11 were within 14-days window of the last dose and 5 were outside this window.

Of the 16 deaths, 4 were reported in long-term OA study.

| | Lumiracoxib 200mg QD n=543 | Lumiracoxib 400mg QD n=550 | Celecoxib 200mg QD n=537 |
|---|---|---|---|
| Acute pancreatitis | 1 | | |
| Myocardial infarction | | 1 | |
| Sudden death | | 1 | |
| Stroke | | | 1 |

These data on deaths in short-term studies in OA are abstracted from table 4-11 in Summary of Clinical Safety (p 90 of 274)

***Assessor's comments on clinical safety of lumiracoxib:***

Lumiracoxib appears to have an acceptable profile of clinical safety. The pattern of events reported with lumiracoxib is typical of COX-2 selective inhibitors that have been approved to date.

As far as the comparison between 200mg QD and 400mg QD doses is concerned, there is a greater frequency of drug-related adverse events with the higher dose in dataset 1 and 7. These events include a range of GI, neurological and psychiatric events.

In dataset 7 in RA, the % of patients who discontinued due to an adverse event was 5.9% with 200mg QD dose and 7.8% with 400mg QD dose.

The CPMP is undertaking a class review of the cardiac safety of COX-2 selective inhibitors. This is prompted by the concerns that COX-2 selective inhibitors may have prothrombotic activity.

There is also an increased concern that COX-2 selective inhibitors may have a greater potential for nephrotoxicity in view of the constitutional role of COX-2 in maintaining renal homeostasis. Recently, the prescribing information for valdecoxib in the US was amended to draw attention to serious hypersensitivity reactions reported with its use.

At present, there is no evidence of serious hypersensitivity reactions or greater nephrotoxicity following the use of lumiracoxib.

The gastrointestinal, hepatic and renal safety of lumiracoxib is discussed in greater details in sections 16 and 18 of this assessment Report.

## 14. LABORATORY SAFETY

Throughout the clinical programme, laboratory safety of lumiracoxib was monitored by measurement of:

- Haematology
- Full biochemistry
- Urinalysis

The hepatic, renal and haemopoietic safety of lumiracoxib are further discussed in detail in sections 18 of this Assessment Report.

### 14.1 Haematology

Dataset 1 Short-term studies in OA

| | **Lum 200 QD (n = 1418)** | **Lum 400 QD (n = 2009)** | **Rof 25 QD (n = 257)** | **Cel 200 QD (n = 1183)** | **Placebo (n = 1168)** |
|---|---|---|---|---|---|
| ≥ 20 g/L fall in haemoglobin | 18 | 30 | 5 | 13 | 9 |
| WBC < 0.8 x LLN | 3 | 7 | 0 | 7 | 5 |
| Neutrophils < 0.9 x LLN | 31 | 41 | 5 | 26 | 19 |
| Eosinophils > 1.1 ULN | 18 | 18 | 6 | 18 | 16 |
| Platelets < LLN | 13 | 22 | 5 | 16 | 9 |

Dataset 7 Short-term studies in RA

| | **Lum 200 QD (n = 595)** | **Lum 400 QD (n = 908)** | **Lum 800 QD (n = 265)** | **Cel 200 BD (n = 525)** | **Placebo (n = 692)** |
|---|---|---|---|---|---|
| ≥ 20 g/L fall in haemoglobin | 11 | 29 | **23** | 6 | 13 |
| WBC < 0.8 x LLN | 3 | 9 | 3 | 5 | 5 |
| Neutrophils < 0.9 x LLN | 14 | 17 | 6 | 14 | 14 |

| | | | | | |
|---|---|---|---|---|---|
| Eosinophils > 1.1 ULN | 8 | 11 | **5** | 6 | 5 |
| Platelets < LLN | 8 | 7 | **5** | 4 | 6 |

Highlighted values denote a relatively high frequency

Dataset 2 Long-term study in OA

| | **Lumiracoxib 200mg QD n = 543** | **Lumiracoxib 400mg QD n = 550** | **Celecoxib 200mg QD n = 537** |
|---|---|---|---|
| ≥ 20 g/L fall in haemoglobin | 16 | **20** | 18 |
| WBC < 0.8 x LLN | 3 | 6 | 5 |
| Neutrophils < 0.9 x LLN | 13 | **21** | 18 |
| Eosinophils > 1.1 ULN | 11 | 7 | 12 |
| Platelets < LLN | 11 | 12 | 12 |

Highlighted values denote a relatively high frequency

## 14.2 Biochemistry

Dataset 1 Short-term studies in OA

| | **Lum 200 QD (n = 1418)** | **Lum 400 QD (n = 2009)** | **Rof 25 QD (n = 257)** | **Cel 200 QD (n = 1183)** | **Placebo (n = 1168)** |
|---|---|---|---|---|---|
| Alanine transaminase (ALT) | | | | | |
| > 3 x ULN | 6 | 24 | 0 | 4 | 2 |
| > 5 x ULN | 2 | 10 | 0 | 0 | 1 |
| > 8 x ULN | **1** | **4** | 0 | 0 | 0 |
| Aspartate transaminase (AST) | | | | | |
| > 3 x ULN | 3 | 8 | 0 | 1 | 3 |
| > 5 x ULN | 1 | 2 | 0 | 0 | 1 |
| > 8 x ULN | 0 | 0 | 0 | 0 | 0 |
| Bilirubin | | | | | |
| 1.2 x ULN | 14 | 18 | 1 | 20 | 10 |
| > 51 umol/L | **1** | **1** | 0 | 0 | 0 |
| Alkaline Phosphatase | | | | | |
| > 1.5 x ULN | 3 | **11** | 0 | 2 | 2 |
| Creatinine | | | | | |
| > 35 umol increase | 32 (2.3%) | 49 (2.4%) | 3 (1.2%) | 5 (0.4%) | 10 (0.9%) |
| > 1.5 x ULN | 2 | 0 | 0 | 1 | 2 |
| > 2 x baseline | 2 | 1 | 0 | 1 | 2 |
| > 88 umol/L increase | 1 | 0 | 0 | 1 | 1 |
| Creatinine clearance | | | | | |
| < 81 ml/min | 605 | 819 | 137 | 433 | 450 |
| < 50 ml/min | 105 | 140 | 19 | 57 | 61 |
| < 30 ml/min | 5 | 5 | 0 | 3 | 5 |
| > 25% decrease from baseline | **106 (7.5%)** | **151 (7.6%)** | 13 (5.1%) | 49 (4.2%) | 50 (4.3%) |
| Potassium | | | | | |
| < 3.0 mmol/L | 0 | 2 | 0 | 1 | 1 |
| > 5.5 mmol/L | **27 (1.9%)** | **38 (1.9%)** | 3 (1.2%) | 14 (1.2%) | 10 (0.9%) |
| Magnesium | | | | | |
| < 0.5 mmol/L | 3 | 0 | 0 | 1 | 2 |
| Blood urea nitrogen | | | | | |
| 50% increase from baseline | 136 (9.6%) | 217 (10.8%) | 25 (9.7%) | 123 (10.4%) | 42 (3.6%) |

Highlighted values denote a relatively high frequency

Dataset 7 Short-term studies in RA

| | **Lum 200 QD (n = 595)** | **Lum 400 QD (n = 908)** | **Lum 800 QD (n = 265)** | **Cel 200 BD (n = 525)** | **Placebo (n = 692)** |
|---|---|---|---|---|---|
| Alanine transaminase (ALT) | | | | | |
| > 3 x ULN | 7 | **19** | 3 | 5 | 3 |
| > 5 x ULN | 2 | **5** | 0 | 3 | 1 |
| > 8 x ULN | 0 | **1** | 0 | **1** | 0 |
| Aspartate transaminase (AST) | | | | | |
| > 3 x ULN | 3 | **5** | 1 | **3** | 1 |
| > 5 x ULN | 0 | 0 | 1 | **2** | 0 |
| > 8 x ULN | 0 | 0 | 0 | **1** | 0 |
| Bilirubin | | | | | |
| 1.2 x ULN | **3** | 3 | 0 | **5** | 2 |
| > 51 umol/L | 0 | 0 | 0 | 0 | 0 |
| Alkaline Phosphatase | | | | | |
| > 1.5 x ULN | 5 | **12** | 4 | 9 | 8 |
| Creatinine | | | | | |
| > 35 umol increase | 9 | **31** | 9 | 1 | 6 |
| > 1.5 x ULN | 3 | 2 | 1 | 0 | 0 |
| > 2 x baseline | 3 | 4 | 1 | 0 | 2 |
| > 88 umol/L increase | **2** | 1 | 0 | 0 | 1 |
| Creatinine clearance | | | | | |
| < 81 ml/min | 199 | 299 | 81 | 148 | 196 |
| < 50 ml/min | 27 | 40 | 11 | 10 | 15 |
| < 30 ml/min | 3 | 3 | 0 | 0 | 0 |
| > 25% decrease from baseline | 68 (11.7%) | 112 (12.6%) | **36 (13.7%)** | 46 (8.9%) | 45 (6.6%) |
| Potassium | | | | | |
| < 3.0 mmol/L | 1 | 0 | 1 | 0 | 0 |
| > 5.5 mmol/L | 8 | **21** | 2 | 4 | 5 |
| Magnesium | | | | | |
| < 0.5 mmol/L | 2 | 1 | 1 | 0 | 1 |
| Blood urea nitrogen | | | | | |
| 50% increase from baseline | 59 (9.9%) | 139 (15.3%) | **49 (18.5%)** | 77 (14.7%) | 38 (5.5%) |

Highlighted values denote a relatively high frequency

Dataset 2 Long-term study in OA

| | **Lumiracoxib 200mg QD n = 543** | **Lumiracoxib 400mg QD n = 550** | **Celecoxib 200mg QD n = 537** |
|---|---|---|---|
| Alanine transaminase (ALT) | | | |
| > 3 x ULN | **14** | **12** | 7 |
| > 5 x ULN | **6** | **5** | 0 |
| > 8 x ULN | **3** | **2** | 0 |
| Aspartate transaminase (AST) | | | |
| > 3 x ULN | **6** | **5** | 2 |
| > 5 x ULN | **4** | **2** | 0 |
| > 8 x ULN | **2** | **0** | 0 |
| Bilirubin | | | |
| 1.2 x ULN | 3 | 3 | **12** |
| > 51 umol/L | 0 | 0 | 0 |
| Alkaline Phosphatase | | | |
| > 1.5 x ULN | **4** | **4** | 1 |
| Creatinine | | | |
| > 35 umol increase | 25 | 39 | 17 |
| > 1.5 x ULN | 2 | 3 | 0 |
| > 2 x baseline | 3 | 3 | 1 |
| > 88 umol/L increase | **2** | 1 | 0 |
| Creatinine clearance | | | |
| < 81 ml/min | 295 | 303 | 247 |
| < 50 ml/min | 67 | 69 | 50 |
| < 30 ml/min | 5 | 10 | 3 |
| > 25% decrease from baseline | **90 (16.6%)** | **105 (19.3%)** | 66 (12.4%) |
| Potassium | | | |
| < 3.0 mmol/L | 0 | 2 | 2 |
| > 5.5 mmol/L | **19** | **19** | 13 |
| Magnesium | | | |
| < 0.5 mmol/L | 1 | 0 | 0 |
| Blood urea nitrogen | | | |
| 50% increase from baseline | 121 (22.3%) | **140 (25.5%)** | 109 (20.3%) |

Highlighted values denote a relatively high frequency

## 14.3 Urinalysis

Dataset 1 Short-term studies in OA

| | Lum 200 QD (n = 1418) | Lum 400 QD (n = 2009) | Rof 25 QD (n = 257) | Cel 200 QD (n = 1183) | Placebo (n = 1168) |
|---|---|---|---|---|---|
| Urine protein (> ++) | 26 | 29 | 7 | 18 | 21 |

Dataset 7 Short-term studies in RA

| | Lum 200 QD (n = 595) | Lum 400 QD (n = 908) | Lum 800 QD (n = 265) | Cel 200 BD (n = 525) | Placebo (n = 692) |
|---|---|---|---|---|---|
| Urine protein (> ++) | 14 | 24 | 2 | 8 | 16 |

Highlighted values denote a relatively high frequency

Dataset 2 Long-term study in OA

| | Lumiracoxib 200mg QD n = 543 | Lumiracoxib 400mg QD n = 550 | Celecoxib 200mg QD n = 537 |
|---|---|---|---|
| Urine protein (> ++) | **19** | 13 | 16 |

Highlighted values denote a relatively high frequency

***Assessor's comments on laboratory safety of lumiracoxib:***

These data confirm that lumiracoxib is a mild to moderate hepatotoxin and a moderate nephrotoxin.

The applicant has provided Special Expert Evaluation Reports (SPERs) addressing hepatic and renal safety of lumiracoxib. These are discussed in sections 18.1 and 18.2 of this Assessment Report.

While it is recognised that the pharmacokinetics of lumiracoxib parent drug are not influenced by renal impairment, one needs to consider the pharmacodynamic effects of lumiracoxib in patients with compromised renal function.

It is also noted that exposure to lumiracoxib is lower in patients with end stage renal disease compared to normal subjects. Compared to normal subjects, mean exposure to 4'-hydroxy-lumiracoxib is slightly increased in ESRD patients and exposure to 4'-hydroxy-5-carboxy-lumiracoxib is increased markedly (by about 7 times).

The assessor is of the view that lumiracoxib should be contraindicated in all patients with moderate or severe renal dysfunction and not just those with estimated creatinine clearance < 30 ml/min – this value should be revised to < 50 ml/min.

Section 4.2 on Posology should also be amended to reflect this change in the use of lumiracoxib in patients with renal impairment.

## 15. ELECTROCARDIOGRAPHIC SAFETY

ECGs were monitored in a range of indications, using different doses and duration of treatment with lumiracoxib.

The Applicant has provided a Special Expert Evaluation Report on the ECG safety of lumiracoxib. It is prepared by a renowned expert in drug-induced proarrhythmias.

As for clinical and laboratory safety, the ECG data are divided into various datasets as described under "Clinical Safety" with the inclusion of a Dataset 0 from clinical pharmacology studies.

This assessment focuses on:

| | |
|---|---|
| Dataset 0 | Clinical pharmacology studies 0101, 0102 and 2312 |
| Dataset 4: | Post-surgical dental pain studies 0103, 0115, 2302, 2329 |
| Dataset 5: | Post orthopaedic surgery pain studies 0131, 0132 |
| Dataset 9: | All OA and RA studies (excluding acute pain studies) |

Outlier values of interest were defined as follows:

| | |
|---|---|
| Heart rate (HR) | A change of ≥ 25% from baseline and a value of < 50 or > 100 bpm |
| PR interval | A change of ≥ 25% from baseline and a value over 200 ms |
| QRS interval | A change of ≥ 25% from baseline and a value over 100 ms |
| QT interval | A new occurrence of ≥ 500 ms not present at baseline |
| QTc interval | A change from baseline (Δ) of:<br>- ≥ 30 - ≤ 60 ms<br>- ≥ 60 ms<br>A new occurrence of ≥ 500 ms |

QT interval measured was corrected for heart rate to derive QTc interval by:
- Bazett's (QTcB) correction as well as
- Fridericia's (QTcF) correction

### 15.1 Dataset 0

Evaluation of multiple ECGs at baseline and after dosing

Study 0101

| | **Dose of lumiracoxib (mg)** | | | | | **Placebo** |
|---|---|---|---|---|---|---|
| Outlier for | **50** | **100** | **200** | **400** | **800** | |
| N = | **6** | **6** | **6** | **6** | **6** | **12** |
| HR | 0 | 0 | 0 | 0 | 0 | 0 |
| PR | 0 | 0 | 0 | 0 | 0 | 0 |
| QRS | 0 | 0 | 0 | 0 | 0 | 0 |
| QT | 0 | 0 | 0 | 0 | 0 | 0 |
| Mean change (QTcB) | - 8.2 | - 9.7 | - 5.5 | - 15.7 | - 4.2 | - 7.1 |
| Max mean change (QTcB) | 7.8 | 4.3 | 9.8 | 1.5 | 13.2 | 7.4 |
| QTcB | | | | | | |
| Δ 30-60 | 0 | 0 | **1** | 0 | 0 | 0 |
| Δ > 60 | 0 | 0 | 0 | 0 | 0 | 0 |
| New 500 | 0 | 0 | 0 | 0 | 0 | 0 |
| QTcF | | | | | | |
| Δ 30-60 | 0 | 0 | **0** | 0 | 0 | 0 |
| Δ > 60 | 0 | 0 | 0 | 0 | 0 | 0 |
| New 500 | 0 | 0 | 0 | 0 | 0 | 0 |

Study 0102

| | Dose of lumiracoxib (mg) | | | | | Placebo |
|---|---|---|---|---|---|---|
| Outlier for | **50 BD** | **100 BD** | **200 BD** | **400 QD** | **300 BD** | |
| N = | **6** | **6** | **6** | **6** | **6** | **10** |
| HR | 0 | 0 | 0 | 0 | 0 | 0 |
| PR | 0 | 0 | 0 | 0 | 0 | 0 |
| QRS | 0 | 0 | 0 | 0 | 0 | 0 |
| QT | 0 | 0 | 0 | 0 | 0 | 0 |
| Mean change (QTcB) | 0 | - 6.3 | - 3.8 | - 6.7 | - 2.0 | - 0.2 |
| Max mean change (QTcB) | 18.5 | 12.0 | 13.5 | 16.5 | 15.7 | 17.4 |
| QTcB | | | | | | |
| Δ 30-60 | **1** | 0 | **1** | **1** | **1** | **2** |
| Δ > 60 | 0 | 0 | 0 | 0 | 0 | 0 |
| New 500 | 0 | 0 | 0 | 0 | 0 | 0 |
| QTcF | | | | | | |
| Δ 30-60 | **0** | 0 | **0** | **0** | **0** | **0** |
| Δ > 60 | 0 | 0 | 0 | 0 | 0 | 0 |
| New 500 | 0 | 0 | 0 | 0 | 0 | 0 |

Study 2312

There were no changes of note in 13 subjects who were dosed with lumiracoxib 800mg daily.

## 15.2 Dataset 4

| | L 200 | L 400 | L 800 | R 50 | C 200 | Placebo |
|---|---|---|---|---|---|---|
| | Age (years) | | | | | |
| N | 52 | 153 | 52 | 153 | 101 | 103 |
| Mean | 22 | 22 | 21 | 22 | 23 | 22 |
| | Gender (%) | | | | | |
| M | 40 | 31 | 46 | 31 | 33 | 37 |
| F | 60 | 69 | 54 | 69 | 67 | 63 |

Results

Evaluation of baseline and single ECGs at about 3 hours after dosing

| Outlier for | **L 200** | **L 400** | **L 800** | **R 50** | **C 200** | **Placebo** |
|---|---|---|---|---|---|---|
| N = | **52** | **457** | **52** | **153** | **101** | **178** |
| HR | 1 | 0 | 0 | 0 | 0 | 0 |
| PR | 0 | 0 | 0 | 0 | 0 | 0 |
| QRS | 1 | 3 | 1 | 0 | 0 | 0 |
| QT | 0 | 0 | 0 | 0 | 0 | 0 |
| Mean change (QTcB) | 1.9 | 2.5 | 2.5 | 2.4 | 0.4 | - 0.9 |
| Max mean change (QTcB) | 1.9 | 2.5 | 2.5 | 2.5 | 0.4 | - 0.9 |
| QTcB | | | | | | |
| Δ 30-60 | **3** | **42** | **6** | **14** | **9** | **5** |
| Δ > 60 | 0 | 0 | 0 | 0 | **1** | 0 |
| New 500 | 0 | 0 | 0 | 0 | 0 | 0 |
| QTcF | | | | | | |
| Δ 30-60 | **2** | **12** | **1** | **5** | **4** | **5** |
| Δ > 60 | 0 | 0 | 0 | 0 | **0** | 0 |
| New 500 | 0 | 0 | 0 | 0 | 0 | 0 |

## 15.3 Dataset 5

Dataset 5 included 120 patients who received 400mg QD of lumiracoxib, 60 patients who received naproxen 500mg BD and 120 who received placebo.

| Outlier for | **L 400 QD** | **N 500 BD** | **Placebo** |
|---|---|---|---|
| | **Age (years)** | | |
| N = | 60 | 60 | 60 |
| Mean | 65 | 64 | 66 |
| | **Gender (%)** | | |
| M | 42 | 55 | 55 |
| F | 58 | 45 | 45 |

Results

Evaluation of baseline and single ECGs at 3 hours after dosing

| Outlier for | **L 400 QD** | **N 500 BD** | **Placebo** |
|---|---|---|---|
| N = | **120** | **60** | **120** |
| HR | 4 | 4 | 30 |
| PR | 0 | 0 | 0 |
| QRS | 2 | 0 | 2 |
| QT | 0 | 0 | 0 |
| Mean change (QTcB) | 5.8 | 7.9 | 7.2 |
| Max mean change (QTcB) | 5.8 | 7.9 | 7.2 |
| QTcB | | | |
| Δ 30-60 | 13 | 11 | 11 |
| Δ > 60 | 0 | 3 | 2 |
| New 500 | 0 | 0 | 0 |
| QTcF | | | |
| Δ 30-60 | 4 | 3 | 2 |
| Δ > 60 | 0 | 0 | 2 |
| New 500 | 0 | 0 | 0 |

## 15.4 Dataset 9

Dose range covered: 50mg BD to 1200mg QD.

In these studies, usually there was a baseline ECG followed by two or more ECGs post-randomisation. The summary of ECG changes for patients with peak ECG measurements (usually within 1-4 hours after a dose) at recommended doses and higher are shown. Data on other COX-2 selective inhibitors have been provided but are not included in the table below:

*The frequency of patients with outlier values is expressed in %*

| Outlier for | **L 200 QD** | **L 200 BD** | **L 400 QD** | **L 800 QD** | **L 1200 QD** | **Placebo** |
|---|---|---|---|---|---|---|
| N = | 2069 | 193 | 2976 | 265 | 41 | 1860 |
| HR Brady | 0.24 | 0 | 0.43 | 0 | 0 | 0.10 |
| Tachy | 0.96 | 0 | 0.85 | 0.51 | 0 | 0.40 |
| PR | 0.32 | 2.56 | 0.59 | 0 | 0 | 0.51 |
| QRS | 1.12 | 0 | 1.44 | 1.54 | 0 | 0.70 |
| QT | 0 | 0 | 0.16 | 0 | 0 | 0.10 |
| Mean change (QTcB) | 1.6 | - 13.5 | 0.6 | 2.4 | - 1.6 | - 1.8 |
| Max mean change (QTcB) | 8.0 | 13.5 | 5.3 | 7.1 | 4.6 | 1.0 |
| QTcB | | | | | | |
| Δ 30-60 | 15.52 | 6.10 | 12.40 | 14.95 | 10.00 | 10.65 |
| Δ > 60 | 1.70 | 1.22 | 1.29 | 1.55 | 0 | 0.91 |

| | | | | | | |
|---|---|---|---|---|---|---|
| New 500 | 0.08 | 0 | 0.37 | 0 | 0 | 0.20 |
| QTcF | | | | | | |
| Δ 30-60 | 12.45 | 6.10 | 9.98 | 10.82 | 7.50 | 8.32 |
| Δ > 60 | 0.81 | 1.22 | 0.59 | 0.52 | 0 | 0.61 |
| New 500 | 0 | 0 | 0.11 | 0 | 0 | 0.10 |

*Rhythm analysis (% of patients with peak ECG measurements)*

| Outlier for | **L 200 QD** | **L 200 BD** | **L 400 QD** | **L 800 QD** | **L 1200 QD** | **Placebo** |
|---|---|---|---|---|---|---|
| N = | 2069 | 193 | 2976 | 265 | 41 | 1860 |
| First degree AV block | 4.0 | 1.2 | 3.9 | 0.5 | 0 | 3.1 |
| Atrial fibrillation | 0.2 | 0 | 0.2 | 0 | 0 | 0.1 |
| Sinus bradycardia | 1.0 | 2.4 | 0.6 | 0.5 | 0 | 0.2 |
| Ventricular tachycardia | 0.1 | 0 | 0 | 0 | 0 | 0 |

One patient [0606-00020] from study 0112E in the lumiracoxib 400mg group had a complete heart block. She was an 87 years old white female with pre-existing LBBB

***Assessor's comments on electrocardiographic safety of lumiracoxib:***

There are very minor changes but given the presence of changes in the placebo group and absence of any dose-effect relationship, these data provide sufficient reassurance. These data show that lumiracoxib has no effect on parameters of cardiac conduction or ventricular action potential duration.

There is no evidence of any concern at present.

## 16. GASTROINTESTINAL SAFETY

The Applicant has provided a Special Expert Evaluation Report on gastrointestinal safety of lumiracoxib.

Prior to the start of the phase III development of lumiracoxib, an independent Gastrointestinal Safety Committee was set up to review and adjudicate all suspected upper gastrointestinal ulcer complications occurring in the phase III clinical studies.

This committee that reviewed all phase III events was composed of three independent gastroenterologists.

The Report reviews:

The results section describes the following data:

- the volunteer endoscopy studies
- the patient endoscopy studies ~xr39i
- the pre-specified gastrointestinal events ~xr40i
- the laboratory data for haematocrit and haemoglobin.
- the complicated ulcers:
  - PUBs (perforations, obstructions, symptomatic ulcers and bleeds)
  - POBs (perforations, obstructions and bleeds) ~

### 16.1 Endoscopy studies in healthy subjects

The two endoscopy studies in healthy volunteers – 0107 and 2311 – have already been described in section 3.1 on Primary Pharmacodynamics.

These studies compared lumiracoxib to naproxen and placebo for their effects on gastroduodenal mucosa (number of erosions).

These studies showed a marked difference between lumiracoxib and naproxen. There was no difference between lumiracoxib and placebo.

## 16.2 Endoscopy studies in patients

Two endoscopy studies – 0110 and 0126 - were undertaken in patients. Patients underwent endoscopy at the start of the study and could enter if free of major lesions, whether H. pylori positive or negative.

Study 0110 was a 13-week, international, multicentre, randomised, double blind, double-dummy parallel group active controlled endoscopic study of gastroduodenal effects of lumiracoxib (400mg and 800mg) in patients with rheumatoid arthritis using ibuprofen (800mg TDS) and celecoxib (200mg BD) as comparators. The primary safety assessment was gastrointestinal tolerability as measured by scheduled UGI endoscopy prior to baseline, at
8 weeks (endoscopy 1) and 13 weeks (endoscopy 2)

Study 0126 was a 13-week, international, multicentre, randomised, double blind, double-dummy, parallel-group, active-controlled, endoscopic study of the gastroduodenal effects of lumiracoxib 200 and 400mg QD in patients with primary osteoarthritis using ibuprofen and celecoxib as comparators. The primary safety assessment was gastrointestinal tolerability as measured by scheduled UGI endoscopy prior to baseline, at 4 weeks (endoscopy 1) and 13 weeks (endoscopy 2).

Pooled data (number and %) from the two studies are as follows:

| | Lumira 200 QD n = 257 | Lumira 400 QD n = 465 | Lumira 800 QD n = 207 | Cele 200 QD n = 253 | Cele 200 BD n = 213 | Ibup 800 TDS n = 447 |
|---|---|---|---|---|---|---|
| Ulcers ≥ 3 mm at | | | | | | |
| - endoscopy 1 | 5 (1.9) * | 9 (1.9) * | 8 (3.9) * | 3 (1.2) * | 2 (0.9) * | 42 (9.4) |
| - endoscopy 2 | 6 (2.3) * | 7 (1.5) * | 1 (0.5) * | 5 (2.0) * | 2 (0.9) * | 24 (5.4) |
| **Total** | **11 (4.3) *** | **16 (3.4) *** | **9 (4.3) *** | **8 (3.2) *** | **4 (1.9) *** | **66 (14.8)** |
| Ulcers ≥ 5 mm at | | | | | | |
| - endoscopy 1 | 5 (1.9) * | 7 (1.5) * | 8 (3.9) | 3 (1.2) * | 2 (0.9) * | 33 (7.4) |
| - endoscopy 2 | 5 (1.9) | 5 (1.1) * | 0 (0) * | 4 (1.6) | 2 (0.9) * | 17 (3.8) |
| **Total** | **10 (3.9) *** | **12 (2.6) *** | **8 (3.9)** | **7 (2.8) *** | **4 (1.9) *** | **50 (11.2)** |
| Erosions > 10 | 3 (1.2) | 12 (2.6) | 5 (2.4) | 6 (2.4) | 2 (0.9) | 28 (6.3) |

* $p < 0.05$ versus ibuprofen

These two studies demonstrate a significant reduction in the frequency of ulcers for lumiracoxib versus ibuprofen in both OA and RA patients.

This difference was independent of H pylori status, previous NSAID use or age. The numbers were too small to assess interactions with presence of previous ulcer history, alcohol use or renal dysfunction.

In a subset using low dose aspirin, at least 50% reduction versus ibuprofen was observed with the exception of lumiracoxib 800mg QD where the frequency was almost twice as high as ibuprofen. In a subset NOT using low dose aspirin, the frequency of ulcers was reduced with lumiracoxib versus ibuprofen by over 75%.

## 16.3 Pre-specified gastrointestinal event rates

In addition to the systemic endoscopy studies, all phase III study protocols included an evaluation of GI specific adverse events in each of the treatment groups. In the pooled datasets used for the summary of clinical safety, the following MedDRA preferred terms were used:

Gastrointestinal ulcers:

Duodenal ulcer, Duodenal ulcer haemorrhage, Duodenal ulcer perforation, Duodenal ulcer perforation, obstructive, Duodenal ulcer reactivated, Duodenal ulcer obstructive, Duodenal ulcer aggravated, Gastric ulcer, Gastric ulcer hemorrhage, Gastric ulcer perforation, Gastric ulcer hemorrhage obstructive, Gastric ulcer perforation obstructive, Gastric ulcer reactivated, Gastric ulcer obstructive, Gastroduodenal ulcer, Gastrointestinal ulcer NOS, Gastrointestinal ulcer perforation NOS, Esophageal ulcer, Esophageal ulcer hemorrhage, Esophageal ulcer perforation, Peptic ulcer, Peptic ulcer hemorrhage, Peptic ulcer perforation, Peptic ulcer perforation obstructive, Peptic ulcer reactivated, Peptic ulcer obstructive, Peptic ulcer aggravated, Prepyloric ulcer.

Gastrointestinal events (excluding ulcers):

Abdominal pain NOS, Abdominal pain lower, Abdominal pain upper, Abdominal pain aggravated, Constipation, Constipation aggravated, Diarrhoea NOS, Diarrhoea aggravated, Nausea, Nausea aggravated, Vomiting NOS, Vomiting aggravated, Dyspepsia, Dyspepsia aggravated, Dysphagia, Dysphagia aggravated, Loose stools.

Results:

| | Gastrointestinal events (excluding ulcers): | Gastrointestinal events (including ulcers): |
|---|---|---|
| | Dataset 1 (Short-term OA studies) | |
| Lumiracoxib 200mg QD | 21.7 % | 21.9 % |
| Lumiracoxib 400mg QD | 21.7 % | 21.8 % |
| Celecoxib 200mg QD | 20.3 % | 20.4 % |
| Ibuprofen 800 TDS | 47.3 % | 48.8 % |
| Placebo | 10.2 % | 10.2 % |
| | Dataset 2 (Long-term OA study) | |
| Lumiracoxib 200mg QD | 20.8 % | 21.0 % |
| Lumiracoxib 400mg QD | 22.2 % | 22.7 % |
| Celecoxib 200mg QD | 18.4 % | 18.6 % |
| | Dataset 7 (Short-term RA studies) | |
| Lumiracoxib 200mg QD | 15.3 % | 15.3 % |
| Lumiracoxib 400mg QD | 21.4 % | 21.7 % |
| Celecoxib 200mg BD | 26.9 % | 27.2 % |
| Ibuprofen 800 TDS | 48.1 % | 50.0 % |
| Placebo | 12.4 % | 12.4 % |

In the short-term OA studies, there was no obvious dose relationship but in the RA studies, the overall frequency was slightly higher with the 400mg dose versus the 200mg dose. This dose-dependency was largely accounted for by the high frequency of dyspepsia with 400mg dose.

## 16.4 Notable laboratory changes related to blood loss

This analysis compares changes in haemoglobin levels from baseline.

Results (% of patients)

| | ≥ 20 g/L decrease in baseline Hb | ≥ 6 points decrease in baseline Hct | Both |
|---|---|---|---|
| | Dataset 1 (Short-term OA studies) | | |
| Lumiracoxib 200mg QD | 1.3 | 3.1 | 0.8 |
| Lumiracoxib 400mg QD | 1.5 | 3.2 | 0.7 |
| Celecoxib 200mg QD | 1.1 | 3.0 | 0.8 |
| Ibuprofen 800 TDS | 6.2 | 5.4 | 4.2 |
| Placebo | 0.8 | 2.7 | 0.6 |
| | Dataset 2 (Long-term OA study) | | |
| Lumiracoxib 200mg QD | 2.9 | 3.1 | 1.8 |
| Lumiracoxib 400mg QD | 3.6 | 5.8 | 2.0 |
| Celecoxib 200mg QD | 3.4 | 3.5 | 2.4 |
| | Dataset 7 (Short-term RA studies) | | |
| Lumiracoxib 200mg QD | 1.8 | 6.1 | 1.0 |
| Lumiracoxib 400mg QD | 3.2 | 6.9 | 2.4 |
| Celecoxib 200mg BD | 1.1 | 5.0 | 0.4 |
| Ibuprofen 800 TDS | 10.2 | 19.4 | 6.5 |
| Placebo | 1.9 | 3.6 | 1.2 |

The above changes may result from chronic blood loss (most likely explanation) or retention of fluid. It is evident that the effect of lumiracoxib is markedly lower than that of ibuprofen in both OA and RA patients and comparable to that of celecoxib.

Again, there appears to be a dose-related effect of lumiracoxib in RA patients.

## 16.5 Complicated ulcers (PUBs and POBs)

Overall, the GI Safety Committee reviewed 336 suspected events as follows:

| | Placebo | Lumiracoxib 200/400mg | Other coxibs | All other NSAIDs |
|---|---|---|---|---|
| N | 1860 | 5431 | 2166 | 981 |
| Events (%) | 38 (2.0) | 167 (3.1) | 60 (2.8) | 61 (6.2) |

PUB Analysis

| | N | Patient-years (pt-years) | Events | Rate per pt-years | 95% CI |
|---|---|---|---|---|---|
| Lumiracoxib 200/400mg | 5431 | 1637 | 27 | 1.65 | 1.09, 2.39 |
| Other coxibs | 2166 | 700 | 10 | 1.43 | 0.69, 2.61 |
| All other NSAIDs | 981 | 227 | 31 | 13.88 | 9.47, 18.82 |

Drug exposure time differed between treatments.

A Kaplan-Meier plot showed that the event rates over time were no different between lumiracoxib and other coxibs but these occurred much earlier and with higher frequency with classical NSAIDs. Time to event analysis in dataset 9 showed the following estimates of % rates:

| Interval end (days) | Placebo | Lumiracoxib 200/400mg | Other coxibs | All other NSAIDs |
|---|---|---|---|---|
| 120 | 0 | 0.5 | 0.4 | 4.5 |
| 210 | 0 | 0.6 | 1.0 | 4.5 |
| 300 | N/A | 0.9 | 1.0 | N/A |
| 390 | N/A | 0.9 | 1.0 | N/A |

Symptomatic ulcers (number of cases and %)

| | Oesophageal | Gastric | Duodenal | Gastroduodenal |
|---|---|---|---|---|
| | Dataset 1 (Short-term OA studies) | | | |
| Lumiracoxib 200mg QD | 0 | 6 (0.4) | 1 (0.07) | 1 (0.07) |
| Lumiracoxib 400mg QD | 1 (0.05) | 2 (0.1) | 1 (0.05) | 0 |
| Celecoxib 200mg QD | 0 | 4 | 0 | 0 |
| Ibuprofen 800 TDS | 0 | 10 | 6 | 0 |
| Placebo | 0 | 0 | 0 | 0 |
| | Dataset 2 (Long-term OA study) | | | |
| Lumiracoxib 200mg QD | 0 | 2 (0.37) | 0 | 0 |
| Lumiracoxib 400mg QD | 1 (0.18) | 1 (0.18) | 2 (0.36) | 0 |
| Celecoxib 200mg QD | 0 | 3 | 0 | 0 |
| | Dataset 7 (Short-term RA studies) | | | |
| Lumiracoxib 200mg QD | 0 | 0 | 0 | 0 |
| Lumiracoxib 400mg QD | 0 | 5 (1.67) | 1 (0.11) | 0 |
| Celecoxib 200mg BD | 1 | 1 | 0 | 0 |
| Ibuprofen 800 TDS | 0 | 8 | 0 | 0 |
| Placebo | 0 | 0 | 0 | 0 |

POB Analysis

Definite and probable complications in dataset 9:

| | N | Patient-years (pt-years) | Events | Rate per pt-years | 95% CI |
|---|---|---|---|---|---|
| Lumiracoxib 200/400mg | 5431 | 1637 | 5 | 0.31 | 0.10, 0.71 |
| Other coxibs | 2166 | 700 | 1 | 0.14 | 0.00, 0.79 |
| All other NSAIDs | 981 | 227 | 5 | 2.21 | 0.72, 5.07 |

Drug exposure time differed between treatments.

A Kaplan-Meier plot showed that the event rates over time were no different between lumiracoxib and other coxibs but these occurred much earlier and with higher frequency with classical NSAIDs. Time to event analysis in dataset 9 showed the following estimates of % rates:

| Interval end (days) | Placebo | Lumiracoxib 200/400mg | Other coxibs | All other NSAIDs |
|---|---|---|---|---|
| 120 | 0 | 0.1 | 0.1 | 0.7 |
| 210 | 0 | 0.1 | 0.1 | 0.7 |
| 300 | N/A | 0.1 | 0.1 | N/A |
| 390 | N/A | 0.1 | 0.1 | N/A |

Lower GI tract events

There were 16 lower GI tract events with the following frequency between the four treatment groups:

| | | |
|---|---|---|
| Placebo | n = 1 | 0.1% |
| Lumiracoxib | n = 6 | 0.1 % |
| Other coxibs | n = 5 | 0.2 % |
| Other NSAIDs | n = 4 | 0.4 % |

***Assessor's comments on gastrointestinal safety of lumiracoxib:***
Lumiracoxib has improved gastrointestinal safety compared to classical non-selective NSAIDs and comparable to other coxibs.

Relative to the200mg QD dose, 400mg QD dose of lumiracoxib is associated with a greater frequency of gastrointestinal effects in terms of pre-specified gastrointestinal events, laboratory data for haematocrit and haemoglobin and symptomatic ulcers in long-term OA and short-term RA dataset.

## 17. LUMIRACOXIB AND PROTHROMBOTIC EFFECTS

The Applicant has provided a Special Expert Evaluation Report on the potential prothrombotic effects of lumiracoxib.

### 17.1 Theoretical issues with COX-2 inhibitors and cardiovascular health

It has been hypothesized that selective COX-2 inhibitors might alter the balance between thromboxane and prostacyclin and promote a more prothrombotic state. This could be caused by a lack of effect of COX–2 inhibitors on platelet thromboxane synthesis, which is under COX-1 control, and an observed decrease in systemic prostacyclin production. Prostacyclin (PGI2) is important in endothelial function and inhibition may also lead to vasoconstriction. COX-2 inhibition of prostacyclin is unlikely to be offset by COX-1 inhibition of thromboxane. All selective COX–2 inhibitors significantly inhibit the COX-2 isoenzyme at therapeutic doses. The contribution of relative selectivity (COX-2 versus COX-1) to increased cardiovascular risk is not clear. PGI2 has been postulated as a modulator of platelet–vascular interaction, with the interaction of thromboxane being relevant in the vessel response to intimal injury.

Investigations using genetically engineered mice have shown the importance of the prostacyclin/thromboxane balance in the proliferative response of vascular smooth muscle cells after intimal injury. An enhanced proliferative response to intimal injury was seen in animals without prostacyclin action.

The cardiovascular effects of COX-2 inhibitors may be related to specific physiochemical or pharmacokinetic properties of different compounds, as there is, in fact, very limited clinical evidence that increased cardiovascular risk is a class effect ~xr10i
There is support for the theory that the COX-2 isoenzyme may be important in the pathogenesis of atherosclerosis. Pathology data from diseased human arteries with atherosclerosis has shown expression of the COX-2 isoenzyme in inflammatory cells of the arteries. Products of COX-2 activity may be important in the pathogenesis of atherosclerosis. Animal data has provided evidence of the importance of COX-2 in early atherosclerotic lesions and a benefit of pharmacologic block of COX-2 isoenzyme in the formation of atherosclerosis.

The importance of the anti-inflammatory properties of NSAIDs in general and COX-2 specific inhibitors in particular, for the development of atherosclerosis are an active focus of research. Aspirin is commonly used for the prevention of cardiovascular disease.

Recommendations from the US Preventive Services Task Force (2002) include consideration of aspirin therapy for patients at increased risk for coronary heart disease, and this is classified as a grade A recommendation (good evidence that benefit outweighs risk. One of the specific concerns about NSAIDs is their interaction with aspirin. There appear to be differences in the ability of specific NSAIDs to interfere with the platelet aggregation inhibition by aspirin. Cardiovascular and cerebrovascular events in the lumiracoxib development program will therefore be analysed with and without aspirin use.

## 17.2 Clinical concern and controversy generated by previous safety studies

In the recently reported clinical trial comparing rofecoxib with naproxen, looking at the risk of gastrointestinal events in patients with rheumatoid arthritis (VIGOR trial), a difference was noted in the rate of myocardial infarctions between treatment groups. In the rofecoxib group there was a greater risk of myocardial infarction (0.4%) than in the naproxen group (0.1%). This finding has been the subject of much controversy regarding the risk of cardiovascular events with COX-2 inhibitors. The hypothesis of alteration in the balance of thromboxane/prostacyclin brought about with use of selective COX-2 inhibitors and/or a possible protective anti-platelet effect of naproxen has been raised.

Data from the large gastrointestinal outcome trial with celecoxib (CLASS trial) did not show an increased risk of myocardial infarction with celecoxib compared with non-selective NSAIDs. The CLASS trial however used patients with both OA and RA and also allowed patients to take aspirin for cardiac protection. Additional data from three large case control studies are consistent with a protective effect of naproxen on risk of myocardial infarction and it is proposed that this effect is primarily from naproxen's anti-platelet effect.

There is at this time, however, no clear consensus of opinion regarding the relationship between naproxen and cardiovascular risk. It is not possible to categorically state which is the more probable reason for the increased cardiovascular effects seen in VIGOR, but it may be a combination of these two effects (i.e. positive naproxen and negative rofecoxib effects).

## 17.3 Lumiracoxib dataset

Dataset 9 is a composite group of outpatient studies that lasted from 1 to 52 weeks in patients treated for OA or RA. This group of adults was treated with lumiracoxib, celecoxib, rofecoxib, diclofenac, ibuprofen, naproxen or placebo and assessed for efficacy and safety of the treatment at frequent intervals. ECGs were taken at baseline and at various times throughout the study. Adverse events were assessed at each interval visit. Several datasets were not included for separate analysis in this report. Dataset 3 (combined OA and RA over short-term) and Dataset 8 (endoscopy studies) are subsets of dataset 9 and therefore a separate analysis was not run.

## 17.4 Assignment of cardiovascular risk

To classify individuals at risk of vascular events the major independent risk factors were used as well as previous cardiovascular or cerebrovascular events. If a patient had one or more of the major independent risk factors or had a previous vascular event, they were classified in the high vascular risk category.

## 17.5 Calculation of % of patients in high cardiovascular risk category

For the purposes of this report, the percentage of patients with high cardiovascular risk is calculated by dividing the number of patients with a vascular risk factor usually defined by the total number of patients, in that treatment group, where information is known about their medical risk factors.

## 17.6 Combined endpoints used to assess vascular event rates

The endpoint defined by the Antiplatelet Trialists' Collaboration (APTC) was the principal means for analysis of AEs of vascular origin.

This combined endpoint is the most frequently used measure in cardiovascular epidemiology. It includes:

1. Non-fatal myocardial infarction
2. Non-fatal stroke
3. Vascular death (which includes all deaths attributed to cardiac, vascular, cerebral, hemorrhagic, embolic, other vascular or unknown causes)

Also included in the analysis was a broader definition of cardiovascular and cerebrovascular events that includes the cardiovascular event definition in the Therapeutic COX189 Arthritis Research and Gastrointestinal Event Trial (TARGET endpoints). TARGET is a large ongoing clinical trial to assess the safety of lumiracoxib in comparison to non-selective NSAIDs in terms of the following endpoints (using MedDRA terms)

1. Non-fatal coronary events
2. Non-fatal cerebrovascular events
3. Non-fatal peripheral thrombosis
4. Cardiovascular death

## 17.7 Results

### 17.7.1 Dataset 9 (all non-acute pain studies)

The percentages of patients with previous cardiovascular events and high cardiovascular risk are shown in the table below:

| | Total patients | Mean Age (yrs) | % with previous vascular events | % with high vascular risk |
|---|---|---|---|---|
| Lumiracoxib 50mg BD | 200 | 58.2 | 9.0 | 40.5 |
| Lumiracoxib 100mg QD | 122 | 62.8 | 23.0 | 65.6 |
| Lumiracoxib 100mg BD | 193 | 58.6 | 6.2 | 39.4 |
| Lumiracoxib 200mg QD | 2069 | 59.5 | 11.7 | 49.8 |
| Lumiracoxib 200mg BD | 193 | 57.6 | 9.3 | 38.3 |
| Lumiracoxib 400mg QD | 2976 | 59.4 | 10.8 | 48.6 |
| Lumiracoxib 800mg QD | 265 | 50.7 | 7.2 | 38.9 |
| Celecoxib 200mg QD | 1239 | 62.2 | 12.8 | 56.8 |
| Celecoxib 200mg BD | 670 | 54.8 | 7.5 | 41.6 |
| Rofecoxib 25mg QD | 257 | 63.9 | 7.8 | 47.9 |
| Naproxen 500mg BD | 320 | 54.0 | 10.9 | 37.5 |
| Ibuprofen 800 TDS | 476 | 55.3 | 18.3 | 47.7 |
| Placebo | 1860 | 59.3 | 10.3 | 47.7 |

The number of patients with vascular events (after adjudication) during treatment is summarised for all groups the following table:

| | Total patients | Exposure Patient-years | APTC Events | Incidence per 100 pt-years |
|---|---|---|---|---|
| Lumiracoxib 50mg BD | 200 | 14.5 | 0 | 0 |
| Lumiracoxib 100mg QD | 122 | 9.4 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| Lumiracoxib 100mg BD | 193 | 14.6 | 0 | 0 |
| Lumiracoxib 200mg QD | 2069 | 719.8 | 9 | 1.25 |
| Lumiracoxib 200mg BD | 193 | 14.1 | 0 | 0 |
| Lumiracoxib 400mg QD | 2976 | 859.4 | 11 | 1.28 |
| Lumiracoxib 800mg QD | 265 | 50.9 | 2 | 3.93 |
| Celecoxib 200mg QD | 1239 | 528.2 | 4 | 0.76 |
| Celecoxib 200mg BD | 670 | 117.8 | 2 | 1.70 |
| Rofecoxib 25mg QD | 257 | 40.1 | 1 | 2.49 |
| Naproxen 500mg BD | 320 | 113.8 | 0 | 0 |
| Ibuprofen 800 TDS | 476 | 99.6 | 1 | 1.00 |
| Placebo | 1860 | 335.8 | 4 | 1.19 |

The percentage individual major events (after adjudication) during treatment is summarised for all groups the following table:

| | Total events | Non-fatal MI | Non-fatal stroke | Vascular death | TIA | DVT |
|---|---|---|---|---|---|---|
| Lumiracoxib 50mg BD | N = 0 | 0 | 0 | 0 | 0 | 0 |
| Lumiracoxib 100mg QD | N = 0 | 0 | 0 | 0 | 0 | 0 |
| Lumiracoxib 100mg BD | N = 0 | 0 | 0 | 0 | 0 | 0 |
| Lumiracoxib 200mg QD | N = 9 | 0.19 | 0.19 | 0.50 | 0.24 | 0.20 |
| Lumiracoxib 200mg BD | N = 0 | 0 | 0 | 0 | 0 | 0 |
| Lumiracoxib 400mg QD | N = 11 | 0.16 | 0.07 | 0.10 | 0.17 | 0.07 |
| Lumiracoxib 800mg QD | N = 2 | 0.80 | 0 | 0 | 0 | 0 |
| Celecoxib 200mg QD | N = 4 | 0.16 | 0.08 | 0.08 | 0 | 0.16 |
| Celecoxib 200mg BD | N = 2 | 0.15 | 0 | 0.15 | 0.16 | 0 |
| Rofecoxib 25mg QD | N = 1 | 0.40 | 0 | 0 | 0 | 0 |
| Naproxen 500mg BD | N = 0 | 0 | 0 | 0 | 0 | 0 |
| Ibuprofen 800 TDS | N = 1 | 0 | 0 | 0.20 | 0 | 0.20 |
| Placebo | N = 4 | 0.05 | 0.11 | 0.05 | 0.05 | 0.05 |

When the adjudicated data on 200mg and 400mg lumiracoxib are pooled for all patients and for high vascular risk, the incidence per 100 patient-years is as follows:

| | All patients (A) | High vascular risk patients (B) | B/A |
|---|---|---|---|
| Lumiracoxib 200mg/400mg | 1.25 | 2.11 | 1.69-fold |
| Other coxibs | 1.02 | 1.09 | 1.07-fold |
| Classical NSAIDs | 0.44 | 0.0 | |
| Placebo | 1.19 | 1.35 | 1.13-fold |

Relative risk (and 95% CI) of APTC vascular events after adjudication and adjusted for exposure in all and various subpopulations in dataset 9 are shown below:

| | Lumiracoxib 200mg/400mg | Other coxibs | Classical NSAIDs | Placebo |
|---|---|---|---|---|
| | **All patients** | | | |
| N | 5431 | 2166 | 981 | 1860 |
| Number of cases | 20 | 7 | 1 | 4 |
| Incidence rate per 100 patient-years | 1.25 | 1.02 | 0.44 | 1.19 |
| Relative risk (95% CI) | 1.04 (0.36, 3.05) | 0.86 (0.25, 2.9) | 0.37 (0.04, 3.31) | 1 |
| | **Patients with high cardiovascular risk** | | | |
| N | 2627 | 1106 | 426 | 888 |
| Number of cases | 13 | 4 | 0 | 2 |
| Incidence rate per 100 patient-years | 1.61 | 1.09 | 0 | 1.40 |
| Relative risk (95% CI) | 1.19 (0.27, 5.29) | 0.81 (0.15, 4.40) | N/A | 1 |

| | | | | |
|---|---|---|---|---|
| | **Patients using low dose aspirin** | | | |
| N | 499 | 207 | 62 | 166 |
| Number of cases | 4 | 1 | 0 | 1 |
| Incidence rate per 100 patient-years | 2.80 | 1.43 | 0 | 3.52 |
| Relative risk (95% CI) | 0.80 (0.09, 7.12) | 0.41 (0.03, 6.5) | N/A | 1 |
| | **Patients with OA** | | | |
| N | 3737 | 1641 | 354 | 1168 |
| Number of cases | 13 | 6 | 1 | 2 |
| Incidence rate per 100 patient-years | 1.09 | 1.10 | 1.60 | 1.10 |
| Relative risk (95% CI) | 0.95 (0.22, 4.22) | 0.92 (0.18, 4.6) | 1.4 (0.13, 15.4) | 1 |
| | **Patients with RA (pre-abjudication)** | | | |
| N | 1694 | 525 | 627 | 692 |
| Number of cases | 7 | 1 | 0 | 2 |
| Incidence rate per 100 patient-years | 1.69 | 0.97 | 0 | 1.24 |
| Relative risk (95% CI) | 1.36 (0.28, 6.53) | 0.70 (0.06, 7.75) | N/A | 1 |

**17.7.2 Conclusions on vascular endpoints (dataset 9)**

As shown above, there is a slightly greater percentage of patients in the lumiracoxib 200/400 combined group with an event when compared with placebo.

Individual assessment by treatment group for the larger group in dataset 9 (Table 7-7 in SPER) showed a slightly greater rate for APTC endpoints for lumiracoxib 200mg QD (0.5%) and 400mg QD (0.4%), compared with placebo (0.2%) and celecoxib 200mg QD (0.3%).

Patients with increased vascular risk had an increased event rate, and that the combined lumiracoxib 200/400mg group showed an APTC event rate of 0.65% compared with 0.22% for placebo (table 7-11 in SPER). However, when the duration of exposure is included in the analysis of incidence rates for dataset 9, the rates for active treatment are similar to or even lower than placebo, because of the longer duration of exposure in the active treatment groups.

Analysis of individual vascular events showed a similar rate of non-fatal MI between the pooled lumiracoxib 200/400 groups (0.22%) and the other coxibs (0.18%). The NSAID treatment groups had no non-fatal MIs but also much shorter exposure durations. Rates of non-fatal stroke were 0.13% for the pooled lumiracoxib 200/400 group compared with 0.05% for the other coxibs and 0.11% for the placebo group. TIA rates were 0.17% in the lumiracoxib 200/400 groups, 0.09% in the other coxibs, and 0.05% in the placebo group. When the exposure time is taken into account, no major differences are observed compared to placebo.

The relative risk for the pooled lumiracoxib 200/400 groups is 1.25 (0.43 – 3.61) prior to adjudication and 1.04 (95% CI 0.36 – 3.05) after blinded independent expert adjudication of the dataset 9. For the group with high cardiovascular risk, the relative risk after adjudication is 1.19 (0.27 - 5.29).

In patients who were using low dose aspirin for vascular protection, presumably because they had a higher cardiovascular risk, the relative risk after adjudication was 0.80 (0.09-7.12). The relative risk for patients with a diagnosis of osteoarthritis after adjudication was 0.95 (0.22 – 4.22) for the lumiracoxib 200/400 group.

The relative risk for patients with a diagnosis of rheumatoid arthritis (these cases were not adjudicated) was 1.36 (0.28 – 6.53) for the lumiracoxib 200/400 groups.

Overall, there may be a slight trend toward an increase in risk in this combined dataset. It is noted that the confidence intervals are very wide and encompass unity. These studies were clearly not powered to detect a small difference in relative risk between treatment groups and therefore conclusions on the relative merits of different treatment groups must be limited.

**17.7.3 Dataset 1 (short-term OA studies)**

The percentages of patients with previous cardiovascular events and high cardiovascular risk are shown in the table below:

| | Total patients | Mean Age (yrs) | % with previous vascular events | % with high vascular risk |
|---|---|---|---|---|
| Lumiracoxib 50mg BD | 98 | 61.3 | 9.2 | 48.0 |
| Lumiracoxib 100mg QD | 122 | 62.8 | 23.0 | 65.6 |
| Lumiracoxib 100mg BD | 96 | 59.8 | 8.3 | 47.9 |
| Lumiracoxib 200mg QD | 1418 | 61.8 | 13.8 | 54.4 |
| Lumiracoxib 200mg BD | 99 | 59.5 | 10.1 | 41.4 |
| Lumiracoxib 400mg QD | 2009 | 62.1 | 12.4 | 54.6 |
| Celecoxib 200mg QD | 1183 | 62.1 | 13.0 | 57.0 |
| Celecoxib 200mg BD | 145 | 65.3 | 13.8 | 62.8 |
| Rofecoxib 25mg QD | 257 | 63.9 | 7.8 | 47.9 |
| Ibuprofen 800 TDS | 260 | 57.9 | 28.5 | 60.0 |
| Placebo | 1168 | 63.0 | 12.8 | 54.9 |

The number of patients with vascular events during follow up in dataset 1 is summarised for all groups the following table:

| | Total patients | APTC Events | Non-fatal MI | Non-fatal stroke | Vascular death |
|---|---|---|---|---|---|
| Lumiracoxib 50mg BD | 98 | 0 | 0 | 0 | 0 |
| Lumiracoxib 100mg QD | 122 | 0 | 0 | 0 | 0 |
| Lumiracoxib 100mg BD | 96 | 0 | 0 | 0 | 0 |
| Lumiracoxib 200mg QD | 1418 | 3 | 2 (0.1%) | 1 | 0 |
| Lumiracoxib 200mg BD | 99 | 0 | 0 | 0 | 0 |
| Lumiracoxib 400mg QD | 2009 | 4 | 3 (0.2%) | 0 | 1 |
| Celecoxib 200mg QD | 1183 | 3 | 2 (0.2%) | 1 | 0 |
| Celecoxib 200mg BD | 145 | 1 | 1 | 0 | 0 |
| Rofecoxib 25mg QD | 257 | 1 | 1 | 0 | 0 |
| Ibuprofen 800 TDS | 260 | 1 | 0 | 0 | 1 |
| Placebo | 1168 | 2 | 1 (0.1%) | 1 | 0 |

| | Lumiracoxib 200mg/400mg | Other coxibs | Classical NSAIDs | Placebo |
|---|---|---|---|---|
| N | 3622 | 1585 | 354 | 1168 |
| APTC endpoints | 7 (0.2%) | 5 (0.3%) | 1 (0.3%) | 2 (0.2%) |
| Non-fatal MI | 5 | 4 | 0 | 1 |
| Non-fatal stroke | 1 | 1 | 0 | 1 |
| Vascular death | 1 | 0 | 1 | 0 |

**17.7.4 Conclusions on vascular endpoints (dataset 1)**

Data for pooled treatment groups by type of drug shows that there was no difference in the overall frequency of vascular disease between lumiracoxib, other coxibs, NSAIDs and placebo.

The event rate in pooled groups was comparable between treatment groups (0.2 – 0.3%). Looking at individual events, the most frequent APTC endpoint was non-fatal MIs, incidence 5 (0.1%) in the combined lumiracoxib (200/400) group and 4 (0.3%) in the other coxibs.

In summary, dataset 1 does not reveal any evidence of prothrombotic risk from lumiracoxib in the vascular system for this group of OA patients. Event rates were comparable to placebo and other anti-inflammatory comparators. The major limitation, however, is the short duration of follow up and relatively small number of patients. Both these contribute to a lack of the required statistical power.

**17.7.5 Dataset 7 (RA studies to 26 weeks)**

The percentages of patients with previous cardiovascular events and high cardiovascular risk are shown in the table below:

| | Total patients | Mean Age (yrs) | % with previous vascular events | % with high vascular risk |
|---|---|---|---|---|
| Lumiracoxib 50mg BD | 102 | | 8.8 | 33.3 |
| Lumiracoxib 100mg BD | 97 | | 4.1 | 30.9 |
| Lumiracoxib 200mg QD | 595 | | 6.7 | 37.3 |
| Lumiracoxib 200mg BD | 94 | | 8.5 | 35.1 |
| Lumiracoxib 400mg QD | 908 | | 7.1 | 35.2 |
| Lumiracoxib 800mg BD | 265 | | 7.2 | 38.9 |
| Lumiracoxib 1200mg QD | 41 | | 0 | 24.4 |
| Celecoxib 200mg BD | 525 | | 5.7 | 35.8 |
| Naproxen 500mg BD | 320 | | 10.9 | 37.5 |
| Ibuprofen 800 TDS | 216 | | 6.0 | 32.9 |
| Placebo | 692 | | 6.2 | 35.6 |

The number of patients with vascular events during follow up in dataset 7 is summarised for all groups the following table:

| | Total patients | APTC Events | Non-fatal MI | Non-fatal stroke | Vascular death |
|---|---|---|---|---|---|
| Lumiracoxib 50mg BD | 102 | 0 | 0 | 0 | 0 |
| Lumiracoxib 100mg BD | 97 | 0 | 0 | 0 | 0 |
| Lumiracoxib 200mg QD | 595 | 3 (0.5%) | 0 | 2 | 1 |
| Lumiracoxib 200mg BD | 94 | 0 | 0 | 0 | 0 |
| Lumiracoxib 400mg QD | 908 | 4 (0.4%) | 1 | 2 | 1 |
| Lumiracoxib 800mg BD | 265 | 2 (0.8%) | 2 | 0 | 0 |
| Lumiracoxib 1200mg QD | 41 | 0 | 0 | 0 | 0 |
| Celecoxib 200mg BD | 525 | 1 (0.2%) | 0 | 0 | 1 |
| Naproxen 500mg BD | 320 | 0 | 0 | 0 | 0 |
| Ibuprofen 800 TDS | 216 | 0 | 0 | 0 | 0 |
| Placebo | 692 | 2 (0.3%) | 0 | 1 | 1 |

| | Lumiracoxib 200mg/400mg | Other coxibs | Classical NSAIDs | Placebo |
|---|---|---|---|---|
| N | 1694 | 525 | 627 | 692 |
| APTC endpoints | 7 (0.4%) | 1 (0.2%) | 0 | 2 (0.3%) |
| Non-fatal MI | 1 | 0 | 0 | 0 |
| Non-fatal stroke | 4 | 0 | 0 | 1 |
| Vascular death | 2 | 1 | 0 | 1 |

**17.7.6 Conclusions on vascular endpoints (dataset 7)**

Reviewing the different treatment groups and patient risk of development of a vascular event shows an apparent increase in the number of patients reaching APTC endpoints in the lumiracoxib 200 and 400 mg groups (0.5% and 0.4%) when compared with placebo (0.3%) and celecoxib 200 mg bid (0.2%), although the number of patients experiencing events was low.

**17.7.7 Dataset 2 (Long-term OA study)**

The percentages of patients with previous cardiovascular events and high cardiovascular risk are shown in the table below:

| | Total patients | Mean age (yrs) | Mean Exposure (days) | % with previous vascular events | % with high vascular risk | % taking aspirin |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 543 | 64.3 | 249 | 12.2 | 54.5 | 12.2 |
| Lumiracoxib 400mg QD | 550 | 64.4 | 255 | 12.0 | 57.1 | 10.7 |
| Celecoxib 200mg QD | 537 | 64.0 | 254 | 10.8 | 56.8 | 11.0 |

The number of patients with vascular events during follow up in dataset 2 is summarised for all groups the following table:

| | Total patients | APTC Events | Non-fatal MI | Non-fatal stroke | Vascular death |
|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 543 | 6 (1.1%) | 3 | 3 | 0 |
| Lumiracoxib 400mg QD | 550 | 6 (1.1%) | 4 | 0 | 2 |
| Celecoxib 200mg QD | 537 | 3 (0.6%) | 2 | 0 | 1 |

The number of patients with vascular events (after adjudication) during follow up in dataset 2 is summarised for all groups the following table:

| | Total patients | APTC Events | Non-fatal MI | Non-fatal stroke | Vascular death |
|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 543 | 4 (0.7%) | 2 | 2 | 0 |
| Lumiracoxib 400mg QD | 550 | 4 (0.7%) | 2 | 0 | 2 |
| Celecoxib 200mg QD | 537 | 3 (0.6%) | 2 | 0 | 1 |

**17.7.6 Conclusions on vascular endpoints (dataset 2)**

The crude rate for APTC endpoints was 1.1% in both the lumiracoxib 200 and 400 mg dose groups and 0.6% in the celecoxib 200 mg od group. After adjudication of these vascular events by the blinded independent expert adjudication committee, the incidence of the adjudicated events for the combined endpoint APTC was 0.7% for the lumiracoxib 200mg and 400 mg groups and 0.6% for the celecoxib 200 mg group.

The adverse event "myocardial infarction" reported by the investigator in 2 patients in the lumiracoxib 400mg group (112E11130007 and 112E000600014) was re-classified as “no event” by the committee. Both these patients were removed from the APTC count.

One patient in the lumiracoxib 200mg group (112E000900021) had a change in MI pattern reported by eRT and recorded as an adverse event by the investigator; the ECG tracings were re-classified as “no new MI present” by the expert committee and the patient was removed from the APTC endpoint count. One patient in the lumiracoxib 200mg group (112E060300008) had a stroke event recorded by the investigator and a TIA diagnosis adjudicated by the expert committee; this patient was removed from the APTC count.

**The Expert concludes:**

"In summary, the crude frequency of vascular endpoints was higher in the lumiracoxib 200mg and 400 mg groups than in the celecoxib group. There was no predominant type of vascular event which accounted for this difference, and when the cases were adjudicated by a panel of blinded independent experts, there was no difference in vascular endpoint rate between groups. However, the absolute numbers of events in this dataset is relatively low, and there was no placebo arm in the long-term study, so quantification of the relative cardiovascular and cerebrovascular risk of lumiracoxib and other COX-2 inhibitors must await definitive outcome studies."

***Assessor's comments on prothrombotic effects of lumiracoxib:***
Despite the small sample sizes across all the datasets, the Expert has dismissed differences between treatment groups but has emphasized lack of differences between treatment groups to support the cardiovascular safety of lumiracoxib.

Dataset 2 is probably the most revealing since patients are well matched across the three treatment groups and the mean exposure is about 250 days. It is noteworthy that a dataset of only 12-months duration at the most should uncover a point estimate that is indicative of slightly greater prothrombotic risk associated with lumiracoxib relative to placebo.

The sample size and the duration of the studies are such that 95% confidence intervals of the risk WILL be wide and encompass unity.

There is a biological plausibility to the prothrombotic risk and a small increase in risk especially in those with high cardiovascular risk cannot be excluded. Use of low dose aspirin reduces this risk.

More importantly, this slight increase in prothrombotic risk has to be seen in the context of considerable improvement in gastrointestinal risk conferred by lumiracoxib over the classical NSAIDs.

It is therefore appropriate to include the following warnings and precautions:

**Caution should be exercised in patients with a medical history of ischemic heart disease. Appropriate measures should be taken and discontinuation of lumiracoxib therapy should be considered if there is clinical evidence of symptomatic deterioration in the condition of these patients. The lack of antiplatelet activity of COX-2 selective inhibitors should also be considered in patients with a history of cerebrovascular disease.**

## 18. OTHER SAFETY ISSUES

This section reviews the safety of lumiracoxib in terms of its:
18.1 Hepatotoxicity
18.2 Nephrotoxicity
18.3 Myelotoxicity
18.4 Effect on joint structure

### 18.1 Hepatotoxicity

The Applicant has provided a Special Expert Evaluation Report on hepatic effects of lumiracoxib.

During clinical development, a Liver Safety Committee (LSC) was established to blindly review each case of aminotransferase elevations >3 times the upper limit of normal and/or all bilirubin cases over 3 mg/dl and to adjudicate the mechanism of hepatic injury and judge relationship of the abnormalities to the study drug according to prespecified criteria. In

addition, upon completion of the phase III trials, the LSC in addition reviewed and adjudicated also all cases of bilirubin increase > 2 x ULN in patients in whom there were no elevations in aminotransferases >3 ULN.

Members of the LSC provided a written expert evaluation on the adjudicated cases from phase II and III trials

A large outcome study (Therapeutic Arthritis Gastrointestinal Event Trial - TARGET) is currently ongoing and has an estimated overall exposure, as of August 2002, of approximately 4000 patient years (2000 patient years with lumiracoxib 400mg QD and 2000 patient years with naproxen 500mg BD or ibuprofen 800mg TDS). Serious events related to liver safety observed in the TARGET study have also been evaluated in this report.

### 18.1.1 Patient population

For this expert evaluation the following slightly modified datasets (described under "Clinical Safety" were used:

**OA and RA up to 52 weeks (Dataset 9):**

This dataset contains the pooled data from all non–acute pain studies. This group of adults were treated with lumiracoxib (N=6059), celecoxib (N=1909), rofecoxib (N=257), diclofenac (N=185), naproxen (N=320), ibuprofen (N=476) or placebo (N=1860). Blood samples were taken at baseline and at various times throughout the study. The following datasets are subsets of dataset 9:

- OA up to 52 weeks (Dataset 2): Dataset 2 consists of OA patients who were treated with lumiracoxib or celecoxib for up to 1 year. This dataset includes patients treated with lumiracoxib (N=1093) and celecoxib (N=537).
- OA up to 13 weeks (Dataset 1): Dataset 1 consists of patients with a primary indication of OA who were treated in a study of 13 weeks duration or less. This dataset includes patients treated with lumiracoxib (N=3842), rofecoxib (N=257), celecoxib (N=1328), diclofenac (N=94), ibuprofen (N=260) and placebo (N=1168).
- RA up to 26 weeks (Dataset 7a): Dataset 7a consists of RA patients included in study CCOX189A 0111 who were treated up to 26 weeks. This dataset includes patients treated with lumiracoxib (N=561), naproxen (N=279) and placebo (N=284). The original dataset 7 also includes those patients participating to studies in 13-week duration or less.
- RA up to 13 weeks (Dataset 7 modified): Dataset 7 modified consists of RA patients treated up to 13 weeks and includes data up to week 13 from the pivotal RA 26 week study CCOX189A 0111. The dataset includes patients treated with lumiracoxib (N=2102), celecoxib (N=525), diclofenac (N=91), naproxen (N=320) ibuprofen (N=216) and placebo (N=692). The original SCS dataset 7 includes all data up to 26 weeks from study 0111.
- OA and RA up to 13 weeks (Dataset 3 modified): Dataset 3 modified includes pooled data from all OA and RA studies up to 13 weeks and includes data up to 13 weeks from study CCOX189A 0111 (not originally included in dataset 3). This dataset includes patients treated with lumiracoxib (N=2102), celecoxib (N=525), diclofenac (N=91), naproxen (N=320), ibuprofen (N=216) and placebo (N=692).

- **Acute pain studies (datasets 4, 5 and 6)**

  These include patients/volunteers post oral surgery, post orthopaedic surgery and dysmenorrhoea studies. A total of 1698 patients and volunteers were randomised to single dose and multiple dose (up to 5 days) studies. Of these, 956 were treated with lumiracoxib, 235 with rofecoxib, 101 with celecoxib, 51 with ibuprofen, 149 with naproxen, 59 with oxycodone and 465 with placebo. It is important to note that two cross-over studies were performed in the dysmenorrhoea model.

### 18.1.2 Adjudication by the Liver safety Committee

The LSC reviewed all cases with AST/ALT elevations > 3 x ULN and bilirubin

>3mg/dl ("biochemical events") blind to the actual patient treatment. The LSC categorized significant liver events as hepatocellular, mixed or cholestatic. Following assignment of events to one of these categories, the usual relationship to study drug intake was assessed as either probable, possible A, possible B, not related or not possible:

### 18.1.3 Results from Phase II/III OA/RA Programme

Evaluation of serious clinical events

The LSC in their expert evaluation state that:

*"In the phase III program, based on the lack of clinical symptoms, absence of increased bilirubin in patients with elevated aminotransferases and resolution of the liver tests, the clinical significance of the observed toxicity was modest. Specifically there were no instances of hepatic failure, nor drug related AST/ALT elevations associated with jaundice. Except for one patient no individual with aminotransferases levels >3 ULN had an increase in serum bilirubin.*

*In 1 patient (CCOXA0126 0203-00034) with concomitant increase in bilirubin (mostly unconjugated), biliary tract disease was felt to be the most likely diagnosis, although relationship to lumiracoxib 200mg QD could not be completely ruled out. The bilirubin level reached 2.8 x ULN and resolved fully*".

**Further information provided on this patient:**

A liver ultrasound confirmed 2 stones in gall bladder (diameter 9 mm).

Evaluation of all adverse events related to the liver

The results can be summarized as follows:

- Over long term treatment in OA (dataset 2), the incidence of AEs was slightly higher with both lumiracoxib doses compared to celecoxib. No dose response between 200mg and 400mg lumiracoxib doses was observed.
- Over short term (up to 13 weeks) treatment in OA (dataset 1), the incidence of AEs was similar in the lumiracoxib 200mg QD group when compared to placebo and all other treatment groups (<1%), while a slightly higher incidence of AEs was observed in the lumiracoxib 400mg QD group.
- In RA patients over long term (dataset 7a), a placebo-like incidence of AEs was observed with naproxen 500mg BD and lumiracoxib 200mg QD (<1%). A higher incidence of AEs was observed with lumiracoxib 400mg (2.5%).
- In RA patients treated up to 13 weeks (dataset 7 modified), a higher incidence of AEs was observed with celecoxib 200mg BD compared to the other treatment groups, who had significant exposure.

Overall, a very low incidence of AEs related to the hepatobiliary systems was observed in all treatment groups, while higher incidence of laboratory abnormalities was reported as AEs with lumiracoxib, especially at the 400mg QD dose, and with celecoxib 200mg BD as compared to other treatments.

Crude rate (%) of biochemical events (all patients)

| | N | AST/ALT >3x ULN | AST/ALT >5x ULN | AST/ALT >8x ULN | AST/ALT >3x ULN + Bilirubin > 3 mg/dl |
|---|---|---|---|---|---|
| L 50 BD | 200 | 0 | 0 | 0 | 0 |
| L 100 QD | 122 | 1.64 | 0.82 | 0 | 0 |
| L 100 BD | 193 | 0 | 0 | 0 | 0 |
| L 200 QD | 2069 | 1.30 | 0.48 | 0.19 | 0.05 (1 patient) |
| L 200 BD | 193 | 1.04 | 0.52 | 0 | 0 |
| L 400 QD | 2976 | 1.78 | 0.64 | 0.24 | 0 |
| L 800 QD | 265 | 1.51 | 0.38 | 0 | 0 |
| L 1200 QD | 41 | 4.88 | 0 | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| R 25 QD | 257 | 0 | 0 | 0 | 0 |
| C 200 QD | 1239 | 0.65 | 0 | 0 | 0 |
| C 200 BD | 670 | 0.75 | 0.45 | 0.15 | 0 |
| | | | | | |
| Dic 75 BD | 185 | 1.08 | 0 | 0 | 0 |
| Nap 500 BD | 320 | 0.94 | 0 | 0 | 0 |
| Ibu 800 TDS | 476 | 0.63 | 0.21 | 0.21 | 0 |
| | | | | | |
| Placebo | 1860 | 0.43 | 0.11 | 0 | 0 |

It is evident that:

- The incidence of AST/ALT >3 x ULN with lumiracoxib 400mg QD was 1.78%, which was higher than that with lumiracoxib 200mg QD (1.30%). The incidence of ALT/AST > 5 ULN with lumiracoxib 200mg QD is 0.48 % which is similar to the incidence with lumiracoxib 400mg QD of 0.64 %. The incidence of ALT/AST > 8 ULN with lumiracoxib 200mg QD is 0.19 % and with lumiracoxib 400mg QD 0.24 %.
- Higher doses of lumiracoxib were associated with a higher incidence of significant aminotransferase elevations.
- The majority of aminotransferase elevations >5 and 8 x ULN were reported with lumiracoxib, although few cases are reported with celecoxib 200mg BD, ibuprofen 800mg TDS, and placebo.
- One case (0203-00034) of concomitant elevation of ALT/AST >3ULN and bilirubin >3 mg/dl was observed in the lumiracoxib 200mg QD group.

Adjudication of biochemical events

The following table summarises the incidence of hepatocellular, cholestatic and mixed events in all the 119 cases:

| | **Total cases** | **Probable** | **Possible A** | **Possible B** | **NOT related** | **Not assessable** |
|---|---|---|---|---|---|---|
| | | **Hepatocellular injury (n = 95)** | | | | |
| L 100 QD | **2** | 2 | 0 | 0 | 0 | 0 |
| L 200 QD | **24** | 8 | 11 | 1 | 4 | 0 |
| L 200 BD | **1** | 1 | 0 | 0 | 0 | 0 |
| L 400 QD | **40** | 11 | 18 | 8 | 2 | 1 |
| L 800 QD | **3** | 0 | 3 | 0 | 0 | 0 |
| L 1200 QD | **1** | 0 | 1 | 0 | 0 | 0 |
| C 200 QD | **6** | 1 | 2 | 2 | 0 | 1 |
| C 200 BD | **5** | 3 | 1 | 1 | 0 | 0 |
| Dic 75 BD | **1** | 0 | 1 | 0 | 0 | 0 |
| Nap 500 BD | **3** | 1 | 1 | 0 | 1 | 0 |
| Ibu 800 TDS | **3** | 1 | 1 | 1 | 0 | 0 |
| Placebo | **6** | 1 | 2 | 2 | 1 | 0 |
| | | **Cholestatic (n = 6)** | | | | |
| L 200 BD | **1** | 0 | 1 | 0 | 0 | 0 |
| L 400 QD | **4** | 1 | 2 | 1 | 0 | 0 |
| Placebo | **1** | 0 | 1 | 0 | 0 | 0 |
| | | **Mixed (n = 16)** | | | | |
| L 200 QD | **3** | 0 | 2 | 0 | 1 | 0 |
| L 400 QD | **9** | 4 | 3 | 2 | 0 | 0 |
| C 200 QD | **2** | 0 | 0 | 1 | 0 | 1 |
| Dic 75 BD | **1** | 0 | 1 | 0 | 0 | 0 |
| Placebo | **1** | 0 | 1 | 0 | 0 | 0 |
| | | **Not assessable (n = 2)** | | | | |
| L 800 QD | **1** | 0 | 0 | 0 | 1 | 0 |
| L 1200 QD | **1** | 1 | 0 | 0 | 0 | 0 |
| **All** | **119** | **35** | **52** | **19** | **10** | **3** |

The vast majority of events reported were classified as hepatocellular injury (approximately 80%) with approximately 15% mixed and less than 5% cholestatic.

Thus, 87 cases (73%) of the cases were considered probably or possible A related to study drug. Less than 10% of cases reported (n=10) were considered to be unrelated to the study medication, with approximately half of these (n=4) in the lumiracoxib 200mg group. Only 3 cases (2.5%) were not assessable for causality.

An analysis of the overall incidence of events possibly or probably related to the study medication in dataset 9 (Table 3-4 in Prof Maddrey's Report) shows that:

- There was a higher incidence of liver enzyme elevations with lumiracoxib 400mg QD (1.68%) compared to lumiracoxib 200mg QD (1.06%), celecoxib 200mg BD (0.75%), naproxen 500mg BD and ibuprofen 800mg TDS (0.63% each), and celecoxib 200mg QD (0.48%).
- For AST/ALT elevations > 8 x ULN, the incidence was less than 0.3% in all treatment groups with comparable incidence between the lumiracoxib 200mg QD (4 cases, 0.19%), lumiracoxib 400mg QD (7 cases, 0.24%), ibuprofen 800 mg TDS (1 case, 0.21%) and celecoxib 200mg BD (1 case, 0.15%) groups.
- A similar trend for elevations of AST/ALT >5 x ULN was observed.
- Only one case had an increase of AST/ALT with concomitant bilirubin >3 mg/dl in the 200mg QD group. This case is the one discussed above under serious events.
- It should be noted that one patient with an AST/ALT > 5 x ULN (patient 109-0141-00002) in the lumiracoxib 200mg QD group is counted in the group as > 3 x ULN, since the highest follow up was observed in a local laboratory.

In dataset 1 (OA studies up to 13 weeks):

- A statistically significant higher incidence of AST/ALT elevations >3 x ULN was observed in the lumiracoxib 400mg QD group (1.19%) compared to the lumiracoxib 200mg QD group (0.28%, p=0.001). In addition, there was a significantly lower incidence of AST/ALT elevations >3 x ULN in the rofecoxib 25mg QD group (0%) compared to lumiracoxib 400mg QD group (1.19%, p=0.045). However the exposure in the rofecoxib group is much lower than in the lumiracoxib 200mg QD group. Incidence rates comparable to that in the lumiracoxib 200mg QD group were observed in all other treatment groups, including the celecoxib 200mg QD (0.34%), ibuprofen 800mg TDS (0.77%) and placebo (0.26%) groups.
- There was a statistically significant higher incidence of AST/ALT increases >5 x ULN in the lumiracoxib 400mg QD group (0.50%) compared to the lumiracoxib 200mg QD (0.07%) group (p=0.013). The ibuprofen 800mg TDS (0.38%) and placebo (0.09%) groups showed comparable incidence rates to the lumiracoxib 200mg QD group.
- No significant differences were observed across groups for AST/ALT elevations >8 x ULN.

In dataset 7 modified (RA patients up to 13 weeks), the data showed that:

- No statistically significant differences were observed across treatment groups in the incidence of AST/ALT elevations at the different thresholds, with or without bilirubin increases >3 mg/dl.
- However, a dose response for AST/ALT elevations >3 x ULN was detected for the lumiracoxib groups. In the lumiracoxib 200mg QD group, 0.84% of patients had elevations >3 x ULN. This compares to 1.65% in the lumiracoxib 400mg QD group and 4.88% in the lumiracoxib 1200mg QD group. A statistically significant difference can be detected in the odds ratios between the lumiracoxib 1200mg QD group and the

lumiracoxib 200mg QD dose group. All other treatment groups had incidence rates comparable to lumiracoxib 200mg QD and generally below 1%, with the exception of diclofenac 75mg BD (2.25%). It must be noted that patients were exposed to diclofenac for only 4 weeks.

- For AST/ALT elevations >5 x ULN, there were comparable incidences between celecoxib 200mg BD (0.57%) and lumiracoxib 400mg QD (0.55%).
- With lumiracoxib 200mg, there was an incidence rate of 0.34%.
- There were only 2 cases of AST/ALT elevations >8 x ULN. One of these was in the lumiracoxib 400mg group (0.11%) and one was in the celecoxib 200 mg BD group (0.19%).
- There were no cases of concomitant AST/ALT elevations >3 x ULN and bilirubin >3 mg/dl.

**18.1.4 Aminotransferase elevations in acute pain studies**

A total of 1698 patients and volunteers were randomly allocated to receive treatment in single dose and multiple dose (up to 5 days) acute pain studies.

Of these, 956 were treated with lumiracoxib, 235 with rofecoxib, 101 with celecoxib, 51 with ibuprofen, 149 with naproxen, 59 with oxycodone and 465 with placebo.

A total of 13 biochemical events were reported in the post-orthopaedic surgery study, 3 in the post oral surgery studies, and 1 in the dysmenorrhoea studies.

Of the 13 events in the post-orthopaedic surgery study, 13 were adjudicated as possibly related to the study drug.

In the post oral surgery studies, 3 cases (out of 457 patients, 0.65%) were observed in the lumiracoxib 400mg dose group.

In the dysmenorrhoea studies the only case observed was in the naproxen 500mg group (89 patients, 1.12%).

Most cases of aminotransferase elevation (n=9) were observed in the post orthopaedic surgery model. In this dataset one additional case (patient 132-0522-00002) was reported in the controlled release (CR) oxycodone 20mg group which is not included in the database. The reason for this was that the patient experienced an increase in the liver enzymes after having stopped taking the study medication, and was seen by the investigator as an event to be sent to the Liver Safety Committee. Overall, a high background incidence of liver events was observed in this population, most likely due to the postoperative setting. The incidence of biochemical events was similar to that in the placebo group in all groups with the exception of the oxycodone, where the incidence rate was approximately 10%, taking into account the case which is not in the database.

Outcome of liver dysfunction

Of the 119 cases in dataset 9, follow up was available in 108 at the data cut-off date (31 August 2002). All returned to normal (< 2 x ULN) either spontaneously or after discontinuation of study drug except for 1 patient.

After the data cut-off date, follow up on 8 of the remaining 11 patients indicated normal LFTs. One patient could not be contacted. Of the other two, 1 died from acute pulmonary embolism while the third had not fully normalised.

The median time to return to normal was 3 months

**18.1.5 Evaluation of the clinical significance of the biochemical events**

The LSC convened in New York on 24 August 2002 and evaluated the clinical significance of these findings. This is the summary of their expert opinion:

"The LSC adjudicated the 136 events with AST/ALT 3 x ULN in the lumiracoxib clinical program (119 cases in the non acute pain studies and 17 in the acute pain studies).

Among the 119 cases reported in the non-acute pain studies, 106 were considered by the LSC as possibly or probably related to study drug. Of these 36 were > 5 X ULN and 13 were > 8 x ULN. The LSC evaluated the clinical significance of the 23 cases of AST/ALT elevations > 5 x ULN (30 with lumiracoxib, 3 with celecoxib, 1 with ibuprofen and 2 with placebo) and in particular the 13 cases with AST/ALT elevations > 8 x ULN (11 with lumiracoxib, 1 with celecoxib and 1 with ibuprofen).

Among the 17 biochemical events reported in the acute pain studies 14 were considered as possibly or probably related to study drug .Of these 14 cases, 13 of them were reported in the Post orthopaedic surgery model, of which 4 were > 5 x ULN (1 with lumiracoxib, 1 with naproxen and 2 with CR oxycodone) and in particular only 1 case with AST/ALT elevations > 8 x ULN (in the oxycodone group). The 14th event was reported in the dental pain model.

No patient had clinical symptoms associated with aminotransferase elevations, or required hospitalisation felt to be related to lumiracoxib associated liver damage.

Except for a few patients, for whom adequate follow up was not yet available, the aminotransferases returned to or toward normal either spontaneously or after drug discontinuation. Except for one patient, no individual with elevated aminotransferases had an increase in serum bilirubin. In this patient, in whom there was a concomitant increase in bilirubin (mostly unconjugated), biliary tract disease was felt to be the most likely diagnosis, although a relationship of the event with lumiracoxib 200mg QD could not be completely ruled out. The bilirubin level reached 2.8 x ULN and resolved fully."

**18.1.6 Evaluation of the clinical cases from the ongoing TARGET study**

TARGET is an on-going international 52-weeks study comparing the gastrointestinal safety (risk of developing complicated ulcers) of lumiracoxib 400mg QD with naproxen 500mg BD and ibuprofen 800mg TDS in OA and RA patients.

On 24 August 2002, the Applicant provided the LSC with 4 cases of significant aminotransferase abnormalities with concomitant bilirubin increases have been observed. Two of these were in the lumiracoxib 400mg QD group and 1 each was in the naproxen 500mg BD and in the ibuprofen 800mg TDS groups.

One of the patients (0117 0474-00013, **naproxen 500mg BD**), was a 60 years old female, who after 7 weeks of study medication and without significant co-medications developed a 10-fold increase in total bilirubin combined with a 6-fold increase in ALT. Ultrasound showed an intra-hepatic biliary dilatation, with no proper identification of the gallbladder. An endoscopic retrograde cannulation of the pancreas was performed, leading to a diagnosis of an inoperable cholangiocarcinoma.

The second patient (0117 0510-00008, **lumiracoxib 400mg QD**) was a 55 years old female. After 13 weeks of receiving study medication, and concomitant Zithromax for the symptomatic relief of a pharyngitis, the patient developed a 28-fold increase in ALT with a concomitant 11-fold increase in total bilirubin. Liver biopsy showed "acute non-viral hepatitis suggestive of unpredictable drug injury". There was heavy inflammatory infiltrate with

lymphocytes with moderate eosinophils. There was hepatocytes degeneration with mild cholestasis. After hospitalisation and stopping all medication, the patient recovered well.

The third patient (2332 0231-00001, **ibuprofen 800mg TDS**) was a 62 years old female, with known cholecystolithiasis and nephrolithiasis, who developed a 59-fold increase in gamma-glutamyltransferase after being on study medication for 16 weeks. The patient had a concomitant 8-fold increase in ALT combined with a 3-fold increase in total bilirubin. The patient is still under follow up.

The fourth case (0117 0459-00001, **lumiracoxib 400mg QD**) was an 80 years old male. After 25 weeks of receiving the study drug, the patient developed a 32-fold increase in ALT with a concomitant 6-fold increase in total bilirubin. There was no significant co-medication, except for an herbal medication to treat vertigo (started one month before the event). After hospitalisation and stopping of all medication, the patient recovered well. The patient was dismissed from the hospital as the treating physician considered his status to be stable, and ever since there has been an improvement of the liver enzymes.

The case with naproxen appears to be unrelated to study drug and is most likely due to the underlying pathology of cholangiocarcinoma. This case was adjudicated by the Liver Safety Committee not to be related to the study drug. The three other cases, 2 in the lumiracoxib group and 1 in the ibuprofen group, raise concerns as to a possible effect of these drugs on the liver.

For the two lumiracoxib cases it is important to note that the first patient recovered completely and the second patient is still being followed at the time of this report. However, the patient appeared to have recovered and had been discharged from the hospital.

One of the lumiracoxib patients (0117 0459-00001) was adjudicated by the Liver Safety Committee to be most probably due to the study drug. The event in the other lumiracoxib patient (0117 0510-00008) was adjudicated to have a possible confounder in Zithromax and was therefore marked as a possible.

The Liver Safety Committee could not totally rule out the study drug (ibuprofen) in the third case either (2332 0231-00001) and marked it as a possible.

None of the patients developed liver failure.

### 18.1.7 Discussion and conclusions

The Special Expert Evaluation Report concludes:

- There were no instances of hepatic failure, or drug related AST/ALT elevations associated with jaundice in the several studies reported. Only one patient had aminotransferase increases accompanied by a concomitant increase in bilirubin. Biliary tract disease was felt to be the most likely diagnosis in this case, although a relationship to lumiracoxib 200mg QD could not be completely ruled out. The patient fully recovered
- Aminotransferase elevations were more common with lumiracoxib 400mg QD when compared to the other treatments. There appears to be a dose response effect with lumiracoxib between the 200mg QD and 400mg QD doses, especially over the short term (up to 13 weeks).
- Incidence rates of LFT abnormalities in the lumiracoxib 200mg group were comparable to other treatment groups, including celecoxib, ibuprofen, naproxen and placebo.

- Over long term treatment the incidence of biochemical events was comparable between the lumiracoxib 200mg QD and 400mg QD groups. However exposure was limited to approximately 500 patients per treatment group over long term. Demographic characteristics (higher percentage of patients in the 400mg group with longer duration of disease) may have been a factor in this finding.
- There were no clear trends in the analysis of aminotransferase elevations by sex (M/F) or by age (≥ 65 / <65 years).
- Liver enzyme levels normalized in almost all of patients (> 97.5 %) who experienced an elevation in aminotransferases 3 x ULN and for whom follow up values were available. Importantly all cases over 8 x ULN returned to normal.
- TARGET, the large ongoing outcome study, already exceeds the preregistration program in terms of exposure (approximately 4000 patient years, half on lumiracoxib and half on naproxen or ibuprofen). It therefore provides safety information of great value:
    1. There have been 4 cases of significant aminotransferase abnormalities with concomitant bilirubin increase in TARGET to date. Two cases were in the lumiracoxib 400mg QD group and 1 each was in the naproxen 500mg BD and the ibuprofen 800mg TDS groups.
    2. There are possible cofounders in both of the lumiracoxib cases. One patient is taking concomitant Zithromax (known to be associated with liver injury in rare instances). In the second case, intake of herbal medication and/or acetaminophen (rescue medication in TARGET) which may have been taken with alcohol (alcohol consumption was reported by the patient) may provide an alternative explanation for the biochemical event.
- The review of the available data suggests that lumiracoxib has a modest, dose related effect on liver enzymes.
- Therefore, I recommend using the low dose of 200mg QD for chronic use and the 400mg QD dose limited to short term treatment up to 4 weeks.

* * On 6 December 2002, the Applicant provided to the Clinical Assessor details of a further 3 cases reported in the TARGET study.

The fifth case (0117 0376-00016, **lumiracoxib 400mg QD**) was a 51 years old male. After about 20 weeks of receiving the study drug, the patient developed a 95-fold increase in ALT with a concomitant 20-fold increase in total bilirubin. There was no significant co-medication. Liver biopsy showed periportal infiltration by granulocytes and toxic hepatitis. After hospitalisation and stopping the study drug, the patient recovered well and his liver function tests had almost recovered to normal after 7 weeks off the treatment.

The sixth case (0117 0510-00009, **lumiracoxib 400mg QD**) was a 59 years old male. After about 16 weeks of receiving the study drug, the patient developed a 12-fold increase in ALT with a concomitant 4-fold increase in total bilirubin. He was on a number of medications including pioglitazone and metformin and three antihypertensive medications. After hospitalisation and stopping the study drug, his liver function tests continued to deteriorate with bilirubin increasing to 12-fold 2 weeks later but ALT decreasing slightly to 7-fold the ULN. Liver biopsy showed basic normal architecture with no necrosis, hepatitis or fibrosis. A liver ultrasound showed that there was a hypoechogenic area seen in the region of the head of the pancreas measuring 3.7 cm in diameter. This had internal echoes and did not have the appearance of a simple cyst. According to the latest information received, the patient underwent surgery, a choledochojejunostomy was performed, and a recent liver biopsy showed metastatic carcinoma in the liver. The patient is recovering well after the operation.

The seventh case (2332 0415-00010, **ibuprofen 800mg TDS**) was a 62 years old female. After about 10 weeks of receiving the study drug, the patient developed a 2-fold increase in ALT with a concomitant 7-fold increase in total bilirubin. There was no significant co-medication. She had abdominal pain, nausea, fever, malaena, heartburn and dyspnoea. A diagnosis of drug-induced hepatitis, renal failure and gastritis was made, patient hospitalised and the study drug discontinued. A month later, her liver function tests had normalised but her creatinine had stabilised to 2-fold the ULN.

* * On 27 January 2003, the Applicant provided to the Clinical Assessor details of a further case reported in the TARGET study.

The eighth case (2332 0415-00009, **lumiracoxib 400mg QD**) was a 65 years old female with osteoarthritis and no other past medical history and normal biochemistry at baseline. About 12 weeks after receiving the study drug, she began to feel unwell and had abnormal liver function tests. She was asked to discontinue the study drug but continued to deteriorate and was later jaundiced. She required hospitalisation. Her peak abnormalities included raised bilirubin (13 x ULN), ALT (27 x ULN), AST (40 x ULN) and Alkaline phosphatase (2.5 x ULN). A liver biopsy showed evidence of acute cholestatic hepatitis with signs of confluent liver necrosis, regeneration and early fibrosis.

## 18.2 Nephrotoxicity

The Applicant has provided a Special Expert Evaluation Report on renal effects of Lumiracoxib.

### 18.2.1 Patient population

For this expert evaluation, the dataset used was the same as that used for hepatic safety.

Although the Special Expert Evaluation Report discusses many parameters of renal safety, this Assessment Report focuses on the following parameters in dataset 9 (all non-acute OA and RA studies):

- Incidence of post-baseline increase in serum creatinine concentration of > 35.36 μmol/L (0.4 mg/dl) above baseline value
- Monitoring of creatinine values in individual patients for whom an increase in serum creatinine concentration of > 35.36 μmol/L (0.4 mg/dl) above baseline had occurred.
- Incidence of post-baseline increase in serum potassium concentration of > 5.5 mmol/L
- Change of ≥ 25% in baseline diastolic blood pressure.
- Incidence of oedema

### 18.2.2 Results

Incidence of post-baseline increase in serum creatinine concentration of > 35.36 μmol/L (0.4 mg/dl) above baseline value (Dataset 9)

| | N | Anytime (%) | End of study (%) |
|---|---|---|---|
| L 200 QD | 2069 | 2.71 | 0.97 |
| L 400 QD | 2976 | 3.49 | 1.28 |
| R 25 QD | 257 | 1.17 | 0.39 |
| C 200 QD | 1239 | 1.53 | 0.48 |
| Ibu 800 TDS | 476 | 4.83 | 1.68 |
| Nap 500 BD | 320 | 0.31 | 0.31 |
| Placebo | 1860 | 0.86 | 0.32 |

* *The incidence of a rise in serum creatinine above the preset threshold*

*(35.36 µmol/L above the baseline) in OA patients receiving 400mg QD of lumiracoxib was 4-fold greater with concomitant diuretics and/or ACE inhibitors as compared to patients not receiving these medications.*

A number of patients had increased serum creatinine at baseline – placebo (59), lumiracoxib 200mg QD (43), lumiracoxib 400mg QD (66), other coxibs (49) and classical NSAIDs (24).

Three of these patients with pre-existing increased serum creatinine at baseline who had received lumiracoxib had a creatinine elevation of > 35.36 µmol/L (0.4 mg/dl) at the end of study.

| | **Creatinine** | **Potassium** | **Uric acid** |
|---|---|---|---|
| | **Patient 0109-0538-00008 (L 200mg)** | | |
| Baseline | 124 | 5.4 | 464 |
| Peak study value | 159 | 6.2 | 529 |
| End of study | 177 | 5.5 | 500 |
| | **Patient 0112E-0107-00012 (L 400mg)** | | |
| Baseline | 131 | 5.4 | 563 |
| Peak study value | 178 | 5.6 | 541 |
| End of study | 187 | 5.9 | 533 |
| | **Patient 0112E-0201-00053 (L 400mg)** | | |
| Baseline | 120 | 5.2 | 504 |
| Peak study value | 151 | 5.7 | 569 |
| End of study | 175 (119 on F/U) | 5.8 | 274 |

Incidence of post-baseline increase in serum potassium concentration of > 5.5 mmol/L (Dataset 9)

| | | **K > 5.5** | **K > 6.0** | |
|---|---|---|---|---|
| | **N** | **Anytime (%)** | **Anytime (%)** | **At study end (%)** |
| L 200 QD | 2069 | 2.17 | 0.19 | 0.05 (n = 1) |
| L 400 QD | 2976 | 2.22 | 0.34 | 0.07 (n = 2) |
| R 25 QD | 257 | 1.17 | 0 | 0 |
| C 200 QD | 1239 | 1.53 | 0.56 | 0.16 (n = 2) |
| Ibu 800 TDS | 476 | 3.57 | 0.63 | 0.42 (n = 2) |
| Nap 500 BD | 320 | 2.50 | 0.94 | 0 |
| Placebo | 1860 | 0.81 | 0.05 | 0.05 (n = 1) |

Change of ≥ 25% in baseline diastolic blood pressure (% of patients in Dataset 9).

| | **N** | **Increase of ≥ 25% from baseline** | **Increase of ≥ 25% from baseline AND DBP ≥ 90** |
|---|---|---|---|
| L 50 BD | 200 | 5.50 | 3.50 |
| L 100 QD | 122 | 3.28 | 3.28 |
| L 100 BD | 193 | 5.18 | 3.63 |
| L 200 QD | 2069 | 7.97 | 5.80 |
| L 200 BD | 193 | 5.18 | 3.11 |
| L 400 QD | 2976 | 7.56 | 4.97 |
| L 800 QD | 265 | 6.79 | 3.02 |
| L 1200 QD | 41 | 4.88 | 4.88 |
| R 25 QD | 257 | 5.84 | 4.28 |
| C 200 QD | 1239 | 9.28 | 6.94 |
| C 200 BD | 670 | 7.61 | 2.99 |
| Dic 75 BD | 185 | 6.49 | 3.78 |
| Nap 500 BD | 320 | 7.50 | 6.25 |
| Ibu 800 TDS | 476 | 8.82 | 5.04 |
| Placebo | 1860 | 6.45 | 4.25 |

Incidence (%) of oedema in Dataset 9

| | N | Oedema | Peripheral oedema |
|---|---|---|---|
| L 50 BD | 200 | 1.5 | 3.5 |
| L 100 QD | 122 | 0 | 0 |
| L 100 BD | 193 | 1.6 | 4.1 |
| L 200 QD | 2069 | 0.1 | 1.3 |
| L 200 BD | 193 | 0.5 | 5.7 |
| L 400 QD | 2976 | 0.3 | 1.5 |
| L 800 QD | 265 | 0 | 2.6 |
| L 1200 QD | 41 | 0 | 0 |
| | | | |
| R 25 QD | 257 | 0.4 | 3.5 |
| C 200 QD | 1239 | 0.2 | 2.1 |
| C 200 BD | 670 | 0.1 | 1.6 |
| | | | |
| Dic 75 BD | 185 | 0.5 | 5.4 |
| Nap 500 BD | 320 | 0.3 | 1.3 |
| Ibu 800 TDS | 476 | 0.2 | 2.7 |
| | | | |
| Placebo | 1860 | 0.1 | 1.2 |

Other renal adverse events

**Patient 0126-0201-00010** was a 70 years old female who was receiving lumiracoxib 200mg QD developed mild nephrotic syndrome on study day 61 which progressed to severe on day 73. Her serum creatinine increased from 119 μmol/L at baseline to 149 μmol/L on day 69. The drug was discontinued on day 77. A renal ultrasound on day 2 post-stop and a CT scan on day 30 post-stop were normal. The Expert is of the view that diagnostic criteria for nephrotic syndrome are not met and a transient decline in renal function should be considered the likely diagnosis.

**Patient 0109-0403-00014** was a 65-years old male who was receiving a number of antihypertensive agents in addition to lumiracoxib 200mg QD. On study day 34, the patient developed urinary retention and was hospitalised. Acute renal failure and E coli prostatitis were diagnosed. Following appropriate treatment, the patient improved and renal function tests normalized.

**Patient 0109-0524-00009** was a 68 years old female who was randomised to lumiracoxib 200mg QD. She was in receipt of a number of antihypertensive agents. She had a complex pre-randomisation history of urinary problems. On study day 4, she was admitted with acute severe renal failure (creatinine 477 μmol/L from baseline of 88 μmol/L). The study drug was discontinued, acute renal failure treated and discharged. Three months later, her creatinine was normal (115 μmol/L).

Subgroup analysis found the nephrotoxic risk to be greater in those receiving diuretics or ACE inhibitors.

The report author concludes that because COX-2 is involved in renal homeostasis, renal effects are not unexpected. A small, predicted rise in serum creatinine tends to occur earlier and may be slightly greater in patients treated with lumiracoxib compared to other "coxibs". This is compatible with the notion that lumiracoxib blocks *renal* COX-2 perhaps more effectively.

## 18.3 Myelotoxicity

The Applicant has provided a Special Expert Evaluation Report on haematological safety of lumiracoxib.

### 18.3.1 Patient population

For this expert evaluation, the datasets used are 1 (short-term studies in OA), 2 (long-term studies in OA) and 7 (short-term studies in RA to 26 weeks). 43-52% of the patients in RA studies had received methotrexate as a co-medication.

## 18.3.2 Results

Although the Special Expert Evaluation Report discusses many parameters of haematological safety, this Assessment Report focuses on the following parameters:

**Anaemias:**

| Treatment | N | N (%) |
|---|---|---|
| | ***Dataset 1 in short-term OA*** | |
| L 200 QD | 1418 | 6 (0.42) |
| L 200 BD | 99 | 1 (1.01) |
| L 400 QD | 2009 | 8 (0.40) |
| R 25 QD | 257 | 2 (0.78) |
| C 200 QD | 1183 | 8 (0.68) |
| Ibu 800 TDS | 260 | 6 (2.31) |
| Placebo | 1168 | 7 (0.60) |
| | ***Dataset 7 in short-term RA*** | |
| L 200 QD | 595 | 7 (1.18) |
| L 200 BD | 93 | 1 (1.06) |
| L 400 QD | 908 | 14 (1.54) |
| L 800 QD | 265 | 3 (1.13) |
| C 200 BD | 525 | 3 (0.57) |
| N 500 BD | 320 | 3 (0.94) |
| I 800 TDS | 207 | 9 (4.35) |
| Placebo | 692 | 2 (0.29) |

Many of the above were associated with GI tract blood loss.

In the TARGET study, there were 4 cases of anaemia – all associated with GI erosions, ulcers or haemorrhage.

**Severe anaemia:**

There were two cases of severe anaemia in dataset 1 – one each on lumiracoxib and a classical NSAID. In dataset 2, there was one case in lumiracoxib group and none in celecoxib group.

**Cytopenia:**

| Treatment | N | N (%) |
|---|---|---|
| | ***Dataset 1 in short-term OA*** | |
| L 200 QD | 1418 | 3 (0.21) |
| L 200 BD | 99 | 0 |
| L 400 QD | 2009 | 1 (0.05) |
| R 25 QD | 257 | 0 |
| C 200 QD | 1183 | 2 (0.17) |
| Ibu 800 TDS | 260 | 0 |
| Placebo | 1168 | 2 (0.17) |
| | ***Dataset 7 in short-term RA*** | |
| L 200 QD | 595 | 2 (0.34) |
| L 200 BD | 93 | 0 |
| L 400 QD | 908 | 4 (0.44) |
| L 800 QD | 265 | 0 |
| C 200 BD | 525 | 2 (0.38) |
| N 500 BD | 320 | 1 (0.31) |
| I 800 TDS | 207 | 1 (0.46) |
| Placebo | 692 | 2 (0.29) |

In three RA patients, cytopenia was reported as a serious adverse event – 1 on lumiracoxib 200mg and 2 on 400mg. These cases are:

0114-109-00007: onset after 14 days
0114-204-00001: onset after 23 days
0114-403-00021: onset after 89 days (diagnosis of SLE suspected)

In the context of cytopenias, it is worth bearing in mind that in RA patients treated with methotrexate, the incidence of cytopenias is 5-25% and of severe cytopenia 1.4%.

One report of cytopenia due to ibuprofen has been reported from the TARGET study.

**18.4 Effect on joint structure**

In study 0112E (long-term use in OA), semi-flexed weight-bearing x-rays of the target knee were obtained at baseline and after a minimum of 10 months for the assessment of joint space width. Radiographs were corrected for magnification.

The applicant has provided a special report on this aspect. This is Appendix 8.2.3 to Study Report

The following table is the summary of the results on joint space width (mm):

| | Unadjusted | Adjusted |
|---|---|---|
| | Baseline | |
| N | 642 | 638 |
| Medial | 3.16 | 2.90 |
| Lateral | 6.14 | 5.64 |
| | Change in 1 year | |
| N | 642 | 627 |
| Medial | - 0.08 | - 0.08 |
| Lateral | - 0.04 | - 0.05 |

| | | Baseline JSW adjusted (mm) | | Change in JSW adjusted in 1 year (mm) | |
|---|---|---|---|---|---|
| Treatment | N | Medial | Lateral | Medial | Lateral |
| Placebo | 114 | 2.98 | 5.68 | - 0.08 | 0.00 |
| Lumira 200 | 247 | 3.03 | 5.66 | - 0.07 | - 0.05 |
| Lumira 400 | 242 | 2.71 | 5.59 | - 0.09 | - 0.02 |
| Cele 200 | 247 | 2.78 | 5.81 | - 0.05 | - 0.05 |

There was no statistically significant difference between any of the 6 comparisons.

***Assessor's comments on hepatic and renal safety of lumiracoxib:***

The data on hepatic effects of lumiracoxib are a matter of concern. The frequency is relatively high and dose-related within the proposed therapeutic range. The results from datasets 1 and 9 clearly show that the frequency of abnormal serum transaminases is greater with 400mg dose than with 200mg dose.

It is noted that even in the clinical trials, there was one case (0203-00034) of concomitant elevation of ALT/AST >3ULN and bilirubin >3 mg/dl in the lumiracoxib 200mg QD group. Of greater concern are the 4 reports associated with 400mg QD dose of lumiracoxib in TARGET study (after excluding the case with tumour near the head of pancreas liver metastasis). This study does not include a 200mg dose.

Relative to 200mg QD dose, the 400mg QD dose of lumiracoxib has a higher frequency of patients with respect to post-baseline increase in serum creatinine concentration of > 35.36 μmol/L (0.4 mg/dl) above baseline value, potassium levels
> 6.0 mmol/L or oedema.

This dose-related hepatotoxicity and nephrotoxicity also influences the risk/benefit of the proposed posology.

The current proposal by the applicant of dose regimen in osteoarthritis is:

> "200mg once daily. Some patients may receive additional benefit from short-term use of 400mg once daily"

This should be revised as follows:

> "100mg daily in one or two divided doses. In patients who fail to respond, the dose may be increased to 200mg daily in one or two divided doses."

Available data are consistent with a notion that lumiracoxib may be more nephrotoxic that other coxibs and therefore, the drug should be contraindicated in patients with moderate to severe renal dysfunction.

The Applicant needs to address this potential for serious hepatotoxicity by recommending that liver function tests should be measured before starting therapy with lumiracoxib and at monthly interval thereafter for the first 6 months.

***Assessor's comments on myelotoxicity of lumiracoxib:***

Available data are consistent with a notion that lumiracoxib:

1. may produce anaemia due to its effect on GI tract
2. may produce cytopenias usually in combination with methotrexate.
3. treatment is not associated with significant myelotoxicity compared to other coxibs or classical NSAIDs

There is no evidence of any concern at present.

***Assessor's comments on the effect of lumiracoxib joint structure***

The rate of joint space narrowing in osteoarthritis reported in the literature ranges from -0.06 mm per year to -0.23 mm per year.

In a population of 691 patients treated by rofecoxib and diclofenac, the mean rate of change in minimal joint space width over one year of treatment was:

- -0.14 mm per year for 12.5mg rofecoxib
- -0.27 mm per year for 25mg rofecoxib
- -0.18 mm per year for diclofenac group.

There was no statistically significant difference among these groups.

The assessor concludes that lumiracoxib does not have any adverse effect on articular structure over a 1-year period.

There is no evidence of any concern at present.

## 19. EVALUATION OF CLINICAL DATA AND DISCUSSION

The Clinical Assessor has assessed the clinical trials data provided by the applicant and the clinical details on the Summary of Product Characteristics with regard to the CPMP documents entitled:

*"Points to Consider on clinical investigation of medicinal products used in the treatment of osteoarthritis"*
*and*
*"Points to Consider on clinical investigation of slow-acting anti-rheumatic medicinal products in rheumatoid arthritis"*

**The document on osteoarthritis** distinguishes between symptom modifying and structure modifying drugs. It recommends a focus on pain for the primary endpoint, which may be measured by VAS or Likert scale. Assessment of functional disability is recommended an additional important primary endpoint. The use of a disease-specific and joint-specific instrument (WOMAC) is recommended. It is conceded that the design and duration of Phase III studies may differ according to the properties of the drug under investigation. The primary analysis population should be defined according to intention-to-treat principle. For symptom-modifying drugs in osteoarthritis, it is recommended to use a three-arm placebo and active controlled Phase III studies.

**The document on Rheumatoid Arthritis** focuses heavily on disease-modifying or disease-controlling drugs and makes only passing references to symptom modifying drugs. The duration of the study is left to the sponsor, depending on the endpoints chosen, sensitivity and the magnitude of the effect anticipated. For the investigation of symptom-modifying drugs like NSAIDs in rheumatoid arthritis, the CPMP document recommends:

| | |
|---|---|
| Primary endpoints: | Pain score (Patient's assessment of pain on VAS) |
| | Physical function including morning stiffness assessed by patients (eg HAQ, AIMS) |
| Secondary endpoints: | Swollen joint count |
| | Tender joint count |
| | Physician's global assessment of disease activity |
| | Patient's global assessment of disease activity |
| | Acute phase reactants (eg ESR or C-reactive protein) |

The applicant has chosen:

| | |
|---|---|
| *Primary endpoints:* | Tender Joint Count. |
| | Swollen Joint Count. |
| | Patient Global Assessment of Disease Activity. |
| | Investigator Global Assessment of Disease Activity. |
| *Key Secondary endpoints* | Health Assessment Questionnaire (HAQ; disability scales). |
| | Patient Global Assessment of Pain. |
| | The American College of Rheumatology 20% (ACR20) Responders and Completers Index (proportion of patients both achieving an ACR20 response and completing the 12-week study period). |

By and large, the applicant's clinical development programme of lumiracoxib is in compliance with these documents.

The main deficiencies or areas of clinical concern perceived by the Clinical Assessor are summarised below:

## 19.1 Pharmacology:

| | |
|---|---|
| Pharmacodynamics: | Satisfactory. |
| Pharmacokinetics: | Dose-linearity is lost at doses of 1200mg QD and higher. The drug is metabolised by CYP2C9 and highly bound to plasma albumin. |
| Special populations: | Lumiracoxib has not been studied in juvenile arthritis.<br><br>It is possible that individuals who are homozygous for *3 allele would have very high plasma levels but this genotype is extremely rare in Western Caucasian population.<br><br>Exposure to lumiracoxib is lower in patients with end stage renal disease compared to normal subjects. Compared to normal subjects, mean exposure to 4'-hydroxy-lumiracoxib is not significantly increased in ESRD patients and exposure to 4'-hydroxy-5-carboxy-lumiracoxib is increased substantially (by about 7 times). |

## 19.2 Dose-response:

| | |
|---|---|
| Osteoarthritis | Poor characterization of optimal dose |
| Rheumatoid arthritis | No dose was found to be effective relative to placebo. |
| Primary dysmenorrhoea | No specific study – dose selection extrapolated from studies in acute pain in post-dental surgery patients. 400mg QD dose appears appropriate. |
| Acute pain | The model used is acute pain in post-dental surgery patients. It is difficult to distinguish clearly between 100mg and 200mg doses of lumiracoxib since these two doses have not been compared directly. |

## 19.3 Efficacy:

| | |
|---|---|
| Osteoarthritis | Lumiracoxib is effective in the symptomatic relief of OA but a dose of 200mg QD has a better risk/benefit profile |
| Rheumatoid arthritis | Lumiracoxib is **NOT** effective in the symptomatic treatment of RA. |
| Primary dysmenorrhoea | 400mg QD dose is appropriate as long as the indication is restricted to moderate to severe primary dysmenorrhoea. |
| Acute pain | 400mg QD dose is appropriate as long as the indication is restricted to short-term relief of moderate to severe acute pain associated with dental surgery and orthopaedic surgery |

## 19.4 Safety:

| | |
|---|---|
| Drug interactions: | Lumiracoxib is metabolised by CYP2C9 and highly protein bound. The possibility of protein-displacement interactions with |

| | |
|---|---|
| | other CYP2C (substrates of narrow therapeutic index (phenytoin) is a real one.<br><br>Drugs that are likely to be used by the target population include prednisolone and aspirin. No interaction studies have been carried out against these drugs. Neither is there an interaction study with digoxin. |
| Clinical safety: | Lumiracoxib has an acceptable profile of clinical safety. But certain renal and immunologic reactions need to be included in SPC. The clinical safety of 400mg QD dose is worse than that of 200mg QD dose. |
| Laboratory safety | Lumiracoxib is a potentially moderate nephrotoxin and renal adverse effects are a source of concern. |
| Gastrointestinal safety | Satisfactory relative to other coxibs and superior to classical non-selective NSAIDs but there is good evidence of a dose-toxicity relationship within the dose range proposed by the applicant. |
| Hepatotoxicity: | Lumiracoxib is a potentially moderate, dose-dependent hepatotoxin with reports of hepatitis at 200mg QD dose in clinical trials and 4 reports at 400mg QD dose in one major ongoing outcome study (TARGET) |
| Nephrotoxicity: | Although pre-existing renal dysfunction does not influence lumiracoxib pharmacokinetics, the pharmacodynamic effects of lumiracoxib in patients with renal dysfunction is a potential issue of clinical relevance. |
| Prothrombotic | Lumiracoxib has a slightly higher risk of prothrombotic effects events relative to placebo. |
| Myelotoxicity: | No evidence of any concern at present. |
| ECG effects: | No evidence of any concern at present. |
| Articular safety: | No evidence of an adverse effect on joint structure in osteoarthritis following a year of treatment. |
| SPC: | Needs a number of changes, in particular:<br>1. Removing the indication in rheumatoid arthritis<br>2. The indication in primary dysmenorrhoea should be restricted to the population studied (that is, patients with moderate to severe primary dysmenorrhoea).<br>3. The indication should be restricted to the population studied (that is, patients with moderate to severe pain following dental or orthopaedic surgery).<br>4. Downward revision to the posology for osteoarthritis<br>5. Additional or amended contraindications in respect of patients with renal or hepatic dysfunction.<br>6. Inclusion of a caution for use in patients with ischaemic heart disease |

7. Inclusion of an advice to monitor renal and liver function tests at baseline and every month for the first 6 months.
8. Addition of other adverse drug events and drawing attention to the greater frequency of certain events with 400mg QD dose relative to 200mg QD dose.
9. Revisions to the texts of section 5.1 on Pharmacodynamics to reflect better and briefly the data from the clinical trials.

## 20. PRECLINICAL AND CLINICAL ASSESSORS' CONCLUSIONS

On the basis of evidence available, the Assessors conclude that, on grounds relating to efficacy and safety, marketing authorisations for **PREXIGE Tablets** may be granted provided following amendments, as detailed below.

**The Committee** are asked to consider the evidence presented in these papers, the Applicant's Expert Reports and the comments and conclusions of the Assessors and to advise the Licensing Authority.

Major changes proposed by the Clinical Assessor for consideration by the Committee are:

1. Removing the indication in rheumatoid arthritis
2. The indication in primary dysmenorrhoea should be restricted to the population studied (that is, patients with moderate to severe primary dysmenorrhoea).
3. The indication in acute pain should be restricted to the population studied (that is, patients with moderate to severe pain following dental or orthopaedic surgery).
4. Downward revision to the posology for osteoarthritis
5. Additional or amended contraindications in respect of patients with renal or hepatic dysfunction.
6. Inclusion of a caution for use in patients with ischaemic heart disease
7. Inclusion of an advice to monitor renal and liver function tests at baseline and every month for the first 6 months.
8. Addition of other adverse drug events and drawing attention to the greater frequency of certain events with 400mg QD dose relative to 200mg QD dose.
9. Revisions to the texts of section 5.1 on Pharmacodynamics to reflect better and briefly the data from the clinical trials.

The patient information leaflet should be amended as required to the satisfaction of the Secretariat. In particular, it should be amended to reflect the changes to the Summary of Product Characteristics.

# Assessment of Responses – 1 September 2003

Following the CSM Conditional grant letter dated 28 March 2003, the assessors concerned have had at least three meetings with the Company to discuss the conditions.

The applicant has now responded, accepting all the conditions. The applicant has also agreed to a discussion on Risk Management Strategy with the Post-Licensing Division which was represented in all these meetings.

There is an on-going review of the dossier of the 100mg formulation.

The revised SPC is acceptable and fully meets with all the conditions set by CSM. As agreed with CSM, the recommendation to monitor renal and liver functions tests have been waived since the applicant has agreed to a lower dose schedule and that these effects are dose-related.

The Patient Information Leaflet required amendments and these have now been agreed and the revised draft PIL is satisfactory.

# UPDATE to Clinical Assessment 27 July 2004

## 1. Introduction

Lumiracoxib was approved in the United Kingdom on 12 September 2003 as PREXIGE tablets. Three branded clones (FREXOCEL, STELLIGE and EXFORGE) have also been approved recently. All are approved in 100mg, 200mg and 400mg strengths. These four clone products have been the subject of a Mutual Recognition Procedure.

With regard to osteoarthritis, the phase II dose-ranging programme had essentially failed to distinguish between any of the 4 doses of lumiracoxib, ranging from 50mg BD to 400mg OD. Among the four doses, 50mg BD was consistently superior to 100mg BD dose. There was no difference between 200mg OD and 400mg OD doses of lumiracoxib. The risk/benefit ratio for a 400mg OD dose was considered unfavourable because of dose-related clinical and laboratory safety, particularly the gastro-intestinal, hepatic and renal safety of lumiracoxib.

At the time of its approval, lumiracoxib was found to be effective in the symptomatic relief of OA but a dose of 100mg OD, which may be increased to 200mg OD, was determined to have a better risk/benefit profile. The dose schedule approved by the RMS in September 2003 was based on three dose-ranging studies that had been submitted (0104, 2316 and 2301) covering a dose range from 50mg BD to 400mg OD.

At the time of its approval, a large study, Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), was ongoing. TARGET is an international, multicentre, stratified, randomised, double-blind, double-dummy, parallel-group, 52-week gastrointestinal clinical safety study to demonstrate that lumiracoxib 400mg daily reduces the risk to develop complicated ulcers compared to NSAIDs (naproxen 500 mg twice daily and ibuprofen 800 mg thrice daily), in osteoarthritis patients. This is now complete with a study report available.

Since TARGET did not include a 100mg or 200mg dose, the applicant has completed and submitted a specific study (Study 2361) comparing lumiracoxib 100mg OD with celecoxib 200mg OD and placebo.

## 2. New studies provided

The applicant has now provided the following studies:

| Studies since MAA submission | Dosing Regimen | Study Status | CSR Status |
|---|---|---|---|
| TARGET | Lumiracoxib 400mg OD<br>Naproxen 500mg BD<br>Ibuprofen 800 TDS | Completed | June 2004 |
| OA 100mg<br>3 months core study<br>(Study 2361) | Lumiracoxib 100mg OD<br>Lumiracoxib 100mg OD with a 2 week 200 mg OD starting dose<br>Celecoxib 200mg OD<br>Placebo | Completed. | June 2004 |
| RA 2335<br>3 months core study | Lumiracoxib 200mg OD<br>Naproxen 500mg BD<br>Placebo | Completed | May 2003 |
| Dental pain<br>(Study 2362) | Lumiracoxib 200mg<br>Lumiracoxib 200mg with an optional re-dose<br>Placebo | Completed | Completed |
| Dental pain<br>(Study 2336) | Lumiracoxib 400 mg<br>Rofecoxib 50 mg | Completed | Completed |

| | | | |
|---|---|---|---|
| | Placebo | | |
| Tension-type headache, single dose (Study 2351) | Lumiracoxib 200mg<br>Lumiracoxib 400mg<br>Placebo | Completed | Completed |
| CP study<br>PK in mild and moderate renal impaired patients (Study 2350) | Lumiracoxib 200mg SD in<br>Mild and moderate RI and matched healthy subjects<br>PK of Lumiracoxib and 3 metabolites | Completed. | Completed |
| CP DDI<br>Study with low-dose aspirin (Study 2349) | Lumiracoxib 400 mg OD for 11 days and Aspirin 75 mg OD on Days 5-11<br>Platelet aggregation and serum and urine thromboxane and prostacyclin determined on Days 4 and 11 | Completed | Completed |

This Update to original Clinical Assessment includes the assessment of following additional studies/documents provided by the applicant to RMS prior to commencing the Mutual Recognition procedure.

1. Osteoarthritis 100mg 3-months core study (Study 2361)
2. TARGET Study
3. Low dose aspirin interaction study (Study 2349)
4 An Addendum to the Clinical Overview

In addition, the safety data from those studies that have been completed but not submitted (**see overleaf**) are also reviewed in this Update.

The following studies have been completed but the Study Reports are still under preparation:

| **Studies since MAA submission** | **Dosing Regimen** | **Study Status** | **CSR Status** |
|---|---|---|---|
| OA 100mg<br>3 months core study,<br>(Study 2360) | Lumiracoxib 100mg OD<br>Lumiracoxib 100mg OD with a two week 200 mg OD starting dose<br>Celecoxib 200mg OD<br>Placebo | Completed. | In preparation |

| | | | |
|---|---|---|---|
| Dental pain<br>(Study 2336)<br>PK/PD additional study | Lumiracoxib 400 mg<br>Rofecoxib 50 mg<br>Placebo | Completed | In preparation |
| Dysmenorrhoea 200mg<br>(Study 2353) | Lumiracoxib200mg OD<br>Lumiracoxib 200mg with an optional re-dose<br>Naproxen.500 mg BD<br>Placebo | Completed | In preparation |
| Dysmenorrhoea 200mg<br>(Study 2358) | Lumiracoxib 200mg OD<br>Lumiracoxib.200mg with an optional re-dose<br>Placebo | Completed | In preparation |
| CP COX-2 selectivity versus Naproxen<br>(Study 2320) | Lumiracoxib 400 mg OD<br>Lumiracoxib 800 mg OD<br>Placebo (to Lum.) OD<br>Naproxen 500 mg BD<br>Ex vivo whole blood inhibition of PGE2 and TXB2 to measure COX-2 and COX-1 inhibition | Completed | In preparation |

Data from the following study are also briefly reviewed in this Update:
1. Osteoarthritis 100mg 3-months core study (Study 2360)

# 3. Study 2361 (Osteoarthritis 100mg 3-months core study)

## 3.1 Design

This was a 13-week, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel groups trial of 2 different dose regimens of lumiracoxib (100 mg once daily and 200 mg once daily initial dose for two weeks followed by 100 mg once daily) in patients with **primary knee osteoarthritis**, using celecoxib (200 mg once daily) as a comparator.

116 centers in 15 countries participated in the study as follows: Australia (4), Austria (2), Czech Republic (3), Finland (7), Germany (43), Hungary (5), Israel (4), The Netherlands (11), New Zealand (1), Poland (3), Slovakia (4), South Africa (3), Spain (11), Sweden (10), and Turkey (5).

## 3.2 Objective

The primary objective was to determine if lumiracoxib (100 mg once daily and 200 mg once daily Initial Dose [ID] followed by 100 mg once daily) was effective in treating osteoarthritis (OA) in the target knee as compared to placebo with respect to:

- Overall OA pain intensity in the target knee on a 0-100 mm Visual Analog Scale (VAS) after 13 weeks of treatment
- Patient's global assessment of disease activity on a 0-100 mm VAS after 13 weeks of treatment
- Patient's functional status (using the WOMAC total score) after 13 weeks of treatment.

Secondary objective included an assessment of the effect of lumiracoxib on other joints with respect to patient's global assessment of disease, physician's global assessment of disease and for OA of hands, also AUSCAN questionnaire.

## 3.3 Patient population

The planned sample size was 1464 patients - 366 in each of the four treatment arms.

First patient was enrolled on 19 September 2003
Last patient completed the study on 16 February 2004

1684 patients were randomised and treated:
- 420 with lumiracoxib 100 mg once daily for 13 weeks
- 420 with lumiracoxib 200 mg once daily for two weeks followed by 100mg daily for weeks 3-13 (ID)
- 420 with celecoxib 200 mg once daily for 13 weeks, and
- 424 with placebo for 13 weeks

## 3.4 Duration of treatment

The planned duration of treatment was 13 weeks.

## 3.5 Endpoints

### 3.5.1 Efficacy

The three joint **primary efficacy variables** were:
- Overall OA pain intensity in the target knee after 13 weeks of treatment using a 0-100 mm VAS.
- Patient's global assessment of disease activity after 13 weeks of treatment using a 0-100 mm VAS.
- Patient's functional status after 13 weeks of treatment using WOMAC total score.

### 3.5.2 Safety

Safety variables included serious adverse events, adverse events, physical examinations, vital sign measurements, and laboratory evaluations (including glomerular filtration rate derived from plasma creatinine). All suspected gastrointestinal complications, liver, selected cardiovascular and cerebrovascular events were also monitored.

## 3.6 Results

Exposure:

| | Lumiracoxib 100mg QD | Lumiracoxib 200mg QD ID | Celecoxib 200mg QD | Placebo |
|---|---|---|---|---|
| N randomised | 420 | 420 | 420 | 424 |
| N completed | 381 | 379 | 368 | 360 |
| | Discontinued because of | | | |
| Safety | 10 | 14 | 20 | 16 |
| Lack of efficacy | 8 | 10 | 13 | 31 |
| Others | 21 | 17 | 19 | 7 |
| Mean exposure in days | 87.4 | 87.0 | 85.0 | 82.7 |
| Number of patients exposed in days | | | | |
| 0 | 1 | 0 | 1 | 0 |
| 1 to < 7 | 4 | 4 | 3 | 4 |
| 7 to < 29 | 10 | 14 | 20 | 32 |
| 29 to < 57 | 10 | 8 | 15 | 18 |
| 57 to < 92 | 171 | 170 | 166 | 155 |
| ≥ 92 | 224 | 224 | 215 | 215 |
| Dosage compliant patients | 400 | 409 | 401 | 409 |

Baseline demography:

| | Lumiracoxib 100mg QD | Lumiracoxib 200mg QD ID | Celecoxib 200mg QD | Placebo |
|---|---|---|---|---|
| Mean age (yrs) | 62.2 | 62.9 | 62.9 | 61.7 |
| % Females | 68.1 | 69.8 | 68.3 | 71.9 |
| % Caucasians | 99.5 | 98.3 | 98.1 | 98.9 |
| Mean years disease duration | 4.4 | 4.2 | 4.4 | 3.9 |

3.6.1 Efficacy at the target joint

After 13 weeks (ITT, LOCF)

| | Lumiracoxib 100mg QD | Lumiracoxib 200mg QD ID | Celecoxib 200mg QD | Placebo |
|---|---|---|---|---|
| OA Pain VAS Score | | | | |
| Baseline | 64.1 | 64.4 | 64.8 | 63.8 |
| Change at 13 weeks | - 26.8 | - 26.2 | - 26.6 | - 21.4 |
| Patient global assessment | | | | |
| Baseline | 63.1 | 61.6 | 62.9 | 62.9 |
| Change at 13 weeks | - 25.1 | - 21.9 | - 22.9 | - 18.9 |
| WOMAC Total score | | | | |
| Baseline | 49.2 | 49.7 | 50.5 | 49.7 |
| Change at 13 weeks | - 15.18 | - 14.82 | - 14.69 | - 11.32 |

Treatment comparisons

| Variable / Contrasts | Est. Diff. | 95% CI of Difference | p-value[1] |
|---|---|---|---|
| **OA pain intensity (VAS mm) after 13 weeks** | | | |
| Treatment comparison with "All LUM" | | | |
| All LUM – Placebo | -4.71 | -7.26, -2.16 | <0.001 |
| Treatment comparisons | | | |
| LUM 100 mg QD – placebo | -5.09 | -8.04, -2.15 | < 0.001 |
| LUM 200 mg QD ID – placebo | -4.33 | -7.28, -1.39 | 0.004 |
| **Patient's assessment of disease activity (VAS mm) after 13 weeks** | | | |
| Treatment comparison with "All LUM" | | | |
| All LUM – Placebo | -4.79 | -7.34, -2.25 | <0.001 |
| Treatment comparisons | | | |
| LUM 100 mg QD – placebo | -5.93 | -8.87, -2.99 | < 0.001 |
| LUM 200 mg QD ID – placebo | -3.66 | -6.60, -0.71 | 0.015 |
| **WOMAC Total score after 13 weeks** | | | |
| Treatment comparison with "All LUM" | | | |
| All LUM – Placebo | -3.63 | -5.41, -1.84 | <0.001 |
| Treatment comparisons | | | |
| LUM 100 mg QD – placebo | -3.92 | -5.98, -1.86 | < 0.001 |
| LUM 200 mg QD ID – placebo | -3.33 | -5.40, -1.27 | 0.002 |

LUM = lumiracoxib

[1] ANCOVA with center, treatment, and corresponding baseline value. Contrasts tested at the 5% significance level.

"All lumiracoxib" was non-inferior to celecoxib 200 mg (p=0.024 for overall pain in the target joint, p=0.007 for patient's global assessment of disease activity, and p=0.004 for WOMAC Total score).

No statistically significant difference could be detected between either lumiracoxib 100 mg or lumiracoxib 200 mg ID and celecoxib 200 mg, or between the two lumiracoxib dose groups, for all three co-primary efficacy variables.

3.6.2 Efficacy at the non-target joint(s)

In the subgroup of patients who had OA in at least one joint other than the knee, all active treatments were significantly more effective than placebo in both the patient's global assessment of pain and the physician's global assessment of disease activity after 13 weeks of treatment. For the subgroup of patients with no other affected joint, none of the active treatments were significantly better than placebo for either assessment.

With respect to changes in AUSCAN scores in patients with OA of the hand joints, there were **no statistically significant differences** between any treatment comparisons with placebo.

3.6.3 Safety

| n (%) | Lumiracoxib 100 mg od | Lumiracoxib 200mg od ID | Celecoxib 200 mg od | Placebo |
|---|---|---|---|---|
| Total number of patients studied | 420 (100) | 420 (100) | 420 (100) | 424 (100) |
| Total number of patients with AEs | 200 (47.6) | 204 (48.6) | 180 (42.9) | 178 (42.0) |
| **Patients with serious AEs:** | | | | |
| Deaths | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Non-fatal SAEs | 5 (1.2) | 7 (1.7) | 6 (1.4) | 7 (1.7) |
| **Patients with other significant AEs:** | | | | |
| AEs leading to study drug dose adjustment/interruption | 15 (3.6) | 11 (2.6) | 16 (3.8) | 9 (2.1) |
| Discontinuations due to: | | | | |
| Any AEs including SAEs | 10 (2.4) | 14 (3.3) | 23 (5.5) | 17 (4.0) |
| SAEs | 4 (1.0) | 3 (0.7) | 5 (1.2) | 5 (1.2) |
| AEs (non-serious) | 6 (1.4) | 11 (2.6) | 18 (4.3) | 12 (2.8) |

The most frequent adverse events (≥ 5% in any group) were headache and nasopharyngitis. Gastrointestinal events dyspepsia, diarrhea, nausea or upper abdominal pain occurred in 2-4% of patients in any group, and were usually mild to moderate in severity.

One death occurred during the study. A 66-year-old white female in the lumiracoxib 100 mg group experienced sudden death while skiing. The patient had a history of hypertension and obesity. The event was not considered related to study medication.

**Laboratory evaluations:**
Clinical laboratory values outside normal ranges and notable laboratory abnormalities were infrequently reported either as adverse events or in association with adverse events (see table overleaf).

Two lumiracoxib-treated patients discontinued due to elevated liver enzymes. However, one of these patients entered the study in error as the elevated values occurred at screening (protocol violation). The other patient was on 200mg daily dose of lumiracoxib.

**Vital signs:**
No relevant between-group differences in systolic or diastolic blood pressure, mean pulse rate, or weight were observed.

**Newly occurring, notable biochemistry abnormalities (safety population)**

| Variable | Notable criteria† | Lumiracoxib 100mg QD N=420 | Lumiracoxib 200mg QD ID N=420 | Celecoxib 200mg QD N=420 | Placebo N=424 |
|---|---|---|---|---|---|
| **Biochemistry** | | n (%) | n (%) | n (%) | n (%) |
| SGPT (ALT) | > 3 x ULN | **0 (0.0)** | 1 (0.2) | **1 (0.2)** | 2 (0.5) |
| | > 5 x ULN | **0 (0.0)** | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| | > 8 x ULN | **0 (0.0)** | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| SGOT (AST) | > 3 x ULN | **0 (0.0)** | 2 (0.5) | **1 (0.2)** | 1 (0.2) |
| | > 5 x ULN | **0 (0.0)** | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| | > 8 x ULN | **0 (0.0)** | 0 (0.0) | 0 (0.0) | 0 (0.0) |

| | | | | | |
|---|---|---|---|---|---|
| Bilirubin (total) | > 1.2 x ULN | 5 (1.2) | 4 (1.0) | 4 (1.0) | 2 (0.5) |
| | > 51 umol/L | **0 (0.0)** | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Alkaline phosphatase | > 1.5 x ULN | 5 (1.2) | 4 (1.0) | 4 (1.0) | 1 (0.2) |
| Creatinine | > 35.36 µmol/L increase from baseline | 3 (0.7) | 7 (1.7) | 1 (0.2) | 0 (0.0) |
| | > 1.5 x ULN | **0 (0.0)** | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| | > 2 x baseline | **0 (0.0)** | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Creatinine clearance‡ | < 81 mL/min | 33 (7.9) | 47 (11.2) | 19 (4.5) | 25 (5.9) |
| | < 50 mL/min | 13 (3.1) | 16 (3.8) | 6 (1.4) | 5 (1.2) |
| | < 30 mL/min | 1 (0.2) | 2 (0.5) | 2 (0.5) | 0 (0.0) |
| | > 25% decrease from baseline | **11 (2.6)** | 11 (2.6) | **6 (1.4)** | 2 (0.5) |
| Potassium | < 3.0 mmol/L | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | > 5.5 mmol/L | 23 (5.5) | 20 (4.8) | 18 (4.3) | 17 (4.0) |
| Magnesium | < 0.5 mmol/L | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

LLN=lower limit of normal; ULN=upper limit of normal
† Notable criteria defined in the protocol or by the Data Safety Monitoring Board.
‡ Patients with creatinine clearance >200mL/min at baseline are excluded from analysis

## 3.7 Overall clinical assessment

These data confirm that lumiracoxib 100mg once a day is effective in the symptomatic treatment of osteoarthritis.

These data confirm the hepatic and renal safety of 100mg dose.

In terms of hepatic effects, there is no difference between lumiracoxib 100mg and celecoxib 200mg once daily.

The number of patients with > 25% decrease in creatinine clearance from baseline is 2.6% with lumiracoxib 100mg but 1.4% with celecoxib 200mg once daily. This difference is related to the greater COX-2 selectivity of lumiracoxib and is pharmacologically expected.

Since lumiracoxib 200mg dose was given for only 2 weeks, it is not surprising that the number of patients with > 25% decrease in creatinine clearance from baseline is 2.6% in both the lumiracoxib groups.

The data also suggest that hepatic effects manifest themselves well before the renal effects.

# 4. Study 2360 (Osteoarthritis 100mg 3-months core study)

This study is identical to study 2361 – the only difference is that this one has not been formally reported.

The efficacy and safety data are summarised below:

## 4.1 Efficacy of 100mg dose

Efficacy results of individual treatments on the primary endpoints (at 13 weeks, ITT (LOCF)) are presented in the table below:

| | | | | Comparison versus placebo | | |
|---|---|---|---|---|---|---|
| Variable | Treatment | Baseline | Endpoint LS Mean | Estimate of effect | 95% CI | P-value |
| OA pain intensity (VAS mm) | Lum 100 | 66.4 | 40.84 | -6.69 | -10.09 , -3.30 | <0.001 |
| | Lum 200 / 100 | 65.4 | 39.42 | -8.11 | -11.52 , -4.71 | <0.001 |
| | Celecoxib | 66.4 | 41.83 | -5.70 | - 9.09 , -2.32 | <0.001 |
| | Placebo | 66.2 | 47.54 | | | |
| Patient assessment of disease activity (VAS mm) | Lum 100 | 63.1 | 39.62 | -9.10 | -12.41 , -5.80 | <0.001 |
| | Lum 200 / 100 | 63.8 | 38.63 | -10.10 | -13.42 , -6.77 | <0.001 |
| | Celecoxib | 61.7 | 42.06 | -6.66 | - 9.96 , -3.36 | <0.001 |
| | Placebo | 62.5 | 48.72 | | | |
| WOMAC score | Lum 100 | 52.86 | 35.62 | -7.42 | - 9.75 , -5.09 | <0.001 |
| | Lum 200 / 100 | 52.86 | 35.30 | -7.75 | -10.09 , -5.41 | <0.001 |
| | Celecoxib | 52.59 | 36.70 | -6.35 | - 8.67 , -4.02 | <0.001 |
| | Placebo | 53.13 | 43.05 | | | |

After 13 weeks of treatment, "all lumiracoxib" (average effect of the two lumiracoxib regimens) was significantly more effective than placebo for treatment of OA of the knee with respect to the three co-primary efficacy variables.

| Variable / Contrasts | Est. Diff. | 95% CI of Difference | p-value[1] |
|---|---|---|---|
| **OA pain intensity (VAS mm) after 13 weeks** | | | |
| Treatment comparison with "All LUM" | | | |
| All LUM – Placebo | -7.40 | -10.35, -4.46 | <0.001 |
| Treatment comparisons | | | |
| LUM 100mg od – placebo | -6.69 | -10.09, -3.30 | <0.001 |
| LUM 200mg od ID – placebo | -8.11 | -11.52, -4.71 | <0.001 |
| **Patient's assessment of disease activity (VAS mm) after 13 weeks** | | | |
| Treatment comparison with "All LUM" | | | |
| All LUM – Placebo | -9.60 | -12.47, -6.72 | <0.001 |
| Treatment comparisons | | | |
| LUM 100mg od – placebo | -9.10 | -12.41, -5.80 | <0.001 |
| LUM 200mg od ID – placebo | -10.10 | -13.42, -6.77 | <0.001 |
| **WOMAC Total score after 13 weeks** | | | |
| Treatment comparison with "All LUM" | | | |
| All LUM – Placebo | -7.59 | -9.61, -5.56 | <0.001 |
| Treatment comparisons | | | |
| LUM 100mg od – placebo | -7.42 | -9.75, -5.09 | <0.001 |
| LUM 200mg od ID – placebo | -7.75 | -10.09, -5.41 | <0.001 |

LUM = lumiracoxib

[1] ANCOVA with center, treatment, and corresponding baseline value. Contrasts tested at the 5% significance level.

"All lumiracoxib" was non-inferior to celecoxib 200mg od for all three primary efficacy variables ($p<0.001$ for overall pain in the target joint, patient's global assessment of disease activity, and WOMAC Total score). The magnitude of efficacy for "All lumiracoxib" was slightly better than celecoxib 200 mg od for all three primary efficacy variables.

**Secondary Efficacy**:
Results for OA pain intensity in the target joint by visit for the ITT population (LOCF) are summarized below. All active treatments were significantly more effective than placebo with respect to overall OA pain intensity in the target joint after 2, 4, 8, and 13 weeks of treatment ($p<0.001$).

| | | Lumiracoxib 100mg od N=391 | Lumiracoxib 200mg od ID N=385 | Celecoxib 200mg od N=393 | Placebo N=382 |
|---|---|---|---|---|---|
| **Overall OA pain intensity (VAS mm):** | | | | | |
| n | | 391 | 385 | 393 | 381 |
| Baseline | Mean | 66.4 | 65.4 | 66.4 | 66.2 |
| Visit 3 (week 2) | Mean | 43.7*** | 41.3*** | 43.3*** | 53.2 |
| | mean change | -22.7 | -24.1 | -23.1 | -13.0 |
| Visit 4 (week 4) | Mean | 44.0*** | 42.7*** | 44.5*** | 50.7 |
| | mean change | -22.4 | -22.7 | -21.9 | -15.5 |
| Visit 5 (week 8) | Mean | 41.3*** | 39.7*** | 41.1*** | 48.1 |
| | mean change | -25.1 | -25.7 | -25.3 | -18.2 |
| Visit 6 (week 13) | Mean | 41.3*** | 39.5*** | 42.3*** | 48.1 |
| | mean change | -25.1 | -25.9 | -24.1 | -18.1 |

Symbols: comparison with placebo, ANCOVA, *p<0.05, **p<0.01, ***p<0.001; p-values not adjusted for multiplicity.
Note: Mean change is change from baseline.

## 4.3 Clinical safety

An overview of adverse events is provided below:

| n (%) | Lumiracoxib 100mg od | Lumiracoxib 200mg od ID | Celecoxib 200mg od | Placebo |
|---|---|---|---|---|
| Total number of patients studied | 391 (100) | 385 (100) | 393 (100) | 382 (100) |
| Total number of patients with AEs | 253 (64.7) | 258 (67.0) | 231 (58.8) | 223 (58.4) |
| **Patients with serious AEs:** | | | | |
| Deaths | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) |
| Non-fatal SAEs | 6 (1.5%) | 4 (1.0%) | 3 (0.8%) | 6 (1.6%) |
| **Patients with other significant AEs:** | | | | |
| AEs leading to study drug dose adjustment/interruption | 9 (2.3%) | 4 (1.0%) | 11 (2.8%) | 16 (4.2%) |
| Discontinuations due to: | | | | |
| Any AEs including SAEs | 21 (5.4%) | 15 (3.9%) | 16 (4.1%) | 24 (6.3%) |
| SAEs | 3 (0.8%) | 3 (0.8%) | 2 (0.5%) | 3 (0.8%) |
| AEs (non-serious) | 20 (5.1%) | 12 (3.1%) | 14 (3.6%) | 21 (5.5%) |

One death occurred during the study. A 65-year-old white male (0615-00009) in the lumiracoxib 200mg initial dose group died of a myocardial infarction.

## 4.4 Laboratory safety of 100mg dose

Newly occurring, notable biochemistry abnormalities (safety population)

| Variable | Notable criteria† | Lumiracoxib 100mg QD N=391 | Lumiracoxib 200mg QD ID N=385 | Celecoxib 200mg QD N=393 | Placebo N=382 |
|---|---|---|---|---|---|
| **Biochemistry** | | n (%) | n (%) | n (%) | n (%) |
| SGPT (ALT) | > 3 x ULN | **1 (0.3)** | **1 (0.3)** | 0 (0.0) | 0 (0.0) |
| | > 5 x ULN | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | > 8 x ULN | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| SGOT (AST) | > 3 x ULN | 0 (0.0) | 0 (0.0) | **1 (0.3)** | 0 (0.0) |
| | > 5 x ULN | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | > 8 x ULN | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Bilirubin (total) | > 1.2 x ULN | **9 (2.3)** | **2 (0.5)** | **6 (1.5)** | **5 (1.3)** |
| | > 51 umol/L | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Alkaline phosphatase | > 1.5 x ULN | **6 (1.5)** | 0 (0.0) | **3 (0.8)** | **4 (1.0)** |
| Creatinine | > 35.36 µmol/L increase from | **7 (1.8)** | **5 (1.3)** | **1 (0.3)** | **2 (0.5)** |

| | | | | | |
|---|---|---|---|---|---|
| | baseline | | | | |
| | > 1.5 x ULN | 0 (0.0) | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| | > 2 x baseline | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Creatinine clearance‡ | < 81 mL/min | 29 (7.5) | 28 (7.3) | 23 (5.9) | 23 (6.0) |
| | < 50 mL/min | 8 (2.1) | 12 (3.1) | 2 (0.5) | 6 (1.6) |
| | < 30 mL/min | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | > 25% decrease from baseline | **11 (2.8)** | **11 (2.9)** | **2 (0.5)** | **2 (0.5)** |

## 4.5 Conclusion

1. After 13 weeks of treatment, "All lumiracoxib" (the average effect of the two lumiracoxib regimens) was statistically superior to placebo and non-inferior to celecoxib 200mg for treatment of OA of the knee with respect to all three co-primary efficacy variables.
   - Overall OA (VAS) pain intensity in the target joint,
   - patient's assessment of disease activity, and
   - patient functional status measured by the WOMAC total score.
2. Lumiracoxib 100mg, lumiracoxib 200mg od initial dose (ID), and celecoxib 200mg od were statistically superior to placebo for treatment of OA of the knee with respect to:
   - Overall OA (VAS) pain intensity in the target joint, after 2, 4, 8, and 13 weeks of treatment,
   - patient's and physician's assessment of disease activity after 2, 4, 8, and 13 weeks of treatment, and
   - WOMAC total and WOMAC stiffness, pain and DPDA scores, after 2, 8, and 13 weeks of treatment
3. No statistically significant difference was seen between lumiracoxib 100mg and 200mg od ID at week 2 for any primary efficacy variable.
4. Lumiracoxib and celecoxib are comparable in terms of effects on liver enzymes Lumiracoxib appears a little more nephrotoxic than celecoxib

# 5. Statistical Assessment of Efficacy - 100mg dose in OA

An Addendum by Statistical Assessor

Following initial assessment of this dossier as a National Application, two further studies in osteoarthritis have been presented (2360 and 2361). The studies are reviewed here and comment is made on their implications for overall evidence of efficacy in osteoarthritis.

For Study 2361, a full clinical trial report was available for review. For Study 2360, a full report was not available and the assessment below is based on a synopsis report, the trial protocol (plus amendments) and finalised summary tables and individual patient listings. The MAH confirms that the results presented for 2360 are final. The UK considers that this constitutes sufficient information on which to base a detailed assessment of these relevant data.

## I.2 **Studies 2360 and 2361**

The two studies were identical in design. Both were 13-week, multicentre, randomised, double-blind, double-dummy, placebo- and active- controlled, parallel-group trials of two different dose regimens of lumiracoxib (100mg once daily for 13 weeks and 200mg once daily for two weeks followed by 100mg once daily for 11 weeks) in patients with primary knee osteoarthritis, using celecoxib (200mg once daily) as a control.

In Study 2360, a total of 1551 adult patients with symptomatic primary knee osteoarthritis (pain ≥ 40mm VAS at target joint) who required NSAID or other analgesic therapy were randomised, 391 to lumiracoxib 100mg once daily, 385 to lumiracoxib 200mg / 100mg once daily, 393 to celecoxib and 382 to placebo. In Study 2361, a total of 1684 adult patients with symptomatic primary knee osteoarthritis who required NSAID or other analgesic therapy were randomised, 420 to lumiracoxib 100mg once daily, 420 to lumiracoxib 200mg / 100mg once daily, 420 to celecoxib and 424 to placebo.

The primary efficacy variables in both studies were pain intensity in target joint, patient global assessment of disease activity and functional status (WOMAC) after 13 weeks of therapy. A hierarchical testing strategy was in place to control for the multiple treatment group comparisons on these three primary endpoints. There were a number of secondary efficacy endpoints including the assessment of hand osteoarthritis in the relevant sub-population (approximately 43% of all randomised patients in 2360 and 20% in 2361). The confirmatory analyses of the primary endpoints were based on ANCOVA allowing for baseline and centre in addition to treatment group. Treatment-by-centre interactions were separately examined. The primary analyses were based on 'ITT' populations (including all randomised patients who were given - though did not necessarily take - study medication) and used LOCF to impute missing values.

Patient withdrawals were highest from the placebo group in both studies, primarily because of a difference in the number of withdrawals due to unsatisfactory therapeutic effect. Similar proportions of patients were withdrawn from celecoxib and lumiracoxib treatment.

The mean number of rescue tablets taken by patients was higher in the placebo group than in any active treatment group. There was some indication in 2360 of a greater rescue medication use by patients on celecoxib compared with lumiracoxib.

Efficacy results on the primary endpoints (at 13 weeks, ITT (LOCF)) are presented in the table below for **Study 2360**:

| | | | | I.2.1 Comparison versus placebo | | |
|---|---|---|---|---|---|---|
| **Variable** | **Treatment** | **Baseline** | **Endpoint LS Mean** | **Estimate of effect** | **95% CI** | **P-value** |
| OA pain intensity (VAS mm) | Lum 100 | 66.4 | 40.84 | **-6.69** | **(-10.09 , -3.30)** | **<0.001** |
| | Lum 200 / 100 | 65.4 | 39.42 | -8.11 | (-11.52 , -4.71) | <0.001 |
| | Celecoxib | 66.4 | 41.83 | -5.70 | (- 9.09 , -2.32) | <0.001 |
| | Placebo | 66.2 | 47.54 | | | |
| Patient assessment of disease activity (VAS mm) | Lum 100 | 63.1 | 39.62 | **-9.10** | **(-12.41 , -5.80)** | **<0.001** |
| | Lum 200 / 100 | 63.8 | 38.63 | -10.10 | (-13.42 , -6.77) | <0.001 |
| | Celecoxib | 61.7 | 42.06 | -6.66 | (- 9.96 , -3.36) | <0.001 |
| | Placebo | 62.5 | 48.72 | | | |
| WOMAC score | Lum 100 | 52.9 | 35.62 | **-7.42** | **(- 9.75 , -5.09)** | **<0.001** |
| | Lum 200 / 100 | 52.9 | 35.30 | -7.75 | (-10.09 , -5.41) | <0.001 |
| | Celecoxib | 52.6 | 36.70 | -6.35 | (- 8.67 , -4.02) | <0.001 |
| | Placebo | 53.1 | 43.05 | | | |

Lum – lumiracoxib, all doses in mg, once daily

Efficacy results on the primary endpoints (at 13 weeks, ITT (LOCF)) are presented in the table below for **Study 2361**:

| | | | | **Comparison versus placebo** | | |
|---|---|---|---|---|---|---|
| **Variable** | **Treatment** | **Baseline** | **Endpoint LS Mean** | **Estimate of effect** | **95% CI** | **P-value** |
| OA pain intensity (VAS mm) | Lum 100 | 64.1 | 37.05 | **-5.09** | **(-8.04, -2.15)** | **<0.001** |
| | Lum 200 / 100 | 64.4 | 37.81 | -4.33 | (-7.28, -1.39) | 0.004 |
| | Celecoxib | 64.8 | 37.52 | -4.63 | (-7.57, -1.68) | 0.002 |
| | Placebo | 63.8 | 42.14 | | | |
| Patient assessment of disease activity (VAS mm) | Lum 100 | 63.1 | 37.72 | **-5.93** | **(-8.87, -2.99)** | **<0.001** |
| | Lum 200 / 100 | 61.6 | 39.99 | -3.66 | (-6.60, -0.71) | 0.015 |
| | Celecoxib | 62.9 | 39.77 | -3.88 | (-6.82, -0.94) | 0.010 |
| | Placebo | 62.9 | 43.65 | | | |
| WOMAC score | Lum 100 | 49.2 | 34.27 | **-3.92** | **(-5.98, -1.86)** | **<0.001** |
| | Lum 200 / 100 | 49.7 | 34.86 | -3.33 | (-5.40, -1.27) | 0.002 |
| | Celecoxib | 50.5 | 35.24 | -2.95 | (-5.01, -0.89) | 0.005 |
| | Placebo | 49.7 | 38.19 | | | |

There was a similar pattern of results in both studies. There were statistically significant differences between both regimens of lumiracoxib and placebo. There were no statistically significant differences between either the two regimens of lumiracoxib or between either lumiracoxib regimen and celecoxib, which were declared non-inferior. In neither study was there evidence of efficacy from the AUSCAN endpoint in the sub-population of patients with hand osteoarthritis.

**Statistical Assessor's Comments on Methodology and Results**

The trials provide data on the efficacy of two lumiracoxib regimens relative to (i) placebo, (ii) each other and (iii) an active control, celecoxib. Of greatest interest for the purposes of this application are the data comparing the lumiracoxib 100mg group with placebo, as highlighted (in bold) in the tables above.

These two trials were designed and analysed in line with CPMP guidance in this area and were consistent with the other osteoarthritis trials in this programme. There are no major methodological concerns affecting the results of the confirmatory statistical tests. In particular, there are no concerns that the definitions of the primary analysis populations, the handling of multiplicity, the use of rescue medication or the handling of missing values has introduced any biases in favour of lumiracoxib. It is considered that the trials provide statistically significant evidence of efficacy for lumiracoxib 100mg daily versus placebo. The clinical relevance of the results should be considered.

To assist with this consideration, results from previous pivotal studies in osteoarthritis are presented in the table below.

| | | | | | Comparison versus placebo | | |
|---|---|---|---|---|---|---|---|
| **Variable** | **Trial** | **Treatment** | **Baseline** | **Endpoint LS Mean** | **Estimate of effect** | **95% CI** | **P-value** |
| OA pain intensity (VAS mm) | 0128 | Lum 400 | 64.0 | 41.32 | -6.35 | (-10.94, -1.76) | 0.007 |
| | | Placebo | 62.5 | 47.66 | | | |
| | 0112 | Lum 200 | 65.5 | 39.07 | -6.33 | (-9.86, -2.80) | <0.001 |
| | | Lum 400 | 65.1 | 37.46 | -7.94 | (-11.47, -4.41) | <0.001 |
| | | Placebo | 65.7 | 45.40 | | | |
| | 0109 | Lum 200 | 66.9 | 37.29 | -7.39 | (-11.38, -3.40) | <0.001 |
| | | Lum 400 | 65.9 | 35.84 | -8.83 | (-12.82, -4.84) | <0.001 |
| | | Placebo | 66.7 | 44.68 | | | |
| Patient assessment of disease activity (VAS mm) | 0128 | Lum 400 | 61.6 | 42.47 | -7.04 | (-11.67, -2.41) | 0.003 |
| | | Placebo | 61.4 | 49.52 | | | |
| | 0112 | Lum 200 | 62.9 | 39.67 | -7.62 | (-11.05, -4.20) | <0.001 |
| | | Lum 400 | 62.6 | 38.56 | -8.73 | (-12.15, -5.31) | <0.001 |
| | | Placebo | 63.2 | 47.29 | | | |
| | 0109 | Lum 200 | 63.6 | 37.41 | -8.55 | (-12.39, -4.70) | <0.001 |
| | | Lum 400 | 62.8 | 36.53 | -9.42 | (-13.26, -5.58) | <0.001 |
| | | Placebo | 62.4 | 45.95 | | | |
| WOMAC score | 0128 | Lum 400 | 47.3 | 35.25 | -3.21 | (-6.21, -0.22) | 0.036 |
| | | Placebo | 47.9 | 36.46 | | | |
| | 0112 | Lum 200 | 49.0 | 34.48 | -4.82 | (-7.14, -2.50) | <0.001 |
| | | Lum 400 | 48.1 | 34.11 | -5.19 | (-7.52, -2.87) | <0.001 |
| | | Placebo | 49.2 | 39.30 | | | |
| | 0109 | Lum 200 | 49.9 | 30.51 | -7.38 | (-9.97, -4.80) | <0.001 |
| | | Lum 400 | 47.2 | 30.41 | -7.48 | (-10.06, -4.91) | <0.001 |
| | | Placebo | 46.7 | 37.89 | | | |

It is concluded that the magnitudes of effects observed are consistent with those observed elsewhere in the programme.

Evidence for dose-response should also be considered. One source of evidence is Study 0104. This was a 4-week study in knee and hip OA in which patients were randomised to one of four lumiracoxib doses or placebo. Primary efficacy results from this study (overall joint pain intensity, ITT, LOCF) are presented below:

| Treatment Group | Baseline | | | Week 4 | | | Comparison with placebo |
|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | |
| Lum 50mg bd | 96 | 66.9 | 13.97 | 96 | 38.3 | 24.32 | p = 0.001 |
| Lum 100mg bd | 95 | 64.7 | 14.31 | 95 | 38.4 | 24.38 | p = 0.001 |
| Lum 200mg bd | 96 | 67.0 | 13.00 | 96 | 37.4 | 25.39 | p < 0.001 |
| Lum 400mg od | 98 | 66.9 | 12.98 | 98 | 33.7 | 23.74 | p < 0.001 |
| Placebo | 96 | 67.9 | 12.74 | 96 | 50.2 | 24.57 | p < 0.001 |

Lum – lumiracoxib

In 0104, despite a small dose-response being observed across the entire dose range, responses to 50mg twice daily and 100mg twice-daily (which might be thought analogous to 100mg once-daily and 200mg once-daily) on overall joint pain intensity at 4 weeks were similar.

A second source of evidence is the comparison across trials of 100mg once daily (studies 2360 and 2361) with 200mg and 400mg once-daily (studies 0128, 0112 and 0109). Evidence drawn from comparisons across trials has to be particularly compelling because of the methodological concerns associated with making this type of comparison. It is considered that the results from these studies are not consistent with a clear dose-response relationship and that the evidence supports the differences between the efficacy of the 100mg once daily and 200mg once-daily doses of lumiracoxib being negligible.

Whilst not the primary hypothesis in these studies, there are some interesting points relating to the tests of non-inferiority between lumiracoxib and celecoxib.

1. For each endpoint, delta was defined as half the difference between celecoxib and placebo observed in the study. As a general approach this method can be criticised, as the rationale for including a test for non-inferiority in these studies (which include a placebo control) is to exclude clinically relevant differences between the active treatments. It is not obvious that a definition of 'half of the difference to placebo' will achieve this. In 2361, the effects of active treatment relative to placebo are relatively small (see 2) and the non-inferiority margins defined might be considered reasonable. Because of the larger effect sizes the same conclusion would not be drawn from 2360.

2. The non-inferiority margins defined in 2360 and 2361 differ to each other and to those defined in the other studies in this development programme. It is interesting to compare the differences previously defined (and, therefore, thought to be of clinical irrelevance) with differences between active and placebo in the studies. For example, considering pain in the target joint in 2361, a difference of 5mm was previously considered clinically irrelevant and this trial was sized to be adequately powered to detect a difference of 6mm. However, the difference observed in this trial between lumiracoxib (albeit at a different dose with potentially different risks against which to weigh the benefits) and placebo was 4.7mm. The difference between celecoxib and placebo was marginally less. In 2360 there are no similar concerns as the estimated magnitudes of effect were greater and the

overall magnitude of benefit for 100mg is consistent with that observed for 200mg and 400mg once daily elsewhere in the programme.

3. Notwithstanding the weak justification for the choice of non-inferiority margin and criticisms of the method for selecting delta (see 1) there are also methodological concerns over the statistical analysis used to conclude non-inferiority.

The difference between celecoxib and placebo used to define the non-inferiority margin has been incorporated into the statistical model rather than being calculated in advance and considered a constant, which is the preferred method. In technical language, this translates to comparing the contrast of (1/2 1/2 -1/2 -1/2) with zero rather than comparing (1/2 1/2 -1 0). This reduces the variability in the model, which, in turn, increases the likelihood of demonstrating non-inferiority. In 2361 this affects the conclusions of the analysis of pain in target joint, for which a conclusion of non-inferiority has been drawn but, where, by standard criteria (i.e. comparing the confidence interval of the difference between celecoxib and lumiracoxib (-2.65, 2.47) with 2.32) non-inferiority would not have been achieved. Conclusions for the other primary endpoints are not affected.

Despite these issues, it is repeated that the assessment of non-inferiority was of secondary importance in these studies, in which evidence of efficacy relative to placebo is clear. Anyway, there is no evidence to indicate that the efficacy of lumiracoxib at the doses proposed is likely to be less than that of celecoxib 200mg. The points highlighted above are, therefore, considered to be of very minor concern.

**Overall Conclusions on Studies 2360 and 2361**

It is unclear why these particular regimens were examined in these trials. However, the trials do provide clear, statistically significant evidence of superiority to placebo for the 100mg once-daily dose of lumiracoxib. The magnitudes of effects on the primary endpoints should be considered for their clinical relevance. Furthermore, the extrapolation of efficacy from 100mg daily in this study to osteoarthritis of the hip and of the hand should be considered.

This assessor presumes that the Applicant has also concluded that there was no evidence in support using a higher lumiracoxib dose for only the first two weeks of treatment.

**Impact on Evidence of Efficacy in Osteoarthritis in Relation to UK marketing authorisations**

The UK marketing authorisations recommends for osteoarthritis, a starting dose of 100mg once daily, increasing to 200mg daily in patients who fail to respond.

In the initial application, the only evidence for 100mg daily came from the dose-finding study (trial 0104, which examined 50mg twice-daily). Trials 2360 and 2361 provide statistically significant evidence of efficacy for 100mg once daily in osteoarthritis of the knee and, provided the effects are considered clinically relevant and can be extrapolated to osteoarthritis in general, support the inclusion of this dose in the proposed posology. Data on dose response are difficult to assimilate as 100mg and 200mg daily have not been examined in the same study. There are no confirmatory data to suggest that patients not responding to 100mg once daily are more likely to respond to 200mg once daily.

# 6. TARGET study

## 6.1 Design

This was an international, multicentre, randomised, active-controlled, double-blind, double-dummy, parallel group study stratified by low-dose aspirin use and age, comparing the safety of lumiracoxib 400 mg once daily with the non-selective NSAIDs naproxen and ibuprofen, in patients with osteoarthritis treated for 52 weeks.

The study consisted of two sub-studies with identical designs but using different comparators: Study 0117 used naproxen 500 mg twice daily as a comparator whereas ibuprofen 800 mg thrice daily was used in study 2332.

The study was performed in 854 centers in 32 countries: Argentina, Belgium, Brazil, Canada, Chile, China, Colombia, Czech Republic, Ecuador, Estonia, Finland, Germany, Guatemala, Hungary, Italy, Mexico, Malaysia, Netherlands, Peru, Poland, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, UK, Uruguay, USA, Venezuela.

The first patient was randomised on 24 November 2001 and the last patient completed the study on 16 January 2004.

## 6.2 Background

TARGET study design was based on the outcomes studies of celecoxib (Celecoxib Long-term Arthritis Safety Study (CLASS) and rofecoxib (VIGOR). However, the design aimed to avoid some of the pitfalls of these latter studies, based on the following 10 principles:

1. The primary goal of the study was to investigate differences in the incidence of ulcer complications, rather than a less demanding surrogate, since reducing ulcer complications was the purpose of developing COX-2 selective inhibitors. This required a substantial increase in patient numbers in comparison with previous outcomes studies.

2. A further increase in size was needed to take into account the lessons of both the celecoxib and rofecoxib GI outcomes studies. The rofecoxib GI outcomes study showed that it was unrealistic to exclude aspirin use by excluding patients who needed it, and its results show that it would now be unethical to try to do this.

3. However, the celecoxib GI outcomes study emphasized the importance of statistical robustness to allow for aspirin use. In TARGET, this was achieved not only by an increase in study size but also by the third principle of stratifying randomization by aspirin use.

4. Power was maintained throughout the study, and particularly in the second half, by using a fixed-term design, so that all patients were entered for 12 months rather than for a minimum of 6 months (with no maximum) in the celecoxib GI and rofecoxib studies, since the latter approach leads to relentlessly diminishing patient numbers after 6 months.

5. This measure was complimented by symptom control measures to ensure a minimum 12-month patient retention of 60% (compared to only 57% at 6 months and 43% at 12 months, in the celecoxib GI outcomes study). GI events were the primary focus of the study and determined the need to study >18000 patients in a study of 12 months' duration.

6. The study should be able to investigate all major drug-related benefits and hazards, and the size of the study also powered it to detect realistic drug-related differences in thrombotic CV complications, and to assess patients on and off aspirin separately.

7. This related to the evidence that all NSAIDs may not be the same in their effects on thrombosis and bleeding; the study was therefore designed to include NSAID comparators with a potent and a weak effect on platelets (naproxen and ibuprofen, respectively).

8. In contrast to the need for drug diversity, the eighth principle concerned the importance of relative patient homogeneity in giving a stable and predictable base to evaluate other influences. We therefore studied patients with OA, the commonest NSAID indication, as opposed to the mixed population studied in the failed celecoxib GI outcomes study or the more complex and limited RA population studied in the rofecoxib GI outcomes study. A substantial source of imprecision in outcomes studies relates to the impossibility of subjecting endpoints to prospective protocol-driven assessment, requiring retrospective blinded review by expert panels.

9. The design principle of TARGET was, for the first time, to establish individual expert panels and prospective protocols for all the major anticipated drug-related outcomes, from the outset of the study.

10. Finally, the size of TARGET meant that rare events such as renal failure could be evaluated more confidently and a considerable number of tertiary and informative exploratory studies, all appropriately pre-specified in the statistical plan, could be carried out.

## 6.3 Objectives:

**Primary:**

- To demonstrate that lumiracoxib 400 mg once daily decreases the incidence of predefined complicated ulcers (POBs) of the upper gastrointestinal tract (UGIT) compared to NSAIDs (naproxen 500 mg twice daily and ibuprofen 800 mg thrice daily) in osteoarthritis (OA) patients NOT taking low-dose aspirin.
- To demonstrate that lumiracoxib decreases the incidence of pre-defined complicated ulcers (POBs) of the upper gastrointestinal tract compared to NSAIDs (naproxen 500 mg twice daily and ibuprofen 800 mg thrice daily) in the overall TARGET population.

**Secondary:**

- To assess the cardiovascular, and renal safety, as well as the overall safety and tolerability profile of lumiracoxib compared to NSAIDs (naproxen 500 mg twice daily and ibuprofen 800 mg thrice daily) in the overall TARGET population.
- To assess the efficacy of lumiracoxib compared to NSAIDs (naproxen 500 mg twice daily and ibuprofen 800 mg thrice daily) in the overall TARGET population.

***Note:*** *The terms "complicated ulcers" and "ulcer complications" are used synonymously in the study report when referring to perforations, obstructions or bleeds (POBs).*

## 6.4 Indication and main criteria for inclusion:

Male or female outpatients aged ≥ 50 years with active primary OA in joints of the hip, knee, hand, cervical or lumbar spine and symptoms for at least 3 months who required NSAID therapy; continuous daily low-dose aspirin (75 mg – 100 mg) for primary or secondary cardiovascular prevention was allowed (and required if patients were at increased

cardiovascular risk); baseline pain assessment (Likert scale) in the affected joint of moderate, severe or extreme

**6.5 Patients randomised:**

18,325 patients in total: 9156 on lumiracoxib,
9169 on NSAIDs
- 4754 on naproxen
- 4415 on ibuprofen

| | | | |
|---|---|---|---|
| Low dose aspirin strata: | Lumiracoxib | 2176 | (23.8%) |
| | NSAIDs | 2169 | (23.7%) |

**6.6 Duration of treatment:** 52 weeks

**6.7 Criteria for evaluation:**

**Safety:** Safety was assessed by evaluation of adverse events, results of physical examinations, data on vital signs, and data from laboratory and ECG evaluations

**Efficacy:** Efficacy was assessed using the physician's and patient's global assessment of disease activity, the patient's pain assessment, and need for analgesic rescue medication. Pain (always assessed in the most affected joint at baseline) and disease activity assessments used 5-point Likert scales.

Various population subgroups are defined as follows:
The **randomised population** consisted of all patients who were randomised.

The **safety** and **ITT populations** consisted of all patients who were randomised and exposed to study drug. A randomised patient was assumed to have taken at least one dose of study medication unless there was evidence to the contrary.

Two different **per-protocol populations** were defined:
- The **GI per-protocol population** consisted of the subset of the safety population excluding those patients with protocol violations which may impact the primary study endpoint i.e. incidence of suspected UGIT ulcer complications adjudicated by the GISC as definite or probable.
- The **CCV per-protocol population** consisted of the subset of the safety population excluding those patients with protocol violations which may impact the primary CCV endpoint i.e. incidence of MI, silent MI, stroke or CV death adjudicated by the CCVSC as confirmed or probable.

The **modified intent-to-treat** analysis of the primary endpoint was performed on the safety population excluding all suspected complicated UGIT ulcers (confirmed as definite or probable POBs by the GISC) with onset on Days 1 and 2. It was considered that the events occurring so early would possibly be related to the treatments taken before randomization (Silverstein 2000).

**6.8 Interruption or discontinuation of treatment**

A patient was to be immediately discontinued from study treatment if any of the following occurred:
- Hemoglobin value < 100 g/L and decreased by at least 20 g/L from screening
- Creatinine value > 2 x ULN
- Clinical evidence of gastrointestinal perforation, ulcer or bleeding

- AST or ALT value > 5 x ULN (for a value > 2 to 5 x ULN, there were other provisions)
- Total bilirubin value > 51.3 µmol/L (3.0 mg/dL) (for a value > 2 x ULN but ≤ 51.3 µmol/L)

## 6.9 Pharmacogenetic evaluations

Pharmacogenetic evaluations were to be performed on a single blood sample from patients who gave separate written informed consent to participate in these studies. Details are given in the Protocol-Section 3.5.5. The results of these evaluations are not included in the Study Report.

## 6.10 Study monitoring

The Data safety Monitoring Board included a number of relevant specialists and there were also a number of organ-specific safety committees.

## 6.11 Results:

### 6.11.1 Patient disposition

| Disposition/Reason | Lumiracoxib N=9156 n (%) | NSAIDs N=9169 n (%) |
|---|---|---|
| **Total no. of patients:** | | |
| completed | 5686 (62.1) | 5438 (59.3) |
| discontinued | 3470 (37.9) | 3731 (40.7) |
| **Reason for discontinuation:** | | |
| death | 23 ( 0.3) | 22 ( 0.2) |
| adverse event | 1409 (15.4) | 1635 (17.8) |
| abnormal laboratory value(s) | 82 ( 0.9) | 69 ( 0.8) |
| abnormal test procedure results | 24 ( 0.3) | 19 ( 0.2) |
| unsatisfactory therapeutic effect | 754 ( 8.2) | 732 ( 8.0) |
| condition no longer requires study drug | 26 ( 0.3) | 34 ( 0.4) |
| protocol violation | 380 ( 4.2) | 361 ( 3.9) |
| patient withdrew consent | 692 ( 7.6) | 783 ( 8.5) |
| lost to follow-up | 19 ( 0.2) | 21 ( 0.2) |
| administrative problems | 61 ( 0.7) | 55 ( 0.6) |

### 6.11.2 Patient demography

| | Lumiracoxib N=9117 n (%) | NSAIDs N=9127 n (%) |
|---|---|---|
| **Age (years)** | | |
| Mean ± SD | 63.5 ± 8.37 | 63.4 ± 8.35 |
| **Age categories – n (%)** | | |
| <= 49 years | 10 (0.1) | 10 (0.1) |
| 50 - 64 years | 5127 (56.2) | 5158 (56.5) |
| 65 – 74 years | 3005 (33.0) | 2969 (32.5) |
| ≥75 years | 975 (10.7) | 990 (10.8) |
| **Sex – n (%)** | | |
| Male | 2154 (23.6) | 2157 (23.6) |
| Female | 6963 (76.4) | 6970 (76.4) |
| **Weight (kg)** | | |
| Mean ± SD | 78.4 ± 16.99 | 77.8 ± 16.92 |
| **Race – n (%)** | | |

| | Lumiracoxib N=9117 n (%) | NSAIDs N=9127 n (%) |
|---|---|---|
| White/Caucasian | 6892 (75.6) | 6846 (75.0) |
| Black/African American | 187 (2.1) | 190 (2.1) |
| Hispanic | 1476 (16.2) | 1514 (16.6) |
| Other Asian or Pacific Islander | 467 (5.1) | 468 (5.1) |
| Other | 95 (1.1) | 109 (1.2) |
| **Disease duration (years)** | | |
| Mean ± SD | 5.7 ± 6.82 | 5.5 ± 6.88 |
| **Regular NSAID use in last 6 months – n(%)** | 6989 (76.7) | 7005 (76.8) |
| **Most affected (target) joint – n(%)** | | |
| Hip | 884 (9.7) | 950 (10.4) |
| Knee | 5153 (56.5) | 5105 (55.9) |
| Hand | 1482 (16.3) | 1533 (16.8) |
| Spine | 1597 (17.5) | 1537 (16.8) |
| **Other features** | | |
| H. pylori positive – n (%) | 4029 (44.2) | 4028 (44.1) |
| Dyslipidemia | 1829 (20.1) | 1834 (20.1) |
| CCV history | 981 (10.8) | 899 (9.8) |
| Diabetes and diabetic complications | 744 (8.2) | 675 (7.4) |
| History of GI ulcers – n (%) | 260 (2.9) | 319 (3.5) |
| History of GI bleeding – n (%) | 20 (0.2) | 30 (0.3) |
| High CV risk or CCV history – n (%) | 1141 (12.5) | 1066 (11.7) |
| History of GI ulcers – n (%) | 260 (2.9) | 319 (3.5) |
| History of GI bleeding – n (%) | 20 (0.2) | 30 (0.3) |
| SBP ≥140mmHg or DBP ≥90mmHg | 3730 (40.9) | 3692 (40.5) |
| Impaired renal function† – n (%) | 180 (2.0) | 171 (1.9) |
| **Concurrent use of:** | | |
| Use of low-dose aspirin – n (%) | 2167 (23.8) | 2159 (23.7) |
| Diuretics | 1516 (16.6) | 1494 (16.4) |
| ACE-inhibitors | 1975 (21.7) | 1926 (21.1) |
| Anti-hypertensive medications | 4583 (50.3) | 4528 (49.6) |
| Gastroprotective agents | 6022 (66.1) | 6210 (68.0) |

† Impaired renal function at baseline was defined as either creatinine >ULN or urine protein ≥1.0 g/L (by urine dipstick).

### 6.11.3 Patient exposure

| | Lumiracoxib N=9117 and n (%) | NSAIDs N=9127 and n (%) |
|---|---|---|
| **Exposure categories – n (%)** | | |
| 1 – 24 days | 470 (5.2) | 629 (6.9) |
| 25 – 77 days | 841 (9.2) | 980 (10.7) |
| 78 – 168 days | 985 (10.8) | 1002 (11.0) |
| 169 – 259 days | 652 (7.2) | 604 (6.6) |
| 260 – 350 days | 550 (6.0) | 557 (6.1) |
| Mean ± SD | 275.7 ± 130.40 | 265.1 ± 136.85 |
| Median | 361 | 359 |

## 6.11.4 GI safety

Primary analysis:
Definite or probable UGIT ulcer complications (POBs): treatment comparisons using COX proportional hazards model (modified ITT analysis):

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| **TARGET (0117 + 2332)** | | | | | |
| **No low-dose aspirin group** | | | | | |
| Lumiracoxib | 6950 | 14 (0.20) | 0.21 | 0.12 - 0.37 | <0.0001 |
| NSAIDs | 6968 | 64 (0.92) | | | |
| **Overall patient group** | | | | | |
| Lumiracoxib | 9117 | 29 (0.32) | 0.34 | 0.22 - 0.52 | <0.0001 |
| NSAIDs | 9127 | 83 (0.91) | | | |
| **Low-dose aspirin group** | | | | | |
| Lumiracoxib | 2167 | 15 (0.69) | 0.79 | 0.40 - 1.55 | 0.4876 |
| NSAIDs | 2159 | 19 (0.88) | | | |
| **Study 0117** | | | | | |
| **No low-dose aspirin group** | | | | | |
| Lumiracoxib | 3549 | 9 (0.25) | 0.24 | 0.12 - 0.50 | 0.0001 |
| Naproxen | 3537 | 36 (1.02) | | | |
| **Overall patient group** | | | | | |
| Lumiracoxib | 4741 | 19 (0.40) | 0.37 | 0.22 - 0.63 | 0.0002 |
| Naproxen | 4730 | 50 (1.06) | | | |
| **Low-dose aspirin group** | | | | | |
| Lumiracoxib | 1192 | 10 (0.84) | 0.73 | 0.32 - 1.65 | 0.4502 |
| Naproxen | 1193 | 14 (1.17) | | | |
| **Study 2332** | | | | | |
| **No low-dose aspirin group** | | | | | |
| Lumiracoxib | 3401 | 5 (0.15) | 0.17 | 0.07 - 0.45 | 0.0003 |
| Ibuprofen | 3431 | 28 (0.82) | | | |
| **Overall patient group** | | | | | |
| Lumiracoxib | 4376 | 10 (0.23) | 0.29 | 0.14 - 0.59 | 0.0006 |
| Ibuprofen | 4397 | 33 (0.75) | | | |
| **Low-dose aspirin group** | | | | | |
| Lumiracoxib | 975 | 5 (0.51) | 0.92 | 0.27 - 3.20 | 0.9008 |
| Ibuprofen | 966 | 5 (0.52) | | | |

***** p value based on Wald chi-squared statistic for treatment comparison, lumiracoxib vs. comparator, stratified by age and sub-study where appropriate

*Patients NOT taking low-dose aspirin:*

The risk of definite or probable upper gastrointestinal tract (UGIT) ulcer complications (POBs) was reduced by 79% with lumiracoxib vs. NSAIDs in patients not taking low-dose aspirin (hazard ratio 0.21, 95% CI 0.12-0.37), and it was reduced by 66% in the overall population (hazard ratio 0.34, 95% CI 0.22-0.52).

This finding was observed across both sub-studies, with significant reductions in risk of over 60% for comparisons vs. either naproxen or ibuprofen in patients not taking aspirin and in the overall population.

The risk of definite or probable UGIT ulcer complications and/or symptomatic ulcers (PUBs) was significantly lower in the lumiracoxib group vs. NSAIDs in the patients not taking low-dose aspirin (hazard ratio: 0.38, p<0.0001, 95% CI 0.28-0.52) and in the overall population (hazard ratio: 0.46, p<0.0001, 95% CI 0.36-0.60). This significant difference was observed consistently across both sub-studies (vs. naproxen and vs. ibuprofen)

In the patients not taking low-dose aspirin and the overall population, lumiracoxib reduced the incidence of symptomatic ulcers by approximately 50%. The incidence of definite or probable LGIT complications was very low with no statistically significant differences between treatment groups.

*Patients TAKING low-dose aspirin:*

In the group taking low-dose aspirin, the incidence of UGIT POBs was numerically lower with lumiracoxib vs. NSAIDs, but the study was not powered to show a difference in this group and the reduction was not statistically significant (hazard ratio 0.79, 95% CI 0.40-1.55).

In patients taking low-dose aspirin the incidence of PUBs was less with lumiracoxib in the sub-study vs. naproxen (1.7% vs. 2.6%) but similar in the sub-study vs. ibuprofen (1.3% vs. 1.4%). In these patients, the hazard ratio comparing lumiracoxib with NSAIDs was reduced but statistical significance was not reached (1.5% vs. 2.1%, hazard ratio 0.73, p=0.1706, 95% CI 0.47-1.14).

**Frequency of definite or probable UGIT ulcer complications by event type (modified ITT analysis)**

| | TARGET (0117 + 2332) | |
|---|---|---|
| | **Lumiracoxib n (%)** | **NSAIDs n (%)** |
| **No low-dose aspirin group** | **N=6950** | **N=6968** |
| **Total with definite or probable UGIT ulcer complications** | **14 (0.2)** | **64 (0.9)** |
| Gastrointestinal perforation | 0 | 1 (0.0) |
| Gastric outlet obstruction | 0 | 1 (0.0) |
| Hematemesis | 5 (0.1) | 5 (0.1) |
| Hematochezia or melena | 7 (0.1) | 35 (0.5) |
| Laboratory evidence of bleeding | 2 (0.0) | 22 (0.3) |
| **Low-dose aspirin group** | **N=2167** | **N=2159** |
| **Total with definite or probable UGIT ulcer complications** | **15 (0.7)** | **19 (0.9)** |
| Gastrointestinal perforation | 1 (0.0) | 1 (0.0) |
| Gastric outlet obstruction | 0 | 0 |
| Hematemesis | 1 (0.0) | 3 (0.1) |
| Hematochezia or melena | 9 (0.4) | 9 (0.4) |
| Laboratory evidence of bleeding | 4 (0.2) | 6 (0.3) |

## 6.11.5 Cardio- and cerebrovascular safety

The endpoint defined by the Antiplatelet Trialists' Collaboration (APTC 1994) was the principal means for analysis of significant AEs of vascular origin. This composite endpoint includes major non-fatal and fatal CV events: myocardial infarction (clinical or silent (ECG-detected) MI), stroke (ischemic or hemorrhagic) and cardiovascular death which includes all deaths attributed to cardiac, vascular, cerebral, hemorrhagic, embolic, other vascular or unknown causes.

All CCV events studied included those in the APTC endpoint plus cardiac arrest, transient ischemic attack (TIA), unstable angina, deep vein thrombosis (DVT) and pulmonary embolism (PE).

**Frequency of confirmed or probable CCV events (safety population)**

**No low-dose aspirin group**

| | Study 0117 | Study 2332 |
|---|---|---|

| | Lumiracoxib n (%) | Naproxen n (%) | Lumiracoxib n (%) | Ibuprofen n (%) |
|---|---|---|---|---|
| **No low-dose aspirin group** | **N=3549** | **N=3537** | **N=3401** | **N=3431** |
| Total with confirmed or probable CCV events | 30 (0.8) | 23 (0.7) | 20 (0.6) | 18 (0.5) |
| APTC endpoint † | 22 (0.6) | 14 (0.4) | 13 (0.4) | 13 (0.4) |
| Cardiovascular death | 7 (0.2) | 5 (0.1) | 5 (0.1) | 6 (0.2) |
| All MIs | 10 (0.3) | 4 (0.1) | 4 (0.1) | 5 (0.1) |
| MI: | 10 (0.3) | 2 (0.1) | 4 (0.1) | 3 (0.1) |
| fatal | 0 | 1 (0.0) | 0 | 2 (0.1) |
| non-fatal | 10 (0.3) | 1 (0.0) | 4 (0.1) | 1 (0.0) |
| Silent (ECG detected) MI | 0 | 2 (0.1) | 0 | 2 (0.1) |
| Stroke: | 7 (0.2) | 6 (0.2) | 6 (0.2) | 5 (0.1) |
| fatal | 2 (0.1) | 0 | 2 (0.1) | 1 (0.0) |
| non-fatal | 5 (0.1) | 6 (0.2) | 4 (0.1) | 4 (0.1) |
| Ischemic stroke | 6 (0.2) | 6 (0.2) | 6 (0.2) | 2 (0.1) |
| fatal | 1 (0.0) | 0 | 2 (0.1) | 0 |
| non-fatal | 5 (0.1) | 6 (0.2) | 4 (0.1) | 2 (0.1) |
| Hemorrhagic stroke | 1 (0.0) | 0 | 0 | 3 (0.1) |
| fatal | 1 (0.0) | 0 | 0 | 1 (0.0) |
| non-fatal | 0 | 0 | 0 | 2 (0.1) |
| Cardiac arrest | 0 | 0 | 0 | 0 |
| Transient ischemic attack | 1 (0.0) | 4 (0.1) | 2 (0.1) | 1 (0.0) |
| Unstable angina | 4 (0.1) | 1 (0.0) | 1 (0.0) | 4 (0.1) |
| Deep vein thrombosis | 1 (0.0) | 2 (0.1) | 3 (0.1) | 1 (0.0) |
| Pulmonary embolism | 2 (0.1) | 2 (0.1) | 1 (0.0) | 0 |

† APTC endpoint includes MI (clinical or silent), stroke (ischaemic or hemorrhagic) and cardiovascular death

## Low-dose aspirin group

| | Study 0117 | | Study 2332 | |
|---|---|---|---|---|
| | Lumiracoxib n (%) | Naproxen n (%) | Lumiracoxib n (%) | Ibuprofen n (%) |
| **No low-dose aspirin group** | **N=1192** | **N=1193** | **N=975** | **N=966** |
| Total with confirmed or probable CCV events | 22 (1.8) | 20 (1.7) | 13 (1.3) | 14 (1.4) |
| APTC endpoint † | 18 (1.5) | 13 (1.1) | 6 (0.6) | 10 (1.0) |
| Cardiovascular death | 4 (0.3) | 3 (0.3) | 3 (0.3) | 4 (0.4) |
| All MIs | 8 (0.7) | 6 (0.5) | 1 (0.1) | 2 (0.2) |
| MI: | 5 (0.4) | 5 (0.4) | 1 (0.1) | 2 (0.2) |
| fatal | 2 (0.2) | 0 | 0 | 0 |
| non-fatal | 3 (0.3) | 5 (0.4) | 1 (0.1) | 2 (0.2) |
| Silent (ECG detected) MI | 3 (0.3) | 1 (0.1) | 0 | 0 |
| Stroke: | 9 (0.8) | 6 (0.5) | 2 (0.2) | 4 (0.4) |
| fatal | 1 (0.1) | 1 (0.1) | 0 | 0 |
| non fatal | 8 (0.7) | 5 (0.4) | 2 (0.2) | 4 (0.4) |
| Ischemic stroke: | 9 (0.8) | 5 (0.4) | 2 (0.2) | 4 (0.4) |
| fatal | 1 (0.1) | 0 | 0 | 0 |
| non fatal | 8 (0.7) | 5 (0.4) | 2 (0.2) | 4 (0.4) |
| Hemorrhagic stroke | 0 | 1 (0.1) | 0 | 0 |
| fatal | 0 | 1 (0.1) | 0 | 0 |
| non fatal | 0 | 0 | 0 | 0 |
| Cardiac arrest | 0 | 0 | 0 | 0 |
| Transient ischemic attack | 1 (0.1) | 1 (0.1) | 3 (0.3) | 0 |
| Unstable angina | 2 (0.2) | 3 (0.3) | 3 (0.3) | 3 (0.3) |
| Deep vein thrombosis | 1 (0.1) | 2 (0.2) | 1 (0.1) | 2 (0.2) |
| Pulmonary embolism | 0 | 2 (0.2) | 1 (0.1) | 0 |

† APTC endpoint includes MI (clinical or silent), stroke (ischaemic or hemorrhagic) and cardiovascular death

Confirmed or probable APTC endpoint: treatment comparisons using COX proportional hazards model (safety population):

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| **Overall patient group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 9117 | 59 (0.65) | 1.14 | 0.78 - 1.66 | 0.5074 |
| NSAIDs | 9127 | 50 (0.55) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 4741 | 40 (0.84) | 1.46 | 0.89 - 2.37 | 0.1313 |
| Naproxen | 4730 | 27 (0.57) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 4376 | 19 (0.43) | 0.76 | 0.41 - 1.40 | 0.3775 |
| Ibuprofen | 4397 | 23 (0.52) | | | |
| **No low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 6950 | 35 (0.50) | 1.22 | 0.74 - 2.02 | 0.4343 |
| NSAIDs | 6968 | 27 (0.39) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 3549 | 22 (0.62) | 1.49 | 0.76 - 2.92 | 0.2417 |
| Naproxen | 3537 | 14 (0.40) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 3401 | 13 (0.38) | 0.94 | 0.44 - 2.04 | 0.8842 |
| Ibuprofen | 3431 | 13 (0.38) | | | |
| **Low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 2167 | 24 (1.11) | 1.04 | 0.59 - 1.84 | 0.8918 |
| NSAIDs | 2159 | 23 (1.07) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 1192 | 18 (1.51) | 1.42 | 0.70 - 2.90 | 0.3368 |
| Naproxen | 1193 | 13 (1.09) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 975 | 6 (0.62) | 0.56 | 0.20 - 1.54 | 0.2603 |
| Ibuprofen | 966 | 10 (1.04) | | | |

***** p value based on Wald chi-squared statistic for treatment comparison, lumiracoxib vs. comparator, stratified by age; and also by sub-study where appropriate.

Confirmed or probable cardiovascular death: treatment comparisons using COX proportional hazards model (safety population):

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| **Overall patient group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 9117 | 19 (0.21) | 1.00 | 0.52 - 1.91 | 0.9996 |
| NSAIDs | 9127 | 18 (0.20) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 4741 | 11 (0.23) | 1.34 | 0.54 - 3.33 | 0.5293 |
| Naproxen | 4730 | 8 (0.17) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 4376 | 8 (0.18) | 0.72 | 0.28 - 1.82 | 0.4854 |
| Ibuprofen | 4397 | 10 (0.23) | | | |
| **No low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 6950 | 12 (0.17) | 1.02 | 0.45 - 2.31 | 0.9617 |
| NSAIDs | 6968 | 11 (0.16) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 3549 | 7 (0.20) | 1.33 | 0.42 - 4.18 | 0.6285 |
| Naproxen | 3537 | 5 (0.14) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 3401 | 5 (0.15) | 0.79 | 0.24 - 2.58 | 0.6907 |
| Ibuprofen | 3431 | 6 (0.17) | | | |
| **Low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 2167 | 7 (0.32) | 0.98 | 0.34 - 2.79 | 0.9693 |
| NSAIDs | 2159 | 7 (0.32) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 1192 | 4 (0.34) | 1.38 | 0.31 - 6.15 | 0.6760 |
| Naproxen | 1193 | 3 (0.25) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 975 | 3 (0.31) | 0.70 | 0.16 - 3.12 | 0.6379 |
| Ibuprofen | 966 | 4 (0.41) | | | |

***** p value based on Wald chi-squared statistic for treatment comparison, lumiracoxib vs. comparator, stratified by age; and also by sub-study where appropriate.

Confirmed or probable myocardial infarction: treatment comparisons using COX proportional hazards model (safety population):

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| **Overall patient group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 9117 | 20 (0.22) | 1.61 | 0.79 - 3.29 | 0.1932 |
| NSAIDs | 9127 | 12 (0.13) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 4741 | 15 (0.32) | 2.10 | 0.86 - 5.15 | 0.1056 |
| Naproxen | 4730 | 7 (0.15) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 4376 | 5 (0.11) | 0.93 | 0.27 - 3.22 | 0.9100 |
| Ibuprofen | 4397 | 5 (0.11) | | | |
| **No low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 6950 | 14 (0.20) | 2.65 | 0.95 - 7.35 | 0.0617 |
| NSAIDs | 6968 | 5 (0.07) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 3549 | 10 (0.28) | 4.74 | 1.04 - 21.64 | 0.0445 |
| Naproxen | 3537 | 2 (0.06) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 3401 | 4 (0.12) | 1.25 | 0.28 - 5.59 | 0.7699 |
| Ibuprofen | 3431 | 3 (0.09) | | | |
| **Low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 2167 | 6 (0.28) | 0.86 | 0.29 - 2.57 | 0.7911 |
| NSAIDs | 2159 | 7 (0.32) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 1192 | 5 (0.42) | 1.02 | 0.30 - 3.54 | 0.9710 |
| Naproxen | 1193 | 5 (0.42) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 975 | 1 (0.10) | 0.47 | 0.04 - 5.14 | 0.5328 |
| Ibuprofen | 966 | 2 (0.21) | | | |

***** p value based on Wald chi-squared statistic for treatment comparison, lumiracoxib vs. comparator, stratified by age; and also by sub-study where appropriate.

Confirmed or probable ischaemic stroke: treatment comparisons using COX proportional hazards model (safety population):

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| **Overall patient group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 9117 | 23 (0.25) | 1.31 | 0.70 - 2.46 | 0.3939 |
| NSAIDs | 9127 | 17 (0.19) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 4741 | 15 (0.32) | 1.35 | 0.62 - 2.94 | 0.4482 |
| Naproxen | 4730 | 11 (0.23) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 4376 | 8 (0.18) | 1.23 | 0.43 - 3.54 | 0.7058 |
| Ibuprofen | 4397 | 6 (0.14) | | | |
| **No low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 6950 | 12 (0.17) | 1.42 | 0.58 - 3.48 | 0.4403 |
| NSAIDs | 6968 | 8 (0.11) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 3549 | 6 (0.17) | 0.96 | 0.31 - 2.97 | 0.9404 |
| Naproxen | 3537 | 6 (0.17) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 3401 | 6 (0.18) | 2.88 | 0.58 - 14.27 | 0.1957 |
| Ibuprofen | 3431 | 2 (0.06) | | | |
| **Low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 2167 | 11 (0.51) | 1.23 | 0.51 - 2.96 | 0.6516 |
| NSAIDs | 2159 | 9 (0.42) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 1192 | 9 (0.76) | 1.84 | 0.62 - 5.50 | 0.2725 |
| Naproxen | 1193 | 5 (0.42) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 975 | 2 (0.21) | 0.47 | 0.09 - 2.56 | 0.3812 |
| Ibuprofen | 966 | 4 (0.41) | | | |

* p value based on Wald chi-squared statistic for treatment comparison, lumiracoxib vs. comparator, stratified by age; and also by sub-study where appropriate.

There were no significant differences in the total number of patients with confirmed or probable CCV events between lumiracoxib (85 patients, 0.9%) and NSAIDs (75 patients, 0.8%).

The incidence of confirmed or probable events in the APTC endpoint observed with lumiracoxib vs. NSAIDs (0.6% vs. 0.5%) was not statistically significantly different. There was also no statistical difference when comparing lumiracoxib to either naproxen or ibuprofen in the overall patient group in each sub-study.

This absence of statistical difference was also observed in the groups of patients taking or not taking low-dose aspirin.

Confirmed or probable CCV events and APTC endpoint by age, gender, CV risk and geographical region (safety population):

| TARGET (0117 + 2332) | All CCV events ‡ | | APTC endpoint † | |
|---|---|---|---|---|
| **Variable** | **Lumiracoxib** | **NSAIDs** | **Lumiracoxib** | **NSAIDs** |
| **Subgroup** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| **Age** | | | | |
| ≤64 years | 33 (0.6) (N=5137) | 22 (0.4) (N=5168) | 22 (0.4) (N=5137) | 13 (0.3) (N=5168) |
| 65-74 years | 32 (1.1) (N=3005) | 35 (1.2) (N=2969) | 23 (0.8) (N=3005) | 26 (0.9) (N=2969) |
| ≥ 75 years | 20 (2.1) (N=975) | 18 (1.8) (N=990) | 14 (1.4) (N=975) | 11 (1.1) (N=990) |
| **Gender** | | | | |
| Male | 31 (1.4) (N=2154) | 26 (1.2) (N=2157) | 22 (1.0) (N=2154) | 15 (0.7) (N=2157) |
| Female | 54 (0.8) (N=6963) | 49 (0.7) (N=6970) | 37 (0.5) (N=6963) | 35 (0.5) (N=6970) |
| **CV risk** | | | | |
| High CV risk or CCV history | 24 (2.1) (N=1141) | 23 (2.2) (N=1066) | 14 (1.2) (N=1141) | 13 (1.2) (N=1066) |
| Not high CV risk and No CCV history | 61 (0.8) (N=7976) | 52 (0.6) (N=8061) | 45 (0.6) (N=7976) | 37 (0.5) (N=8061) |
| **CV risk and aspirin use** | | | | |
| High CV risk or CCV history but not on low-dose aspirin | 8 (2.4) (N=338) | 2 (0.6) (N=308) | 5 (1.5) (N=338) | 1 (0.3) (N=308) |
| Not high CV risk and No CCV history but on low-dose aspirin | 19 (1.4) (N=1364) | 13 (0.9) (N=1401) | 15 (1.1) (N=1364) | 11 (0.8) (N=1401) |
| **Geographical Region** | | | | |
| USA | 23 (1.0) (N=2279) | 16 (0.7) (N=2215) | 14 (0.6) (N=2279) | 9 (0.4) (N=2215) |
| non-USA | 62 (0.9) (N=6838) | 59 (0.9) (6912) | 45 (0.7) (N=6838) | 41 (0.6) (6912) |

† APTC endpoint includes all confirmed or probable MIs (clinical and silent), strokes (ischemic or hemorrhagic), or cardiovascular deaths.
‡ All CCV events includes the ones in the APTC endpoint and confirmed or probable cardiac arrest, TIA, unstable angina, DVT or PE.

When considering the components of the APTC endpoint separately, the number of events was small in all treatment groups in both sub-studies with no significant differences in incidence for the majority of events.

An imbalance was observed in the incidence of myocardial infarction between lumiracoxib and naproxen in the group not taking low-dose aspirin (0.28% vs. 0.06%, hazard ratio 4.74, p=0.0445), whereas there was no imbalance vs. naproxen in the low-dose aspirin group (same incidence of 0.42%, hazard ratio 1.02).

For cardiovascular death or ischaemic stroke, no significantly lower incidence with naproxen vs. lumiracoxib was found in either of the subgroups by aspirin use.
No differences in the incidence of myocardial infarction were observed between lumiracoxib and ibuprofen, in any of the groups (e.g. no low dose aspirin group: 0.12% vs. 0.09%, hazard ratio 1.25, p=0.7699).

## 6.11.6 Hepatic safety

6.11.6.1 Rise in ALT and/or AST

Increases in ALT and/or AST were seen most often. These were more frequent in the lumiracoxib group, overall and in both sub-studies, and the differences between lumiracoxib and NSAIDs (naproxen and ibuprofen) were statistically significant (COX proportional hazards model. Frequencies of ALT and/or AST elevations in the lumiracoxib groups in the 2 sub-studies were similar

**Frequency of increases in hepatic biochemical events (safety population)**

| | TARGET (0117 + 2332) | |
|---|---|---|
| | **Lumiracoxib N=8948 n (%)** | **NSAIDs N=8939 n (%)** |
| ALT and/or AST borderline (>1.2xULN to ≤3xULN) | 1649(18.4) | 985(11.0) |
| ALT and/or AST >3xULN | 243 (2.7) | 66 (0.7) |
| ALT and/or AST >5xULN | 117 (1.3) | 23 (0.3) |
| ALT and/or AST >8xULN | 59 (0.7) | 9 (0.1) |
| Bilirubin >1.2xULN with | | |
| ALT and/or AST >3xULN | 19 (0.2) | 7 (0.1) |
| ALT and/or AST >5xULN | 18 (0.2) | 6 (0.1) |
| ALT and/or AST >8xULN | 15 (0.2) | 2 (0.0) |
| Bilirubin >1.5xULN with | | |
| ALT and/or AST >3xULN | 14 (0.2) | 5 (0.1) |
| ALT and/or AST >5xULN | 13 (0.1) | 5 (0.1) |
| ALT and/or AST >8xULN | 12 (0.1) | 1 (0.0) |
| Bilirubin >51.3 µmol/L with | | |
| ALT and/or AST >3xULN | 9 (0.1) | 4 (0.0) |
| ALT and/or AST >5xULN | 9 (0.1) | 4 (0.0) |
| ALT and/or AST >8xULN | 8 (0.1) | 1 (0.0) |
| Alkaline Phosphatase >1.5xULN with | | |
| ALT and/or AST >3xULN | 58 (0.6) | 28 (0.3) |
| ALT and/or AST >5xULN | 40 (0.4) | 16 (0.2) |
| ALT and/or AST >8xULN | 27 (0.3) | 5 (0.1) |

The one-year cumulative rate for ALT and/or AST increases to:

- >3 x ULN with lumiracoxib was 3.54% vs. 1.05% for NSAIDs,
- >5 x ULN with lumiracoxib was 1.69% vs. 0.37% for NSAIDs, and
- >8 x ULN with lumiracoxib was 0.85% vs. 0.16% for NSAIDs.

The differences between lumiracoxib and NSAIDs were statistically significant for all thresholds.

There was no obvious relationship between hepatic events and age or gender

**Frequency of hepatic biochemical events adjudicated as hepatocellular, mixed or cholestatic liver injury, by relationship to study drug (safety population)**

| Adjudication | TARGET (0117 + 2332) | |
|---|---|---|
| **Type of liver injury Relationship to study drug †** | **Lumiracoxib N=8948 n (%)** | **NSAIDs N=8939 n (%)** |
| **Hepatocellular** | 152 (1.7) | 23 (0.3) |
| Probable | 65 (0.7) | 3 (0.0) |
| Possible A | 73 (0.8) | 12 (0.1) |
| Possible B | 13 (0.1) | 4 (0.0) |
| Not related | 0 | 3 (0.0) |
| Not assessable | 1 (0.0) | 1 (0.0) |
| **Mixed** | 69 (0.8) | 24 (0.3) |
| Probable | 16 (0.2) | 5 (0.1) |
| Possible A | 40 (0.4) | 13 (0.1) |
| Possible B | 5 (0.1) | 5 (0.1) |
| Not related | 6 (0.1) | 1 (0.0) |
| Not assessable | 2 (0.0) | 0 |
| **Cholestatic** | 17 (0.2) | 16 (0.2) |
| Probable | 4 (0.0) | 1 (0.0) |
| Possible A | 7 (0.1) | 7 (0.1) |
| Possible B | 6 (0.1) | 6 (0.1) |
| Not related | 0 | 2 (0.0) |
| Not assessable | 0 | 0 |

The outcome following rises in AST/ALT is shown in the table below.

**Outcome of notable increases in ALT and/or AST (safety population**

| Maximum post-baseline value | TARGET (0117 + 2332) | |
|---|---|---|
| **Outcome** | **Lumiracoxib** | **NSAIDs** |
| **3xULN < AST/ALT ≤ 5xULN** | | |
| N (%) of patients with event | 126 (100) | 43 (100) |
| n (%) of patients with no follow-up | 0 | 1 (2.3) |
| n (%) of patients not normalizing | 4 (3.2) | 1 (2.3) |
| n (%) of patients normalized | 122 (96.8) | 41 (95.3) |
| Median days to normalization | 20 | 15 |
| Range of days to normalization | 3-303 | 4- 92 |
| **5xULN < AST/ALT ≤ 8xULN** | | |
| N (%) of patients with event | 58 (100) | 14 (100) |
| n (%) of patients with no follow-up | 1 (1.7) | 0 |
| n (%) of patients not normalizing | 0 | 1 (7.1) |
| n (%) of patients normalized | 57 (98.3) | 13 (92.9) |
| Median days to normalization | 27 | 16 |
| Range of days to normalization | 3-295 | 4-286 |
| **AST/ALT >8xULN** | | |
| N (%) of patients with event | 59 (100) | 9 (100) |
| n (%) of patients with no follow-up | 0 | 0 |
| n (%) of patients not normalizing | 0 | 1 (11.1) |
| n (%) of patients normalized | 59 (100) | 8 (88.9) |
| Median days to normalization | 37 | 22 |
| Range of days to normalization | 6-291 | 2- 75 |

6.11.6.2 Severe hepatic events

***Some of these data have been referred to already in the Original Assessment Report.***

A severe hepatic event was defined as one in which ALT **and/or** AST values were >5 x ULN **and** bilirubin was >51.3 µmol/L **and** the LSC adjudicated the event as probably or possibly related to study drug.

The Liver Safety Committee (LSC) reviewed all cases of newly occurring, post-baseline increases of ALT **or** AST to values >3 x ULN **or** total bilirubin >51.3 µmol/L (>3.0 mg/dL), categorizing each case according to the type of liver injury (hepatocellular, mixed, cholestatic, not possible to assess, not related) and the relationship to study drug (**probable, possible A, possible B, not related, not assessable**).

There were 9 patients who had severe hepatic events according to this definition, 6 receiving lumiracoxib (1 also taking low-dose aspirin), 1 naproxen (also taking low-dose aspirin) and 2 ibuprofen (1 also taking low-dose aspirin). The frequencies in each group were very low (<0.1%) with more cases in the lumiracoxib group in study 0117 (4 lumiracoxib vs. 1 naproxen). No statistically significant differences between treatments for the incidence of severe hepatic events were found.

An additional 4 patients had ALT **and/or** AST values >5 x ULN **and** bilirubin >51.3 µmol/L but the Liver Safety Committee adjudicated these 4 cases as not related to study drug.

As well as the 13 patients listed overleaf, there was one other lumiracoxib patient (0117-0191-00006, 65/M/Whi) who had a bilirubin value >51.3 µmol/L (max 58.7 µmol/L, 3.1xULN on day 40) and he discontinued because of this. His baseline bilirubin was already increased at 41.4 µmol/L, follow-up values after discontinuation remained in the region of the baseline value. AST and ALT values were all normal. According to the Liver safety Committee's adjudication, the type of liver injury was not possible to assess and the event was not related to study drug.

The proportion of patients with elevations of ALT and/or AST >3 x ULN was higher with lumiracoxib than NSAIDs (2.7% vs. 0.7%).

A severe hepatic event was defined as one in which ALT and/or AST values were >5 x ULN and bilirubin value was >51.3 µmol/L (3.0 mg/dL) and the event was adjudicated as probably or possibly related to study drug.

The overall incidence of severe hepatic events was low, with no significant differences between groups (6 for lumiracoxib, 0.07%; 3 for NSAIDs, 0.03%). All these 9 patients recovered after study drug discontinuation.

**Patients with ALT and/or AST >5 x ULN and total bilirubin >51.3 µmol/L**

| Patient ID Age/Sex/Race | Maximum value† (day) ALT xULN | AST xULN | Bili xULN | AE Preferred term | SAE Y/N | AED Y/N | LSC adjudication Liver injury type / study drug relationship |
|---|---|---|---|---|---|---|---|
| **Lumiracoxib** | | | | | | | |
| 0117-0086-00010 54/M/Whi | 6.9 (367) | 7.8 (367) | 5.5 (367) | bacterial infection, liver abscess | Y | N | Mixed **not related** |
| 0117-0376-00016 51/M/Whi | 95.1 (161) | 52.7 (161) | 24.3 (168) | hepatitis, jaundice | Y | Y | hepatocellular **probable** |
| 0117-0459-00001 79/M/Whi | 31.7 (175) | N/A | 5.9 (183) | hepatitis | Y | N | hepatocellular **probable** |
| 0117-0510-00008 55/F/Whi | 51.6 (91) | 37.7 (91) | 11.3 (96) | acute hepatitis | Y | Y | hepatocellular **possible A** |
| 0117-0510-00009 58/M/Bl | 11.6 (254) | 7.0 (239) | 20.2 (254) | nausea, pancreatic carcinoma | Y | Y | Mixed **not related** |
| 0117-0534-00019 75/M/Whi | 10.5 (288) | 7.3 (288) | 7.9 (288) | bile duct stone | Y | N | Mixed **not related** |
| 0117-0868-00007 57/F/OAs | 19.1 (377) | 18.3 (377) | 4.5 (317) | cholecystitis, cholelithiasis | Y | N | hepatocellular **possible A** |
| 2332-0081-00036 73/F/His | 27.0 (268) | 18.8 (268) | 5.8 (268) | upper abdominal pain, nausea, vomiting, jaundice | Y | Y | hepatocellular **possible A** |
| 2332-0415-0009 64/F/Oth | 32.9 (124) | 40.0 (120) | 18.3 (128) | hepatitis | Y | Y | hepatocellular **probable** |
| **Naproxen** | | | | | | | |
| 0117-0474-00013 70/F/Whi | 6.1 (35) | 6.8 (35) | 10.3 (42) | bile duct cancer | Y | Y | Mixed **not related** |
| 0117-0694-00026 66/F/Whi | 5.5 (340) | N/A | 3.0 (340) | bile duct obstruction | Y | Y | mixed **possible B** |
| **Ibuprofen** | | | | | | | |
| 2332-0231-00001 62/F/Whi | 8.4 (104) | 10.2 (104) | 3.1 (104) | high GGT, cholecystitis | Y | Y | cholestatic **possible B** |
| 2332-0415-00010 61/F/Oth | N/A | 5.6 (74) | 7.2 (71) | hepatitis, melena, dehydration, renal failure, candidiasis | Y | Y | cholestatic **possible A** |

† Maximum value expressed as a multiple of the upper limit of normal (x ULN). Y/N = Yes/No
N/A = not available/applicable. SAE = serious adverse event. AED = adverse event discontinuation.

### 6.11.6.3 Assessment of hepatic events data

The data from full TARGET study does not give rise to any further concerns. If anything, the data now are more reassuring than the previous interim data in terms of the hepatotoxicity potential of lumiracoxib.

Asymptomatic rises in biochemical parameters of liver injury (AST and AST) are frequently raised in clinical trials. An interesting feature of such rises, observed with numerous drugs, is that these DO NOT predict overt severe hepatic injury during the post-marketing use. Frequent monitoring of patients for their liver function tests during routine clinical use has also been found to be unsatisfactory in early detection of potential overt hepatic injury. In part, this may be because there is a subgroup in whom the progression of the injury is rapid.

### 6.11.7 Renal safety

6.11.7.1 Rise in serum creatinine

6.11.7.1.1 *Increases in creatinine >35.36 µmol/L*

Increases in creatinine >35.36 µmol/L (>0.4 mg/dL) above baseline were more frequent with lumiracoxib than NSAIDs (3.9% vs. 2.4%).

The one-year cumulative rate for lumiracoxib was 5.01% (95% CI 4.48-5.54) and 3.06% (95% CI 2.64-3.47) for NSAIDs.

The statistically significant difference between lumiracoxib and NSAIDs was due to the lower rate for naproxen vs. lumiracoxib in study 0117, but this was not seen for ibuprofen vs. lumiracoxib in study 2332

6.11.7.1.2 *Increases in creatinine > 2 x ULN post-baseline*

Increases in creatinine > 2 x ULN post-baseline were more frequent with lumiracoxib than NSAIDs.
The one-year cumulative rate for lumiracoxib was 0.09% (95% CI 0.02- 0.16) and 0.04% (95% CI 0.00- 0.09) for NSAIDs).
There was however no statistically significant difference between lumiracoxib and NSAIDs, or between lumiracoxib and naproxen or ibuprofen).

6.11.7.1.3 *Increases in creatinine ≥100% above baseline*

Increases in creatinine ≥100% above baseline were statistically significantly less frequent with naproxen than lumiracoxib (0.21% vs. 0.04%, hazard ratio 4.78, 95% CI 1.05-21.80, p=0.0436), but there was no significant difference between lumiracoxib and ibuprofen). The outcome in these patients is shown in the table below:

| | **Lumiracoxib** | **NSAIDs** |
|---|---|---|
| **Creatinine ≥100% above baseline** | | |
| N (%) of patients with event at any time | 18 (100) | 13 (100) |
| n (%) of patients with event at endpoint | 5 (27.8) | 5 (38.5) |
| n (%) of patients with follow-up mean ≥100% above baseline | 2 (11.1) | 2 (15.4) |
| n (%) of patients with no follow-up | 4 (22.2) | 2 (15.4) |
| n (%) of patients not normalizing | 2 (11.1) | 4 (30.8) |
| n (%) of patients normalized | 12 (66.7) | 7 (53.9) |
| Median days to normalization | 50 | 28 |
| Range of days to normalization | 7 - 105 | 10 - 77 |

6.11.7.2 Severe renal events

The increases in serum creatinine have already been described in more detail in the previous section (3.11.7.1) above. A major renal event was defined as one in which serum creatinine increased by ≥100% from baseline and/or urine protein was ≥3.0 g/L (by urine dipstick).

No patient had both these abnormalities at any of the visits during the study.

There were 79 patients who had major renal events according to this definition:
- 46 (0.51%) receiving lumiracoxib and 33 (0.37%) NSAIDs
- 15 (0.32%) naproxen, 18 (0.42%) ibuprofen.
- No statistically significant differences between treatments for the incidence of major renal events were found in the overall patient group.
- In the patients not taking low-dose aspirin, the incidence of major renal events was lower with naproxen (lumiracoxib 0.49%, naproxen 0.20%, hazard ratio 2.32, 95% CI 0.96-5.58, p=0.0615). Incidence rates with lumiracoxib and ibuprofen were similar (0.51% vs. 0.42%, hazard ratio 1.16).

The one-year cumulative rate (KM estimate) for major renal events with lumiracoxib was 0.69% (95% CI 0.48-0.89) vs. 0.48% (95% CI 0.31-0.64) for NSAIDs.

None of the 79 patients with major renal events had both urine protein ≥3.0 g/L (by urine dipstick) **and** serum creatinine increased ≥100% from baseline: 48 had only urine protein ≥3.0 g/L (28 lumiracoxib, 13 naproxen, 7 ibuprofen) and 31 had only creatinine ≥100% above baseline (18 lumiracoxib, 2 naproxen, 11 ibuprofen).

There were no statistically significant differences between lumiracoxib and NSAIDs for major renal events in patients in the two lower age groups ((≤64, 65-74 years).

In patients ≥75 years old, there was an imbalance in study 0117 where 6 lumiracoxib patients vs. no naproxen patients had major renal events, whereas 2 patients in each of the lumiracoxib and ibuprofen groups were affected in study 2332). Of these 10 patients aged ≥75 years, 5 (4 lumiracoxib, 1 ibuprofen) had creatinine values increased by ≥100% from baseline and 5 (4 lumiracoxib, 1 ibuprofen) had urine protein dipsticks ≥3.0 g/L.

Subgroup analyses by gender, showed no significant differences between treatments

Approximately 45% of patients in each of the lumiracoxib and NSAIDs groups were hypertensive at baseline, as assessed from their medical history records). A slightly greater proportion of patients with a history of hypertension at baseline experienced major renal events compared with patients who did not, but no significant differences between treatments occurred in either of these 2 subgroups).
About 2% of patients in each of the lumiracoxib and NSAIDs groups had either creatinine >ULN or urine protein ≥1.0 g/L at baseline. As expected, a greater proportion of patients with these abnormalities at baseline experienced major renal events than those who did not, although there were no statistically significant differences between treatments in either of these 2 subgroups.

Among the notable renal adverse reactions were:

| | **Lumiracoxib N = 9117** | **NSAIDs N = 9127** |
|---|---|---|
| Total renal events | 283 (3.1%) | 261 (2.9%) |
| Renal insufficiency | 17 (0.2%) [7] | 8 (0.1%) [1] |
| Proteinuria | 7 [1] | 7 [1] |
| Renal impairment | 4 [1] | 3 [2] |
| Acute renal failure | 3 [1] | 2 [1] |
| Nephropathy | 1 [0] | 2 [1] |
| Nephritis (all forms) | 0 | 4 [1] |

**[Figures in square parenthesis]** are number of patients who needed discontinuation from study

Lumiracoxib has a slightly greater propensity to produce renal insufficiency. In contrast, cases of nephritis observed with NSAIDs were not reported with lumiracoxib.

Otherwise, there are no obviously significant differences between lumiracoxib and the two non-selective NSAIDs combined.

Major renal events: treatment comparisons using COX proportional hazards model (safety population):

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| **Overall patient group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 8951 | 46 (0.51) | 1.34 | 0.86 - 2.10 | 0.1971 |
| NSAIDs | 8942 | 33 (0.37) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 4658 | 24 (0.52) | 1.56 | 0.82 - 2.97 | 0.1783 |
| Naproxen | 4631 | 15 (0.32) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 4293 | 22 (0.51) | 1.17 | 0.63 - 2.18 | 0.6245 |
| Ibuprofen | 4311 | 18 (0.42) | | | |
| **No low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 6819 | 34 (0.50) | 1.54 | 0.90 - 2.66 | 0.1185 |
| NSAIDs | 6823 | 21 (0.31) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 3486 | 17 (0.49) | 2.32 | 0.96 - 5.58 | 0.0615 |
| Naproxen | 3459 | 7 (0.20) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 3333 | 17 (0.51) | 1.16 | 0.57 - 2.35 | 0.6842 |
| Ibuprofen | 3364 | 14 (0.42) | | | |
| **Low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 2132 | 12 (0.56) | 0.99 | 0.44 - 2.20 | 0.9771 |
| NSAIDs | 2119 | 12 (0.57) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 1172 | 7 (0.60) | 0.88 | 0.32 - 2.42 | 0.7987 |
| Naproxen | 1172 | 8 (0.68) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 960 | 5 (0.52) | 1.21 | 0.32 - 4.50 | 0.7778 |
| Ibuprofen | 947 | 4 (0.42) | | | |

Major renal events are defined as serum creatinine increase by ≥100% from baseline and/or urine protein ≥3.0 g/L (by urine dipstick)

* p value based on Wald chi-squared statistic for treatment comparison, lumiracoxib vs. comparator

### 6.11.7.3 Assessment of renal events data

**Ahmad et al (Drug Safety. 2002; 25: 537-544)** have reviewed 122 and 142 domestic US cases of renal failure associated with the use of celecoxib and rofecoxib, respectively. In the celecoxib case series, the median age of the patients was 72 years.

Common risk factors included concomitant disease states and medications. The most prevalent concomitant disease states reported were hypertension (33%), followed by diabetes mellitus (27%), pre-existing or history of renal failure or renal insufficiency (25%), and congestive heart failure (21%). Co-medication of diuretics was most common (54%), followed by concomitant or recent use of selective or nonselective NSAIDs (42%), and ACE inhibitors (36%).

Given the following demography of the population randomised into TARGET, the renal safety profile is reassuring.

| | Lumiracoxib N=9117 n (%) | NSAIDs N=9127 n (%) |
|---|---|---|
| **Age (years)** | | |
| Mean ± SD | 63.5 ± 8.37 | 63.4 ± 8.35 |
| **Age categories – n (%)** | | |

| | | |
|---|---|---|
| <= 49 years | 10 (0.1) | 10 (0.1) |
| 50 - 64 years | 5127 (56.2) | 5158 (56.5) |
| 65 – 74 years | 3005 (33.0) | 2969 (32.5) |
| ≥75 years | 975 (10.7) | 990 (10.8) |
| Impaired renal function† n (%) | 180 (2.0) | 171 (1.9) |
| **Concurrent use of:** | | |
| Diuretics | 1516 (16.6) | 1494 (16.4) |
| ACE-inhibitors | 1975 (21.7) | 1926 (21.1) |
| Anti-hypertensive medications | 4583 (50.3) | 4528 (49.6) |

## 6.11.8 Electrocardiographic safety

The proportion of patients developing newly occurring ECG abnormalities was similar for lumiracoxib (7.7%) and NSAIDs (7.2%).

There were no notable differences between groups in the number of patients who developed increases in QTc from baseline or newly occurring QTc ≥ 500 ms

Number (%) of patients with QTc increases from baseline (Bazett and Fridericia) (safety population):

| | | Maximum QTc Bazett change from baseline | | Maximum QTc Fridericia change from baseline | |
|---|---|---|---|---|---|
| **Study Treatment** | **N †** | **≥30 and ≤60ms n (%)** | **>60ms n (%)** | **≥30 and ≤60ms n (%)** | **>60ms n (%)** |
| **TARGET** | | | | | |
| Lumiracoxib | 8225 | 597 (7.3) | 46 (0.6) | 405 (4.9) | 36 (0.4) |
| NSAIDs | 8193 | 538 (6.6) | 50 (0.6) | 346 (4.2) | 33 (0.4) |
| **Study 0117** | | | | | |
| Lumiracoxib | 4269 | 338 (7.9) | 31 (0.7) | 245 (5.7) | 24 (0.6) |
| Naproxen | 4241 | 312 (7.4) | 36 (0.8) | 207 (4.9) | 24 (0.6) |
| **Study 2332** | | | | | |
| Lumiracoxib | 3956 | 259 (6.5) | 15 (0.4) | 160 (4.0) | 12 (0.3) |
| Ibuprofen | 3952 | 226 (5.7) | 14 (0.4) | 139 (3.5) | 9 (0.2) |

Number (%) of patients with newly occurring, post-baseline QTc ≥ 500 ms (Bazett and Fridericia) (safety population):

| **Study Treatment** | **N †** | **Maximum QTc Bazett ≥ 500 ms n (%)** | **Maximum QTc Fridericia ≥ 500 ms n (%)** |
|---|---|---|---|
| **TARGET** | | | |
| Lumiracoxib | 8280 | 12 (0.1) | 3 (0.0) |
| NSAIDs | 8240 | 13 (0.2) | 2 (0.0) |
| **Study 0117** | | | |
| Lumiracoxib | 4290 | 6 (0.1) | 2 (0.0) |
| Naproxen | 4263 | 10 (0.2) | 2 (0.0) |
| **Study 2332** | | | |
| Lumiracoxib | 3990 | 6 (0.2) | 1 (0.0) |
| Ibuprofen | 3977 | 3 (0.1) | 0 (0.0) |

### 6.11.8.1 Assessment of ECG safety data

When the data from the two tables are evaluated collectively, they are NOT indicative of potentially serious or clinically relevant any repolarization abnormalities

## 6.11.9 General safety

The proportion of patients with adverse events regardless of relationship to study medication was similar with lumiracoxib (79.3%) and NSAIDs (79.7%). Gastrointestinal disorders were the most common in all groups. The majority of adverse events were mild to moderate in severity, with a slightly lower proportion of severe events reported for lumiracoxib (12.3%) vs. NSAIDs (13.2%).

The proportion of patients with adverse events suspected to be related to study medication was lower with lumiracoxib (44.8%) compared with NSAIDs (48.2%) The most frequent AE for all treatment groups was dyspepsia, followed by upper abdominal pain, and headache.

Overall, 59 deaths occurred, 29 (0.3%) in the lumiracoxib treated patients and 30 (0.3%) in the NSAID treated patients. There were no obvious differences in the primary causes of death across the groups. The most common cause of death in all groups was cardiac disorder.

Five cases of "overdose" occurred in sub-study 0117 at site 0531. Due to an incorrect instruction given by site personnel, patients were taking twice the intended daily dose of study medication for a period of several weeks. When the mistake was detected, the patients were then correctly instructed and continued the study on the correct treatment dose and regimen. Overdose was first reported as SAE, but later downgraded to being non-serious since the overdoses did not result in any clinical adverse events. Four of these patients received lumiracoxib (0117-0531-00002, 0117-0531-00003, 0117-0531-00004, 0117-0531-00005), one patient (0117-0531-00001) received naproxen.

**Number (%) of patients with serious adverse events by primary system organ class (safety population):**

| | TARGET (0117 + 2332) | |
|---|---|---|
| **Primary system organ class affected:** | **Lumiracoxib N=9117 n (%)** | **NSAIDs N=9127 n (%)** |
| Total number with SAEs | 588 (6.4) | 566 (6.2) |
| Musculoskeletal and connective tissue disorders | 91 (1.0) | 65 (0.7) |
| Cardiac disorders | 88 (1.0) | 97 (1.1) |
| Gastrointestinal disorders | 87 (1.0) | 120 (1.3) |
| Nervous system disorders | 76 (0.8) | 50 (0.5) |
| Infections and infestations | 67 (0.7) | 69 (0.8) |
| Injury, poisoning and procedural complications | 59 (0.6) | 67 (0.7) |
| Neoplasms benign, malignant and unspecified | 58 (0.6) | 57 (0.6) |
| Vascular disorders | 38 (0.4) | 40 (0.4) |
| General disorders & administration site conditions | 32 (0.4) | 39 (0.4) |
| Respiratory, thoracic and mediastinal disorders | 31 (0.3) | 28 (0.3) |
| Hepatobiliary disorders | 30 (0.3) | 17 (0.2) |
| Renal and urinary disorders | 22 (0.2) | 14 (0.2) |
| Reproductive system and breast disorders | 11 (0.1) | 20 (0.2) |
| Metabolism and nutrition disorders | 9 (0.1) | 13 (0.1) |
| Skin and subcutaneous tissue disorders | 9 (0.1) | 6 (0.1) |
| Blood and lymphatic system disorders | 7 (0.1) | 12 (0.1) |
| Investigations | 5 (0.1) | 10 (0.1) |
| Eye disorders | 5 (0.1) | 4 (0.0) |
| Psychiatric disorders | 4 (0.0) | 7 (0.1) |
| Endocrine disorders | 3 (0.0) | 4 (0.0) |
| Immune system disorders | 2 (0.0) | 1 (0.0) |
| Ear and labyrinth disorders | 1 (0.0) | 5 (0.1) |
| Congenital, familial and genetic disorders | 1 (0.0) | 0 |
| Surgical and medical procedures | 0 | 1 (0.0) |

**Number (%) of patients <u>discontinued</u> for adverse events by primary system organ class (safety population)**

| | TARGET (0117 + 2332) | |
|---|---|---|
| | **Lumiracoxib N=9117 n (%)** | **NSAIDs N=9127 n (%)** |
| Total number discontinued due to AE | 1441 (15.8) | 1657 (18.2) |
| **Primary system organ class affected:** | | |
| Gastrointestinal disorders | 729 (8.0) | 1023 (11.2) |
| Investigations | 173 (1.9) | 95 (1.0) |
| Musculoskeletal & connective tissue disorders | 115 (1.3) | 109 (1.2) |
| Nervous system disorders | 109 (1.2) | 103 (1.1) |
| General disorders & administration site conditions | 95 (1.0) | 104 (1.1) |
| Skin and subcutaneous tissue disorders | 59 (0.6) | 76 (0.8) |
| Cardiac disorders | 59 (0.6) | 66 (0.7) |
| Vascular disorders | 50 (0.5) | 68 (0.7) |
| Hepatobiliary disorders | 40 (0.4) | 8 (0.1) |
| Neoplasms benign, malignant and unspecified | 33 (0.4) | 34 (0.4) |
| Infections and infestations | 24 (0.3) | 30 (0.3) |
| Blood and lymphatic system disorders | 23 (0.3) | 38 (0.4) |
| Respiratory, thoracic and mediastinal disorders | 22 (0.2) | 36 (0.4) |
| Psychiatric disorders | 22 (0.2) | 25 (0.3) |
| Renal and urinary disorders | 22 (0.2) | 20 (0.2) |
| Injury, poisoning and procedural complications | 21 (0.2) | 24 (0.3) |
| Immune system disorders | 11 (0.1) | 11 (0.1) |
| Ear and labyrinth disorders | 10 (0.1) | 17 (0.2) |
| Metabolism and nutrition disorders | 9 (0.1) | 17 (0.2) |
| Eye disorders | 9 (0.1) | 12 (0.1) |
| Reproductive system and breast disorders | 7 (0.1) | 5 (0.1) |
| Endocrine disorders | 3 (0.0) | 1 (0.0) |

**Cause of <u>death</u> by primary system organ class (safety population)**

| | TARGET (0117 + 2332) | |
|---|---|---|
| | **Lumiracoxib N=9117 n (%)** | **NSAIDs N=9127 n (%)** |
| Total number of deaths in any SOC | 29 (0.3) | 30 (0.3) |
| **Primary system organ class affected:** | | |
| Cardiac disorders | 10 (0.1) | 10 (0.1) |
| Nervous system disorders | 8 (0.1) | 4 (0.0) |
| Infections and infestations | 3 (0.0) | 4 (0.0) |
| Neoplasms, benign, malignant & unspecified | 3 (0.0) | 3 (0.0) |
| Respiratory, thoracic & mediastinal disorders | 2 (0.0) | 1 (0.0) |
| Vascular disorders | 2 (0.0) | 1 (0.0) |
| General disorders & admin. site conditions | 1 (0.0) | 4 (0.0) |
| Injury, poisoning and procedural complications | 0 | 1 (0.0) |
| Psychiatric disorders | 0 | 1 (0.0) |
| Renal and urinary disorders | 0 | 1 (0.0) |

**Number (%) of patients with pre-specified GI adverse events, edemas, *de novo* hypertension (safety population)**

| | TARGET (0117 + 2332) | |
|---|---|---|
| | **Lumiracoxib N=9117 n (%)** | **NSAIDs N=9127 n (%)** |
| **Prespecified GI events** | 3640 (39.9) | 3839 (42.1) |
| Dyspepsia | 2267 (24.9) | 2324 (25.5) |
| Abdominal pain upper | 915 (10.0) | 1147 (12.6) |
| Diarrhea | 558 (6.1) | 442 (4.8) |
| Nausea | 465 (5.1) | 525 (5.8) |
| Abdominal pain | 328 (3.6) | 340 (3.7) |
| Vomiting | 183 (2.0) | 182 (2.0) |
| Loose stools | 71 (0.8) | 37 (0.4) |
| Abdominal pain lower | 16 (0.2) | 32 (0.4) |
| Diarrhea hemorrhagic | 0 | 2 (0.0) |
| **Prespecified edemas** | 432 (4.7) | 446 (4.9) |
| Edema peripheral | 328 (3.6) | 337 (3.7) |
| Edema | 71 (0.8) | 78 (0.9) |
| Pitting edema | 18 (0.2) | 25 (0.3) |
| Face edema | 8 (0.1) | 5 (0.1) |
| Swelling | 6 (0.1) | 4 (0.0) |
| Gravitational edema | 3 (0.0) | 1 (0.0) |
| Periorbital edema | 1 (0.0) | 3 (0.0) |
| Anasarca | 1 (0.0) | 1 (0.0) |
| Localized edema | 1 (0.0) | 0 |
| **Total number with *de novo* hypertension*** | 250 (5.1) (N=4898)* | 330 (6.5) (N=5066)* |

* Denominator = safety population classified as "not hypertensive at baseline"

## 6.12 Overall Assessment of TARGET Data:

▼ In July 2002, France initiated an Article 31 referral for all approved medicinal products containing COX-2 selective inhibitors, namely rofecoxib, celecoxib, etoricoxib, parecoxib, and valdecoxib.

The referral was triggered following concerns over gastrointestinal and cardiovascular safety.

The CPMP also extended the scope of safety evaluation to include observed or potential serious skin effects and hypersensitivity reactions of medicinal products containing the five COX-2 selective inhibitors that were the subject to referral (celecoxib, etoricoxib, parecoxib, rofecoxib and valdecoxib)

▼ The data from TARGET directly address issues relevant to the safety of COX-2 selective inhibitors, which led to Article 31 referral.

The data from TARGET are particularly relevant since the dose used is 2-4 times greater than the recommended dose.

**Gastrointestinal safety of lumiracoxib**

TARGET confirms the gastro-intestinal safety of lumiracoxib relative to naproxen and ibuprofen. The risk of definite or probable upper gastrointestinal tract (UGIT) ulcer complications (POBs) was reduced by 79% with lumiracoxib vs. NSAIDs in patients not taking low-dose aspirin. The incidence of UGIT POBs was numerically lower with

lumiracoxib vs. NSAIDs in the group taking low-dose aspirin, but the study was not powered to show a difference in this group and the reduction was not statistically significant (hazard ratio 0.79, 95% CI 0.40-1.55).

**Cardiovascular safety of lumiracoxib**
For cardiovascular safety, TARGET sheds some light on the controversy coming from VIGOR on the potential cardio-protective role of naproxen.

Because TARGET compared the effects of lumiracoxib with both naproxen and ibuprofen, this landmark study provides a contrasting view of the cardio-protective potential of different NSAIDs.

An imbalance in myocardial infarction, but not on other CV events, was observed between lumiracoxib and naproxen. However, no difference in the risk of developing CV events was observed with lumiracoxib compared to ibuprofen, suggesting a cardio-protective effect by naproxen and not a pro-thrombotic effect of lumiracoxib.

This hypothesis is supported by:
a. An aspirin-like selective effect on myocardial infarctions (but not stroke or CV death) observed with naproxen in sub-study 0117,
b. The lack of any imbalance in myocardial infarctions between naproxen and lumiracoxib when low-dose aspirin was added, and
c. The lack of an imbalance between lumiracoxib and ibuprofen in sub-study 2332.

The POSITIVE risk/benefit ratio for lumiracoxib is provided by a composite endpoint analysis:

**GI and CCV (APTC) combined endpoint**
The incidence of combined GI (definite or probable POBs) and/or CCV (confirmed or probable APTC endpoint) events was statistically significantly lower with lumiracoxib (0.98%) than NSAIDs (1.46%), a 35% decrease in risk (hazard ratio 0.65, 95% CI 0.49-0.84, p=0.0014), driven by the markedly lower incidence of GI events with lumiracoxib.

A lower frequency with lumiracoxib for this combined endpoint was seen consistently in both sub-studies (lumiracoxib 1.24% vs. naproxen 1.63%, a 25% decrease in risk; lumiracoxib 0.69% vs. ibuprofen 1.27%, a 50% decrease in risk).

A greater effect was observed in the group of patients not taking low-dose aspirin

The study was performed with lumiracoxib at a 400 mg once daily dose, which is two to four times the dose proposed for chronic use. While the overall safety profile is favorable, it is expected that the clinical use of lower doses of lumiracoxib will demonstrate an enhanced benefit risk profile.

The two tables overleaf provide a perspective on combining various safety issues.

## Frequency of events in the combined endpoints (safety population)

| | TARGET (0117 + 2332) | |
|---|---|---|
| | **Lumiracoxib n (%)** | **NSAIDs n (%)** |
| **Overall patient group** | N=9117 | N=9127 |
| GI events (definite or probable UGIT ulcer complications) | 30 (0.3) | 84 (0.9) |
| APTC events (confirmed or probable) † | 59 (0.6) | 50 (0.5) |
| **Sub-total: GI and/or APTC events** | **89 (1.0)** | **133 (1.5)** |
| Severe hepatic events ‡ | 6 (0.1) | 3 (0.0) |
| Major renal events ‡ | 46 (0.5) | 33 (0.4) |
| **Total: GI / APTC / severe hepatic / major renal events** | **140 (1.5)** | **166 (1.8)** |
| **No low-dose aspirin group** | N=6950 | N=6968 |
| GI events (definite or probable UGIT ulcer complications) | 15 (0.2) | 65 (0.9) |
| APTC events (confirmed or probable) † | 35 (0.5) | 27 (0.4) |
| **Sub-total: GI and/or APTC events** | **50 (0.7)** | **91 (1.3)** |
| Severe hepatic events ‡ | 5 (0.1) | 1 (0.0) |
| Major renal events ‡ | 34 (0.5) | 21 (0.3) |
| **Total: GI / APTC / severe hepatic / major renal events** | **89 (1.3)** | **111 (1.6)** |
| **Low-dose aspirin group** | N=2167 | N=2159 |
| GI events (definite or probable UGIT ulcer complications) | 15 (0.7) | 19 (0.9) |
| APTC events (confirmed or probable) † | 24 (1.1) | 23 (1.1) |
| **Sub-total: GI and/or APTC events** | **39 (1.8)** | **42 (1.9)** |
| Severe hepatic events ‡ | 1 (0.0) | 2 (0.1) |
| Major renal events ‡ | 12 (0.6) | 12 (0.6) |
| **Total: GI / APTC / severe hepatic / major renal events** | **51 (2.4)** | **55 (2.5)** |

GI and CCV (APTC) combined endpoint: treatment comparisons using COX proportional hazards model (safety population):

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| **Overall patient group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 9117 | 89 (0.98) | 0.65 | 0.49 - 0.84 | 0.0014 |
| NSAIDs | 9127 | 133 (1.46) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 4741 | 59 (1.24) | 0.75 | 0.53 - 1.05 | 0.0961 |
| Naproxen | 4730 | 77 (1.63) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 4376 | 30 (0.69) | 0.50 | 0.32 - 0.79 | 0.0025 |
| Ibuprofen | 4397 | 56 (1.27) | | | |
| **No low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 6950 | 50 (0.72) | 0.52 | 0.37 - 0.74 | 0.0002 |
| NSAIDs | 6968 | 91 (1.31) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 3549 | 31 (0.87) | 0.59 | 0.38 - 0.93 | 0.0219 |
| Naproxen | 3537 | 50 (1.41) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 3401 | 19 (0.56) | 0.44 | 0.26 - 0.76 | 0.0032 |
| Ibuprofen | 3431 | 41 (1.19) | | | |
| **Low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 2167 | 39 (1.80) | 0.93 | 0.60 - 1.43 | 0.7271 |
| NSAIDs | 2159 | 42 (1.95) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 1192 | 28 (2.35) | 1.06 | 0.63 - 1.80 | 0.8263 |
| Naproxen | 1193 | 27 (2.26) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 975 | 11 (1.13) | 0.68 | 0.31 - 1.48 | 0.3336 |
| Ibuprofen | 966 | 15 (1.55) | | | |

GI, CCV (APTC), hepatic and renal combined endpoint: treatment comparisons using COX proportional hazards model (safety population):

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| **Overall patient group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 9117 | 140 (1.54) | 0.82 | 0.65 - 1.02 | 0.0760 |
| NSAIDs | 9127 | 166 (1.82) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 4741 | 86 (1.81) | 0.92 | 0.68 - 1.23 | 0.5596 |
| Naproxen | 4730 | 92 (1.95) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 4376 | 54 (1.23) | 0.69 | 0.49 - 0.99 | 0.0420 |
| Ibuprofen | 4397 | 74 (1.68) | | | |
| **No low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 6950 | 89 (1.28) | 0.77 | 0.58 - 1.01 | 0.0617 |
| NSAIDs | 6968 | 111 (1.59) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 3549 | 51 (1.44) | 0.87 | 0.60 - 1.28 | 0.4816 |
| Naproxen | 3537 | 56 (1.58) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 3401 | 38 (1.12) | 0.66 | 0.44 - 1.00 | 0.0491 |
| Ibuprofen | 3431 | 55 (1.60) | | | |
| **Low-dose aspirin group** | | | | | |
| **TARGET (0117 + 2332)** | | | | | |
| Lumiracoxib | 2167 | 51 (2.35) | 0.92 | 0.63 - 1.35 | 0.6853 |
| NSAIDs | 2159 | 55 (2.55) | | | |
| **Study 0117** | | | | | |
| Lumiracoxib | 1192 | 35 (2.94) | 0.99 | 0.62 - 1.57 | 0.9626 |
| Naproxen | 1193 | 36 (3.02) | | | |
| **Study 2332** | | | | | |
| Lumiracoxib | 975 | 16 (1.64) | 0.80 | 0.41 - 1.56 | 0.5194 |
| Ibuprofen | 966 | 19 (1.97) | | | |

## 6.13 Serious skin effects and hypersensitivity reactions with lumiracoxib

The original Assessment Report described reports of pruritus (in 0.7%) and rash (in 0.3%) of patients and one report of angioneurotic oedema in OA clinical trials programme.

In the RA clinical trials programme, the frequency of rash and pruritus was slightly higher and 1 report of serious skin eruption.

In the TARGET study, the skin reactions, regardless of causality to study drugs, observed are summarised below:

| | **TARGET (0117 + 2332)** | |
|---|---|---|
| | **Lumiracoxib N = 9117** | **NSAIDs N = 9127** |
| **Total number with skin reactions** | **675 (7.4%)** | **634 (6.9)** |
| | ***Frequency ≤1%*** | |
| Pruritus | 94 | 81 |
| Rash | 90 | 98 |
| Eczema | 57 | 61 |
| Urticaria | 52 | 38 |
| Dermatitis | 34 | 32 |
| Contact dermatitis | 24 | 23 |
| Erythema | 19 | 27 |
| Allergic dermatitis | 18 | 23 |
| | ***Frequency ≤0.1%*** | |
| Rosacea | 9 | 3 |
| Exanthem | 8 | 11 |
| **Face oedema** | **8** | **5** |
| Swelling of the face | 8 | 6 |
| Generalised pruritus | 7 | 4 |
| Dermatosis | 6 | 3 |
| Psoriasis | 6 | 10 |

| | | |
|---|---|---|
| Papular rash | 6 | 7 |
| **Angioneurotic oedema** | **5** | **6** |
| Generalised rash | 5 | 2 |
| | ***Frequency ≤0.05%*** | |
| Atopic dermatitis | 4 | 1 |
| **Photosensitivity** | **4** | **4** |
| Macular rash | 4 | 3 |
| Pruritic rash | 4 | 9 |
| Exfoliative dermatitis | 3 | 3 |
| Erythematous rash | 3 | 3 |
| Maculo-papular rash | 2 | 6 |
| Scaly rash | 2 | 0 |
| **Toxic skin eruption** | **2** | **0** |
| | ***Single reports*** | |
| **Dermatitis herpetiformis** | **1** | **0** |
| **Fixed skin eruption** | **1** | **0** |
| **Generalised erythema** | **1** | **0** |
| **Periorobital oedema** | **1** | **3** |
| Photodermatits | 1 | 2 |
| Photosensitive rash | 1 | 0 |
| Skin inflammation | 1 | 0 |
| Generalised urticaria | 1 | 1 |

It appears that the pattern of skin reactions with lumiracoxib is similar, both quantitatively and qualitatively, to that observed with NSAIDs, represented by naproxen and ibuprofen.

It is worth noting that even in this large study, there were no reports of any of the more serious and potentially fatal skin reactions (such as erythema multiforme, toxic epidermal necrolysis or Stevens Johnson syndrome) that are so frequently observed with sulphonamides.

The current SPC statement, shown below, is in line with the data and the general recommendation made by the CPMP for other COX-2 selective inhibitors:

Section 4.8 on Undesirable effects:
**"Skin and subcutaneous tissue disorders**
Uncommon: Contusion, Exanthem, Pruritus, Rash, Urticaria
Rare: Angioneurotic oedema"

"The following rare serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for lumiracoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and jaundice; cutaneo-mucosal adverse effects and severe skin reactions."

# 7. Interaction study 2349 (with low dose aspirin)

This was a randomized, double-blind, placebo-controlled, parallel group study to evaluate the pharmacodynamic effects of concomitant low-dose aspirin and lumiracoxib administration in healthy volunteers

Primary objective

- To measure the effect of concomitant lumiracoxib and low-dose aspirin ministration on platelet aggregation

Secondary objectives

- To directly and indirectly measure serum/urinary eicosanoid production via parent or metabolite concentrations of pro- and anti-thrombotic eicosanoids in order to quantify changes in cyclooxygenase (COX) enzyme activity in relation to aspirin and/or lumiracoxib administration

This was a single center, placebo controlled, randomized, double-blind, parallel group study in 28 healthy subjects, randomized to one of the two treatment arms:

1. 400 mg lumiracoxib QD for 11 days with concomitant administration of low dose aspirin QD for 7 days, from study Day 5 through 11 (n=14)
2. Matching placebo to lumiracoxib QD for 11 days with concomitant administration of low dose (75mg enteric coated) aspirin QD for 7 days, from study Day 5 through 11 (n=14).

In the event of subject discontinuation, for any reason, the subject was to have been replaced to maintain an n=14 in each dosing cohort.

Pharmacodynamic assessments were performed at day 1 (pre-dose), 4, and 11

- Platelet aggregation by arachidonic acid and collagen
- Serum and urinary thromboxane and prostacyclin

**Results:**

Ratio of geometric means for platelet aggregation

| PD parameter | Comparison | Timepoint | Ratio of geometric means adjusted for baseline | Lower 90% CI | Upper 90% CI |
|---|---|---|---|---|---|
| Platelet aggregation by arachidonic acid | L / P | Day 4 | 0.99 | 0.94 | 1.05 |
| Platelet aggregation by collagen | L / P | Day 4 | 1.03 | 0.96 | 1.10 |
| Platelet aggregation by arachidonic acid | L + A<br>-------<br>P +A | Day 11<br>2h post dose | 1.05 | 0.84 | 1.32 |
| Platelet aggregation by collagen | L + A<br>-------<br>P +A | Day 11<br>2h post dose | 1.06 | 0.84 | 1.34 |

Geometric means for each treatment for platelet aggregation

| PD parameter | Timepoint | Treatment | Geometric means adjusted for baseline | Lower 90% CI | Upper 90% CI |
|---|---|---|---|---|---|
| % Platelet aggregation by arachidonic acid | Day 4 | L<br>P | 75.84<br>76.26 | 73.14<br>73.65 | 78.63<br>78.96 |
| % Platelet aggregation by collagen | Day 4 | L<br>P | 79.53<br>77.51 | 75.72<br>73.80 | 83.53<br>81.42 |
| % Platelet aggregation by arachidonic acid | Day 11<br>2h post dose | L + A<br>P + A | 5.07<br>4.82 | 4.32<br>4.14 | 5.95<br>5.62 |
| % Platelet aggregation by collagen | Day 11<br>2h post dose | L + A<br>P + A | 55.85<br>52.77 | 47.26<br>44.65 | 66.00<br>62.36 |

Similar data on serum and urinary thromboxane and prostacyclin levels are tabulated in detail in the study reports (Addendum to Module 5, Volume 85, Section 5.3.1.3.5).

**Conclusions:**

1. Lumiracoxib alone had no effect on arachidonic acid or collagen induced platelet aggregation in comparison to placebo.
2. Low dose aspirin strongly inhibited arachidonic acid stimulated platelet aggregation (geometric mean under placebo 76.3%, geometric mean under placebo and aspirin 4.8%). This inhibition was not effected to any clinically meaningful extent by the concurrent administration of lumiracoxib (geometric mean under lumiracoxib 75.8%, geometric mean under lumiracoxib and aspirin 5.1%).
3. Low dose aspirin had a modest inhibitory effect (approximately 30%) on collagen induced platelet aggregation, 77.5% (placebo) to 52.8% (placebo and aspirin). Again, this mild inhibition was not effected to any clinically meaningful extent by the concurrent administration of lumiracoxib, 79.5% (lumiracoxib) to 55.9% (lumiracoxib and aspirin).
4. The serum and urine eicosanoid endpoints manifested very high variability. All confidence intervals are outside the equivalence limits and therefore it cannot be definitively concluded that lumiracoxib does not affect the serum and urinary eicosanoids in the context of aspirin therapy.
5. Comparing Day 4 and Day 11 data, low dose aspirin strongly inhibited serum thromboxane concentration, 78.6 ng/mL to 3.4 ng/mL. This degree of inhibition was not affected by the concurrent administration of lumiracoxib (geometric mean under lumiracoxib: 65.2 ng/mL, geometric mean under lumiracoxib and aspirin: 2.3 ng/mL).
6. Similarly, low dose aspirin strongly inhibited urine thromboxane concentration (and production) by approximately 50%, 1129.8 pg/mL to 571.2 pg/mL. This inhibition was not effected by the concurrent administration of lumiracoxib: 847.4 pg/mL (lumiracoxib) to 391.4 pg/mL (lumiracoxib and aspirin).
7. Comparing Day 4 and Day 11 data, one week of low dose aspirin treatment strongly decreased serum prostacyclin concentrations, 465.2 pg/mL (placebo) to 34.9 pg/mL (placebo and aspirin). No additional decrease in serum prostacyclin concentration was noted when lumiracoxib was combined with low dose aspirin (343.6 pg/mL (lumiracoxib) to 34.2 pg/mL (lumiracoxib and aspirin).
8. Compared to baseline values, neither low dose aspirin alone nor the combination of low dose aspirin (at day 11) and lumiracoxib (at day 4), had any meaningful effect on the geometric mean urine prostacyclin concentration.

# 8. Addendum to the Clinical Overview

An addendum to the Clinical Overview has been written, entitled "Lumiracoxib for the treatment of osteoarthritis, acute pain (including primary dysmenorrhoea)".

This addendum is an excellent analysis of the risks and benefits of lumiracoxib in the context of TARGET study and identifies a number of unanswered questions which are important regarding the use of COX-2 selective inhibitors generally.

The efficacy conclusions are summarised below:
No studies in acute pain and dysmenorrhoea are presented in this Addendum to the Clinical Overview. However:

- Lumiracoxib 100 mg once daily or 200/100 mg once daily were both efficacious at 13 weeks in knee OA.
- Lumiracoxib 100 mg once daily and 200/100 mg once daily (pooled) showed efficacy comparable to that of celecoxib 200 mg once daily.

The safety conclusions are summarised below:
The conclusions presented in the original Clinical Overview are confirmed by the 2 new studies and are also extended to confirm new safety benefits:

- at 2 to 4 times the intended chronic therapeutic dose (400 mg once daily), there is a much lower risk of upper GI tract ulcer complications than with either naproxen or ibuprofen
- at 2 to 4 times the intended chronic therapeutic dose (400 mg once daily), there is no increase in CV risk compared to either naproxen or ibuprofen
- at the lower, intended therapeutic dose (100 mg once daily), the safety profile was qualitatively similar to that reported previously, with no new or unexpected findings

**The summary of risks is reproduced below:**
The risks of lumiracoxib and the target organs that can be affected remain the same as those associated with the use of any of the NSAID class of drugs. Although the type of risks have not changed, the likelihood of each type of unwanted event is now known to be lower or similar to that of other NSAIDs in common use (naproxen or ibuprofen).
Thus, with lumiracoxib there is a highly significant reduction in the incidence of GI ulcer complications and risks in other organ systems appear to be similar to those for other NSAIDs

**For the known upper GI tract risk** of developing ulcer complications with NSAIDs, lumiracoxib is now shown to be best in class among the NSAIDs with an incidence rate less than with ibuprofen or naproxen and close to that reported in the literature for placebo.

The TARGET study is the first to investigate ulcer complications successfully as a primary endpoint and has shown a substantial and highly significant reduction with lumiracoxib compared with naproxen or ibuprofen (=NSAIDs) (79% less in patients **not taking** aspirin, 66% less in all patients).
In patients **not taking** low dose aspirin, the absolute rate of ulcer complications with lumiracoxib (0.3 events per 100 patient years) is less than with naproxen and than with ibuprofen (1.4 and 1.2 events per 100 patient years with naproxen and ibuprofen, respectively), and similar to background rates reported with placebo in epidemiological studies. There was a trend for less ulcer complications in patients taking low-dose aspirin, but the study was not powered to show this difference.

**For the anticipated CV risks** associated with the potential loss of platelet aggregation inhibition, there were no differences in the incidence rates of the APTC endpoint in TARGET

between lumiracoxib and naproxen or ibuprofen (=NSAIDs), indicating that lumiracoxib at 2 to 4 times the intended therapeutic dose does not increase the overall CV risk.

For MIs, in patients **not taking** low dose aspirin, incidence rates were similar with lumiracoxib and ibuprofen, but lower with naproxen, probably because naproxen is anti-thrombotic at the studied dose (500 mg bid), as suggested in some epidemiologic and clinical studies. Consistent with this view is the finding that the lower incidence rate with naproxen was not seen in patients already receiving anti-thrombotic therapy by taking low dose aspirin.

**For the known liver risk** of developing serious hepatic adverse events, the incidence rate was somewhat higher with lumiracoxib at 2 to 4 times the chronic therapeutic dose than with ibuprofen or naproxen at standard doses. However, the elevations in liver enzymes were reversible after discontinuing treatment with lumiracoxib.
To minimize the risk of liver damage, the hepatic expert has recommended that lumiracoxib be used at 100 to 200 mg od for long-term treatment (OA) and at 400 mg od for short-term treatment (acute pain and dysmenorrhoea).

**For the known renal risks** associated with the reduction in vasodilatory prostaglandins, there were no differences in the incidence rates of renal events or development of hypertension with lumiracoxib compared to ibuprofen or naproxen. In contrast, lumiracoxib appeared to be slightly superior with regard to the development or exacerbation of hypertension.

**The following unanswered risk questions were identified:**
Some unanswered risk questions relevant to the GI benefit of lumiracoxib compared to other NSAID are:

- the degree of benefit with lumiracoxib regarding upper GI tract ulcer complications in patients taking low-dose aspirin, in whom a trend towards less ulcer complications was seen, but which could not be verified statistically.
- how best to use lumiracoxib, or ibuprofen or naproxen, in patients with a high CV risk (e.g. recent MI or stroke, symptomatic congestive heart failure, unstable angina), who were excluded from the TARGET study for safety reasons

<u>The following recommendations on the use of lumiracoxib were made:</u>
As the liver effects are late and probably dose-dependent, and the GI benefits come from the COX-2 selectivity of the drug (not the dose used), this offers 2 strategies for optimizing the benefit/risk profile:

1. To use lower doses for chronic conditions,
2. To limit the duration of treatment when higher doses are needed for acute pain indications.

Both strategies are recommended as follows based on the results of the 2 major clinical studies presented in this Amended Clinical Overview:

- For OA, the recommended starting dose is 100 mg od and in patients who fail to respond, the dose may be increased to 100 mg bid or 200 mg od.
- For acute pain and primary dysmenorrhoea, the originally recommended dose of 400 mg od for up to 1 month is unchanged but the use of an “acute pain pack” is proposed, to prevent chronic use of the 400 mg dose.
- As lumiracoxib was shown **not** to interfere with the beneficial effects of aspirin for CV prophylaxis, patients with high CV risk and taking low dose aspirin can be considered for concomitant lumiracoxib therapy.

Regarding cardiovascular safety, the cardiovascular expert concluded as follows:
*"The principal CV outcome, defined as the APTC endpoint, was infrequent but similar across the treatment groups, suggesting no overall increased risk of cardiovascular events among patients assigned to lumiracoxib. There were no differences in any of the individual components of the composite except myocardial infarction. There were more MIs among the patients assigned lumiracoxib when compared with naproxen but a similar number when comparing lumiracoxib with ibuprofen. Naproxen, at doses of 500 mg bid, has been shown to suppress thromboxane B2 production, a marker of platelet COX-1 activity, to a similar level as seen with low-dose aspirin, 100 mg daily. In TARGET patients taking low-dose ASA, there was no difference noted in MI rates among those assigned to lumiracoxib compared with either of the NSAIDs. There were no differences among the treatment groups in the occurrence of other thrombotic events.*

*Since it is clear that lumiracoxib offers superior GI outcome compared with the NSAIDS, including among the group of patients taking low-dose ASA, the TARGET results carry useful clinical practice implications. In patients with OA but without a history of a past CV event or without enough risk factors to be considered high CV risk, lumiracoxib appears to be a better choice than the NSAIDS given the superior GI benefits. Among patients with CV disease or at high risk for CV disease who require treatment for OA, a reasonable choice would be to balance the GI benefits against the CV risks by treating patients concomitantly with low-dose ASA and lumiracoxib."*

Regarding hepatic safety, the liver expert concluded with the following statements:
*"The data from the TARGET Study indicates that lumiracoxib at a dose of 400 mg od may induce reversible liver enzyme elevations, mostly hepatocellular in nature and in all cases reversible after stopping the drug. Only a small number of cases were assessed as showing evidence of liver injury (defined as ALT > 5 x ULN and bilirubin > 3 mg/dl). Lumiracoxib at a dose of 400 mg od appears to give a higher frequency of adverse liver effects than the comparator NSAIDs (naproxen 500 mg bid and ibuprofen 800 mg tid) used in this study.*

*Therefore, the maximum dose of 200 mg od is recommended for chronic use, and the 400 mg od dose use should be limited to short term treatment up to 4 weeks."*

Regarding renal safety, the renal expert concluded with the following statements:
*"The TARGET trial confirms the overall favorable renal safety of lumiracoxib that has previously been demonstrated in the safety analysis of prior lumiracoxib clinical trials. As predictable from the apparent physiological role of cyclooxygenase and specifically Cox-2 in the regulation and maintenance of glomerular ultrafiltration, lumiracoxib modestly raises serum creatinine levels, usually within the normal range. More severe impairments of renal function that are expected with NSAIDs as well as with coxibs occur rarely with lumiracoxib. Compared to NSAIDs, lumiracoxib may provide a small but nevertheless clinically meaningful safety advantage with respect to hypertension-related side effects. Moreover, the TARGET trial demonstrates that from a renal stand point it is safe to prescribe lumiracoxib concomitantly with low-dose aspirin."*

# 9. Safety data from on-going or unreported studies

The applicant has provided summary safety data from the following studies:

| Studies since MAA submission | Dosing Regimen | Study Status | CSR Status |
|---|---|---|---|
| RA 2335 ** 3 months core study | Lumiracoxib 200mg OD<br>Naproxen 500mg BD<br>Placebo | Completed | May 2003 |
| Dental pain ** (Study 2362) | Lumiracoxib 200mg<br>Lumiracoxib 200mg with an optional re-dose<br>Placebo | Completed | Completed |
| Dental pain ** (Study 2336) | Lumiracoxib 400 mg<br>Rofecoxib 50 mg<br>Placebo | Completed | Completed |
| Dysmenorrhoea ** 200mg (Study 2353) | Lumiracoxib200mg OD<br>Lumiracoxib 200mg with an optional re-dose<br>Naproxen.500 mg BD<br>Placebo | Completed | In preparation |
| Dysmenorrhoea ** 200mg (Study 2358) | Lumiracoxib 200mg OD<br>Lumiracoxib.200mg with an optional re-dose<br>Placebo | Completed | In preparation |
| Tension-type headache, single dose (Study 2351) | Lumiracoxib 200mg<br>Lumiracoxib 400mg<br>Placebo | Completed | Completed |
| CP COX-2 selectivity versus Naproxen (Study 2320) | Lumiracoxib 400 mg OD<br>Lumiracoxib 800 mg OD<br>Placebo (to Lum.) OD<br>Naproxen 500 mg BD<br>Ex vivo whole blood inhibition of PGE2 and TXB2 to measure COX-2 and COX-1 inhibition | Completed | In preparation |
| CP study PK in mild and moderate renal impaired patients (Study 2350) | Lumiracoxib 200mg SD in Mild and moderate RI and matched healthy subjects<br>PK of Lumiracoxib and 3 metabolites | Completed. | Completed |

** These studies were large studies with patient numbers ranging from 140 to 458.

Results are summarized overleaf.

| Study | Pts on Lumira | Safety issues |
|---|---|---|
| 2335 | n = 458 | 2 patients with myocardial infarction |
| | | 3 patient with raised ALT > 3 x ULN |
| | | 1 patient with raised ALT > 5 x ULN |
| | | 62 patients with Cr Clearance > 25% decrease from baseline |
| | | 2 patients with more than doubling of serum creatinine |
| 2362 | n = 140 | Nothing of significance, especially liver problems |
| | | 1 patient with Cr Clearance > 25% decrease from baseline |

| | | |
|---|---|---|
| 2336 | n = 318 | Nothing of significance, especially liver problems |
| 2353 | n = 253 | Nothing of significance, especially liver problems |
| | | 2 patients with Cr Clearance > 25% decrease from baseline |
| 2358 | n = 208 | Nothing of significance, especially liver problems |
| 2351 | | No laboratory monitoring in this single dose study |
| 2320 | n = 33 | Nothing of significance, especially liver problems |
| 2350 | n = 24 | Nothing of significance, especially liver problems |

# 10. Updated Conclusions

The Clinical Assessor's original conclusions (the section number of each item corresponds to the number in the original Assessment Report) are shown below with **updated comments in italics:**

**19.1 Pharmacology:**

Pharmacodynamics: Satisfactory.
***Updated conclusion:*** *No comment*

Pharmacokinetics: Dose-linearity is lost at doses of 1200mg QD and higher. The drug is metabolised by CYP2C9 and highly bound to plasma albumin.
***Updated conclusion:*** *No comment*

Special populations: Lumiracoxib has not been studied in juvenile arthritis.

It is possible that individuals who are homozygous for *3 allele would have very high plasma levels but this genotype is extremely rare in Western Caucasian population.

Exposure to lumiracoxib is lower in patients with end stage renal disease compared to normal subjects. Compared to normal subjects, mean exposure to 4'-hydroxy-lumiracoxib is not significantly increased in ESRD patients and exposure to 4'-hydroxy-5-carboxy-lumiracoxib is increased substantially (by about 7 times).
***Updated conclusion:*** *No comment*

**19.2 Dose-response:**

Osteoarthritis: Poor characterization of optimal dose
***Updated conclusion:*** *New dosing regimen has been studied and found to be effective*

Rheumatoid arthritis: No dose was found to be effective relative to placebo.
***Updated conclusion:*** *No comment – this indication is not requested*

Primary dysmenorrhoea: No specific study – dose selection extrapolated from studies in acute pain in post-dental surgery patients. 400mg QD dose appears appropriate.
***Updated conclusion:*** *No comment*

| | |
|---|---|
| Acute pain | The model used is acute pain in post-dental surgery patients. It is difficult to distinguish clearly between 100mg and 200mg doses of lumiracoxib since these two doses have not been compared directly.<br>***Updated conclusion:*** *No comment* |

**19.3 Efficacy:**

| | |
|---|---|
| Osteoarthritis | Lumiracoxib is effective in the symptomatic relief of OA but a dose of 200mg QD has a better risk/benefit profile<br>***Updated conclusion:*** *The applicant has shown 100mg daily dose to be effective* |
| Rheumatoid arthritis | Lumiracoxib is **NOT** effective in the symptomatic treatment of RA.<br>***Updated conclusion:*** *No comment – this indication is not requested* |
| Primary dysmenorrhoea | 400mg QD dose is appropriate as long as the indication is restricted to moderate to severe primary dysmenorrhoea.<br>***Updated conclusion:*** *No comment – indication restricted as required.* |
| Acute pain | 400mg QD dose is appropriate as long as the indication is restricted to short-term relief of moderate to severe acute pain associated with dental surgery and orthopaedic surgery<br>***Updated conclusion:*** *No comment – indication restricted as required.* |

**19.4 Safety:**

| | |
|---|---|
| Drug interactions: | Lumiracoxib is metabolised by CYP2C9 and highly protein bound. The possibility of protein-displacement interactions with other CYP2C (substrates of narrow therapeutic index (phenytoin) is a real one.<br>***Updated conclusion:*** *A warning on interaction with warfarin and phenytoin has been included*<br><br>Drugs that are likely to be used by the target population include prednisolone and aspirin. No interaction studies have been carried out against these drugs. Neither is there an interaction study with digoxin.<br>***Updated conclusion:*** *An interaction study with aspirin is reassuring* |
| Clinical safety: | Lumiracoxib has an acceptable profile of clinical safety. But certain renal and immunologic reactions need to be included in SPC. The clinical safety of 400mg QD dose is worse than that of 200mg QD dose.<br>***Updated conclusion:*** *These have now been included* |
| Laboratory safety | Lumiracoxib is a potentially moderate nephrotoxin and renal adverse effects are a source of concern. |

| | |
|---|---|
| | ***Updated conclusion:*** *The risk is low but it is now included in the SPC. TARGET confirms the renal safety of lumiracoxib. It is equivalent to other NSAIDs (COX-2 selective and COX-2-non-selective. The safety of 100mg and 200mg doses does not warrant laboratory monitoring of renal function.* |
| Gastrointestinal safety | Satisfactory relative to other coxibs and superior to classical non-selective NSAIDs but there is good evidence of a dose-toxicity relationship within the dose range proposed by the applicant.<br>***Updated conclusion:*** *TARGET confirms the superiority of 100mg dose of lumiracoxib over classical non-selective NSAIDs* |
| Hepatotoxicity: | Lumiracoxib is a potentially moderate, dose-dependent hepatotoxin with reports of hepatitis at 200mg QD dose in clinical trials and 4 reports at 400mg QD dose in one major ongoing outcome study (TARGET)<br>***Updated conclusion:*** *The risk is low but it is now included in the SPC. TARGET confirms the hepatic safety of lumiracoxib. The safety of 100mg and 200mg doses does not warrant laboratory monitoring of hepatic function.* |
| Nephrotoxicity: | Although pre-existing renal dysfunction does not influence lumiracoxib pharmacokinetics, the pharmacodynamic effects of lumiracoxib in patients with renal dysfunction is a potential issue of clinical relevance.<br><br>***Updated conclusion:*** *The risk is low but it is now included in the SPC. TARGET confirms the renal safety of lumiracoxib. The safety of 100mg and 200mg doses does not warrant laboratory monitoring of renal function.* |
| Prothrombotic | Lumiracoxib has a slightly higher risk of prothrombotic effects events relative to placebo.<br>***Updated conclusion:*** *TARGET is a landmark study that has clarified the previous confusion on the prothrombotic potential of COX-2 selective inhibitors. There were more myocardial infarctions among the patients assigned lumiracoxib when compared with naproxen but a similar number when comparing lumiracoxib with ibuprofen. Naproxen, at doses of 500 mg bid, has been shown to suppress thromboxane B2 production, a marker of platelet COX-1 activity, to a similar level as seen with low-dose aspirin, 100 mg daily.* |
| Myelotoxocity: | No evidence of any concern at present.<br>***Updated conclusion:*** *No comment* |
| ECG effects: | No evidence of any concern at present.<br>***Updated conclusion:*** *No comment* |
| Articular safety: | No evidence of an adverse effect on joint structure in osteoarthritis following a year of treatment.<br>***Updated conclusion:*** *No comment* |

SPC: Needs a number of changes described overleaf, in particular:

1. Removing the indication in rheumatoid arthritis
2. The indication in primary dysmenorrhoea should be restricted to the population studied (that is, patients with moderate to severe primary dysmenorrhoea).
3. The indication should be restricted to the population studied (that is, patients with moderate to severe pain following dental or orthopaedic surgery).
4. Downward revision to the posology for osteoarthritis
5. Additional or amended contraindications in respect of patients with renal or hepatic dysfunction.
6. Inclusion of a caution for use in patients with ischaemic heart disease
7. Inclusion of an advice to monitor renal and liver function tests at baseline and every month for the first 6 months.
8. Addition of other adverse drug events and drawing attention to the greater frequency of certain events with 400mg QD dose relative to 200mg QD dose.
9. Revisions to the texts of section 5.1 on Pharmacodynamics to reflect better and briefly the data from the clinical trials.

***Updated conclusion:*** *The SPC has been amended as required – except for item 7 above.*

*An advice to monitor renal and liver function tests at baseline and every month for the first 6 months was* ***NO LONGER CONSIDERED NECESSARY*** *in view of downward dose change.*

Lumiracoxib has an acceptable risk/benefit profile in the indications claimed and at the posology now proposed.

# APPENDIX I

## Variation 1 Assessment Report

# FINAL VARIATION ASSESSMENT REPORT - ADDENDUM

**PL NUMBER :-**

| | |
|---|---|
| Prexige 100mg (lumiracoxib) tablets | PL 00101/ 0677 |
| Prexige 200mg tablets | PL 00101/ 0668 |
| Prexige 400mg tablets | PL 00101/ 0669 |

**APPLICATION NUMBER :-**

**PRODUCT NAME: :-**
Prexige

**ACTIVE INGREDIENT(S)/LEVEL :-**
lumiracoxib 100 mg
lumiracoxib 200 mg
lumiracoxib 400 mg

**LINKED/RELATED VARIATIONS :-**

| | |
|---|---|
| Exforge 100mg tablets | PL 00101/ 0698 |
| Exforge 200mg tablets | PL 00101/ 0699 |
| Exforge 400mg tablets | PL 00101/ 0700 |
| | |
| Stellige 100mg tablets | PL 00101/ 0695 |
| Stellige 200mg tablets | PL 00101/ 0696 |
| Stellige 400mg tablets | PL 00101/ 0697 |
| | |
| Frexocel 100mg tablets | PL 00101/ 0692 |
| Frexocel 200mg tablets | PL 00101/ 0693 |
| Frexocel 400mg tablets | PL 00101/ 0694 |

**FURTHER PROPOSED CHANGES**

**In section 4.2 (Posology and method of administration) after the statement about recommended dose under the heading 'Acute Pain':**

"Relief of acute pain due to dental surgery: the maximum treatment duration in clinical studies was 24 hours.

Relief of acute pain due to orthopaedic surgery: the maximum treatment duration in clinical studies was 5 days.

Relief of pain due to primary dysmenorrhea: the maximum treatment duration in clinical studies was 3 days.

As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used. The patients need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis."

**In section 4.4 (Special warnings and special precautions for use) of the SmPC, to change (under the heading 'GI effects'):**

"Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], potentially resulting in a fatal outcome, have rarely occurred in patients treated with lumiracoxib.

…

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for lumiracoxib, other COX-2 inhibitors and NSAIDs when taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 5.1)."

**To:**
"Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in a fatal outcome, have occurred in patients treated with lumiracoxib. In clinical studies, few patients (<0.3%) treated with lumiracoxib developed perforations, obstruction or bleeds (POBs).
…
There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when lumiracoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 5.1)."

**And to replace the following (under the heading of 'Hepatic Effects':**
Marked elevations (>8xULN) have been observed in 0.0% with 100 mg once or twice daily and 0.19% of patients at 200 mg once daily.

**With:**
"Marked elevations (>8xULN) have been observed in 0.3% with 100 mg once or twice daily and 0.6% of patients at 200 mg once daily."

**And to remove the following sentence under the heading Cardiovascular Effects'):**
"In a metaanalysis of all clinical trials with lumiracoxib including all daily doses tested, the relative risk (95% CI) compared to placebo of myocardial infarction, cardiovascular death or stroke were 1.08 (0.41, 2.86) for the overall population (lumiracoxib n = 7011)."

**And also to change the following under the heading of 'General' the following sentence:**
'If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of lumiracoxib therapy should be discontinued.'

**To:**
'If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of lumiracoxib therapy should be considered.'

**In section 4.5 (Interaction with other medicinal products and other forms of interaction) of the SmPC**
To change the heading 'Diuretics and Antihypertensive Drugs' to "Diuretics, ACE inhibitors and Angiotensin II Antagonists"

**In section 5.1 (Pharmacodynamic properties) to replace the following paragraphs:**
"**Safety**
**The Therapeutic lumiracoxib Arthritis Research and Gastrointestinal Event Trial (TARGET)**
TARGET, a 12-month, double-blind, phase III study included 18,325 OA patients randomized to lumiracoxib 400 mg o.d. (two to four times the recommended OA dose),

naproxen 500 mg b.i.d or ibuprofen 800 mg t.i.d. TARGET included patients taking low-dose ASA (75-100 mg daily) for primary or secondary prevention of coronary heart disease. Randomization was stratified by low-dose ASA use (24 % of patients in the overall study population) and age.

**Gastrointestinal Effect in TARGET (12-month study)**

The primary endpoint was time to event distribution of definite or probable upper gastrointestinal tract ulcer (UGIT) complications (POBs).

- In the population not using low-dose aspirin, the incidence of POBs was 14/6950 patients (0.2%) for lumiracoxib versus 64/6968 patients (0.92%) for NSAIDs, with a HR of 0.21 (p<0•0001).
- In the low dose ASA group the incidence of POBs was 15/2167 patients (0.69%) for lumiracoxib versus 19/2159 patients (0.88%) for NSAIDs, with a hazard ratio (HR) of 0.79 (not statistically significant).
- In the overall population, the incidence of POBs was 29/9117 patients (0.32%) for lumiracoxib versus 83/9127 patients (0.91%) for NSAIDs, with a HR of 0.34 (p<0•0001).

**Cardiovascular Effect in TARGET (12-month study)**

The primary cardiovascular (CV) endpoint studied was the Antiplatelet Trialists' Collaboration (APTC) endpoint: confirmed or probable myocardial infarction (clinical or silent), stroke (ischemic or haemorrhagic) and CV death. There were no significant differences between lumiracoxib and NSAIDs. However, the APTC event rate was numerically higher for lumiracoxib than for naproxen but lower than for ibuprofen.

- In the population not using low-dose aspirin, the incidence of APTC events was 35/6950 patients (0.50%) for lumiracoxib versus 27/6968 patients (0.39%) for NSAIDs, with a HR of 1.22. When compared separately to ibuprofen and naproxen, the HR were 0.94 and 1.49, respectively.
- In the low-dose ASA group, the incidence of APTC events was 24/2167 patients (1.11 %) for lumiracoxib versus 23/2159 patients (1.07%) for NSAIDs, with a hazard ratio (HR) of 1.04. When compared separately to ibuprofen and naproxen, the HR were 0.56 and 1.42, respectively.
- In the overall population, the incidence of APTC events was 59/9117 patients (0.65 %) for lumiracoxib versus 50/9127 patients (0.55%) for NSAIDs, with a HR of 1.14. When compared separtely to ibuprofen and naproxen, the HR were 0.76 and 1.46, respectively.

**MI events in TARGET (12-month study)**

There was no statistically significant difference between lumiracoxib and NSAIDs for incidence of MI (clinical MI and silent MI).

- In the population not using low-dose aspirin, the incidence of MI events was 14/6950 patients (0.20%) for lumiracoxib versus 9/6968 patients (0.13%) for NSAIDs, with a HR of 1.47. When compared separately to ibuprofen and naproxen, the HR were 0.75 and 2.37, respectively.
- In the low-dose ASA group, the incidence of MI events was 9/2167 patients (00.42%) for lumiracoxib versus 8/2159 patients (0.37%) for NSAIDs, with a HR of 1.14. When compared separately to ibuprofen and naproxen, the HR were 0.47 and 1.36, respectively.
- In the overall population, the incidence of MIs was 23/9117 patients (0.25%) for lumiracoxib versus 17/9127 patients (0.19%) for NSAIDs, with a HR of 1.31. When compared separately to ibuprofen and naproxen, the HR were 0.66 and 1.77, respectively.

The cardiovascular safety of lumiracoxib beyond 1 year of use has not been established.

**Cardiorenal effect in TARGET (12-month study)**
For systolic blood pressure, mean change from baseline were +0.4 mmHg for lumiracoxib and +2.1 mmHg for NSAIDs (p<0.0001). For diastolic blood pressure, mean change from baseline were -0.1 mmHg for lumiracoxib and +0.5 mmHg for NSAIDs (p<0.0001). The number of discontinuations in TARGET due to oedema was not significantly different between lumiracoxib (39) and NSAIDs (46). The number of discontinuations due to hypertension-related events was also not significantly different between lumiracoxib (31) and NSAIDs (46).

**With:**
**The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)**
TARGET, a 12-month, double-blind, phase III study included 18,325 OA patients randomized to lumiracoxib 400 mg o.d. (two to four times the recommended OA dose), naproxen 500 mg b.i.d or ibuprofen 800 mg t.i.d. TARGET included patients taking low-dose ASA (75-100 mg daily) for primary or secondary prevention of coronary heart disease. Randomization was stratified by low-dose ASA use (24 % of patients in the overall study population) and age.

**Gastrointestinal Effect in TARGET (12-month study)**
The primary endpoint was time to event distribution of definite or probable upper gastrointestinal tract ulcer (UGIT) complications (POBs).

- In the population not using low-dose aspirin, the incidence of POBs was 14/6950 patients (0.2%) for lumiracoxib versus 64/6968 patients (0.92%) for NSAIDs, with a HR of 0.21 [95% CI 0.12-0.37] (p<0•0001).
- In the low dose ASA group the incidence of POBs was 15/2167 patients (0.69%) for lumiracoxib versus 19/2159 patients (0.88%) for NSAIDs, with a hazard ratio (HR) of 0.79 [95% CI 0.40-1.55] (not statistically significant).
- In the overall population, the incidence of POBs was 29/9117 patients (0.32%) for lumiracoxib versus 83/9127 patients (0.91%) for NSAIDs, with a HR of 0.34 [95% CI 0.22-0.52] (p<0•0001).

**Cardiovascular Effect in TARGET (12-month study)**
The primary cardiovascular (CV) endpoint studied was the Antiplatelet Trialists' Collaboration (APTC) endpoint: confirmed or probable myocardial infarction (clinical or silent), stroke (ischemic or haemorrhagic) and CV death. There were no significant differences between lumiracoxib and NSAIDs. However, the APTC event rate was numerically higher for lumiracoxib than for naproxen but lower than for ibuprofen.

- In the population not using low-dose aspirin, the incidence of APTC events was 35/6950 patients (0.50%) for lumiracoxib versus 27/6968 patients (0.39%) for NSAIDs, with a HR of 1.22 [95% CI 0.74-2.02] p=0.4343. When compared separately to ibuprofen and naproxen, the HR were 0.94 [95% CI 0.44-2.04] p=0.8842 and 1.49 [95% CI 0.76-2.92] p=0.2417, respectively.
- In the low-dose ASA group, the incidence of APTC events was 24/2167 patients (1.11 %) for lumiracoxib versus 23/2159 patients (1.07%) for NSAIDs, with a hazard ratio (HR) of 1.04 [95% CI 0.59-1.84] p=0.8918. When compared separately to ibuprofen and naproxen, the HR were 0.56 [95% CI 0.20-1.54] p=0.2603 and 1.42 [95% CI 0.70-2.90] p=0.3368, respectively.
- In the overall population, the incidence of APTC events was 59/9117 patients (0.65%) for lumiracoxib versus 50/9127 patients (0.55%) for NSAIDs, with a HR of 1.14 [95% CI 0.78-1.66] p=0.5074. When compared separately to ibuprofen and naproxen, the HR were 0.76 [95% CI 0.41-1.40] p=0.3775 and 1.46 [95% CI 0.89-2.37] p=0.1313, respectively.

**MI events in TARGET (12-month study)**

There was no statistically significant difference between lumiracoxib and NSAIDs for incidence of MI (clinical MI with silent MI).

- In the population not using low-dose aspirin, the incidence of MI events was 14/6950 patients (0.20%) for lumiracoxib versus 9/6968 patients (0.13%) for NSAIDs, with a HR of 1.47 [95% CI 0.63-3.39] p=0.3706. When compared separately to ibuprofen and naproxen, the HR were 0.75 [95% CI 0.20-2.79] p=0.6669 and 2.37 [95% CI 0.74-7.55] p=0.1454, respectively.
- In the low-dose ASA group, the incidence of MI events was 9/2167 patients (0.42%) for lumiracoxib versus 8/2159 patients (0.37%) for NSAIDs, with a HR of 1.14 [95% CI 0.44-2.95] p=0.7899. When compared separately to ibuprofen and naproxen, the HR were 0.47 [95% CI 0.04-5.14] p=0.5328 and 1.36 [95% CI 0.47-3.93] p=0.5658, respectively.
- In the overall population, the incidence of MIs was 23/9117 patients (0.25%) for lumiracoxib versus 17/9127 patients (0.19%) for NSAIDs, with a HR of 1.31 [95% CI 0.70-2.45] p=0.4012. When compared separately to ibuprofen and naproxen, the HR were 0.66 [95% CI 0.21-2.09] p=0.4833 and 1.77 [95% CI 0.82-3.84] p=0.1471, respectively.

The cardiovascular safety of lumiracoxib beyond 1 year of use has not been established.

**Cardiorenal effect in TARGET (12-month study)**

For systolic blood pressure, mean change from baseline were +0.4 mmHg for lumiracoxib and +2.1 mmHg for NSAIDs (p<0.0001). For diastolic blood pressure, mean change from baseline were -0.1 mmHg for lumiracoxib and +0.5 mmHg for NSAIDs (p<0.0001). The number of discontinuations in TARGET due to oedema was not significantly different between lumiracoxib (43) and NSAIDs (55). The number of discontinuations due to hypertension-related events was also not significantly different between lumiracoxib (37) and NSAIDs (52).

## BACKGROUND

Following a European-wide Article 31 referral, a number of core changes to be made to the SmPC for all COX-2 selective inhibitors were agreed by members of the CHMP. Available evidence suggests that use of any selective COX-2 inhibitor may increase risk of thrombotic events (e.g. myocardial infarction and stroke) compared with placebo and some NSAIDs. This risk may increase with dose and duration of exposure. The MA holder for each COX-2 selective inhibitor has been asked to submit a type II variation to update the SmPC and PIL for their COX-2 inhibitor to include these core changes. These changes were outlined in the preliminary assessment report.

## SUPPORTING EVIDENCE

The MA holder has supplied amended SmPCs for Prexige 100mg lumiracoxib, Prexige 200 mg lumiracoxib and Prexige 400 mg lumiracoxib. They have also supplied an updated PIL which applies to all 3 lumiracoxib products, as well as summary tables which detail where the SmPC has changed for 100 mg and 200 mg lumiracoxib (same changes apply to both concentrations), and for 400 mg.

This is a bulk variation which also deals with the duplicate products Stellige, Exforge and Frexocel.

## EVALUATION

## CHANGES TO THE SmPC

**Section 4.2 (Posology and method of administration)**

***Assessor's comment:*** *These changes are acceptable.*

**Section 4.4 (Special warnings and special precautions for use)**

***Assessor's comment:*** *These changes are acceptable.*

**Section 4.5 (Interaction with other medicinal products and other forms of interaction)**

***Assessor's comment:*** *These changes are acceptable.*

**Section 5.1 (Pharmacodynamic properties):**

***Assessor's comment:*** *These changes are acceptable.*

**DECISION –**
This variation is approved.

**DATE :-** 28 Sep. 07

# VARIATION ASSESSMENT REPORT

**PL NUMBER :-**

| | |
|---|---|
| Prexige 100mg (lumiracoxib) tablets | PL 00101/ 0677 |
| Prexige 200mg tablets | PL 00101/ 0668 |
| Prexige 400mg tablets | PL 00101/ 0669 |

**APPLICATION NUMBER :-**

**PRODUCT NAME: :-**
Prexige

**ACTIVE INGREDIENT(S)/LEVEL :-**

lumiracoxib 100 mg
lumiracoxib 200 mg
lumiracoxib 400 mg

**LINKED/RELATED VARIATIONS :-**

| | |
|---|---|
| Exforge 100mg tablets | PL 00101/ 0698 |
| Exforge 200mg tablets | PL 00101/ 0699 |
| Exforge 400mg tablets | PL 00101/ 0700 |
| | |
| Stellige 100mg tablets | PL 00101/ 0695 |
| Stellige 200mg tablets | PL 00101/ 0696 |
| Stellige 400mg tablets | PL 00101/ 0697 |
| | |
| Frexocel 100mg tablets | PL 00101/ 0692 |
| Frexocel 200mg tablets | PL 00101/ 0693 |
| Frexocel 400mg tablets | PL 00101/ 0694 |

**PROPOSED CHANGES**

**In section 4.1 (Therapeutic Indications) of the SmPC, to add:**
'The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see sections 4.3, 4.4)'

**In section 4.2 (Posology and method of administration) of the SmPC, to add after the existing sentence under the heading 'Osteoarthritis':**
'Patients should not exceed this dose. The clinical experience was restricted to 12 months'

**And after the statement about recommended dose under the heading 'Acute Pain':**

'Patients should not exceed this dose and the treatment duration should not exceed 5 days.

Relief of acute pain due to dental surgery: the clinical experience was restricted to a single dose treatment (24 hours).

Relief of acute pain due to orthopaedic surgery: the clinical experience was restricted to 5 days of treatment.

Relief of pain due to primary dysmenorrhea: the clinical experience was restricted to 3 days of treatment.'

**In section 4.3 (Contra-indications) of the SmPC, to change:**

'Patients with severe congestive heart failure' **to** 'Patients with congestive heart failure (NYHA II-IV).'

**And to add:**

'Established ischaemic heart disease and/or cerebrovascular disease.'

**In section 4.4 (Special warnings and special precautions for use) of the SmPC, to change (under the heading 'GI effects'):**

'In clinical studies, few patients (<0.1%) treated with lumiracoxib developed perforations, obstruction or bleeds (POBs). Independent of treatment, patients with a history of gastrointestinal (GI) ulcer, bleed, perforation, or obstruction, and patients greater than 65 years of age are known to be at a higher risk of upper GI tract complications. '

**To:**

'Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], potentially resulting in a fatal outcome, have rarely occurred in patients treated with lumiracoxib.

Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs: the elderly, patients using any other NSAID or ASA concomitantly, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for lumiracoxib, other COX-2 inhibitors and NSAIDs when taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 5.1).

In clinical studies, few patient (<0.1%) treated with lumiracoxib developed perforations, obstructions or bleeds (POBs).'

**And also to replace the following paragraph (under the heading 'Cardiovascular Effects'):**

'COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for cardiovascular prophylaxis because of their lack of effect on platelets. Because lumiracoxib, a member of this class, does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued and if indicated should be considered in patients at risk of or with a history of cardiovascular or other thrombotic events (See 4.5 Interaction with other medicinal products and other forms of interaction and 5.1 pharmacodynamic properties)'

**With:**

'COX-2 selective inhibitors are not a substitute for ASA for prophylaxis of cardiovascular thromboembolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued. (See 4.5 Interaction with other medicinal products and other forms of interaction and 5.1 pharmacodynamic properties)'

**And also to replace the following paragraphs (under the heading 'Cardiovascular Effects'):**

'Because of the lack of antiplatelet activity of COX-2 selective inhibitors, caution should be exercised in patients with a medical history of ischaemic heart disease, peripheral vascular disease and cerebrovascular disease. In clinical trials with lumiracoxib at daily doses of

200mg and 400mg, the relative risk (95% CI) compared to placebo of myocardial infarction, cardiovascular death or stroke were 1.04 (0.36, 3.05) for the overall population (lumiracoxib n = 5431) and 1.19 (0.27, 5.29) for patients at high CV risk (lumiracoxib n = 2627).
Appropriate measures should be taken and discontinuation of lumiracoxib therapy should be considered if there is clinical evidence of symptomatic deterioration in the condition of these patients.'

**With:**
'Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAID's. As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used. The patients need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis. (See section 4.2, 4.3, 4.8 and 5.1)
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with lumiracoxib after careful consideration (see section 5.1)
In a metaanalysis of all clinical trials with lumiracoxib including all daily doses tested, the relative risk (95% CI) compared to placebo of myocardial infarction, cardiovascular death or stroke were 1.08 (0.41, 2.86) for the overall population (lumiracoxib n = 7011).'

**And also to add under a heading of 'General' the following sentence:**
'If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of lumiracoxib therapy should be discontinued.'

**In section 4.5 (Interaction with other medicinal products and other forms of interaction) of the SmPC, to change the following paragraph under the heading 'Diuretics and Antihypertensive Drugs':**

'NSAIDs may reduce the effect of diuretics and antihypertensive drugs. In some patients with compromised renal function, the co-administration of an ACE inhibitor and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, which is usually reversible. These interactions should be given consideration in patients taking lumiracoxib concomitantly with ACE-inhibitors.'

**To:**
'NSAIDs may reduce the effect of diuretics and antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking lumiracoxib concomitantly with ACE-inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.'

**Also in section 4.5, to remove the following subheading:**
'The effect of lumiracoxib on the PK of other drugs'

**In section 5.1 (Pharmacodynamic properties) to replace the following paragraphs:**

'Lumiracoxib is an orally active, selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range.

Cyclo-oxygenase is responsible for the generation of prostaglandins. Two isoforms, COX-1 and COX-2, have been identified. COX-1 is constitutively expressed in a number of tissues, including stomach, intestine, kidney, and in platelets. COX-2 has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever.

Across clinical pharmacology studies, lumiracoxib produced dose-dependent inhibition of COX-2 in plasma without inhibition of COX-1. Selective inhibition of COX-2 by lumiracoxib provides anti-inflammatory and analgesic effects. Administration of 100mg, 200 mg or 400 mg once daily leads to > 90% peak inhibition of COX-2. There is no significant inhibition of COX-1 (assessed as *ex vivo* inhibition of thromboxane $B_2$) up to 800 mg in healthy volunteers.

Lumiracoxib at 800 mg daily did not lead to clinically meaningful inhibition of gastric prostaglandin synthesis and had no effect on platelet function.

Approximately 5400 patients were treated with lumiracoxib 200 mg or 400 mg once daily up to 52 weeks. There was no discernible difference in the rate of serious thrombotic cardiovascular events between patients receiving lumiracoxib 200 mg, 400 mg, placebo, non-selective NSAIDs or other COX-2 inhibitors. In the lumiracoxib 200 mg and 400 mg group the relative risk to develop a myocardial infarction, cardiovascular death and stroke was 1.04 (95% CI 0.36-3.05) compared to placebo.'

**With:**
'Lumiracoxib is an orally active, selective cyclooxygenase-2 (COX-2) inhibitor within the clinical dose range.

Cyclo-oxygenase is responsible for generation of prostaglandins. Two isoforms, COX-1 and COX-2 have been identified. COX-2 is the isoform of the enzyme that has been shown to be induced by pro-inflammatory stimuli and has been postulated to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established. Across clinical pharmacology studies, lumiracoxib produced dose-dependent inhibition of COX-2 in plasma without inhibition of COX-1. Selective inhibition of COX-2 by lumiracoxib provides anti-inflammatory and analgesic effects. Administration of 100mg, 200 mg or 400 mg once daily leads to > 90% peak inhibition of COX-2. There is no significant inhibition of COX-1 (assessed as *ex vivo* inhibition of thromboxane $B_2$) up to 800 mg in healthy volunteers.

Lumiracoxib at 800 mg daily did not lead to clinically meaningful inhibition of gastric prostaglandin synthesis and had no effect on platelet function.'

**And to introduce a subheading of 'Efficacy' before the paragraph that starts with** 'In patients with osteoarthritis, lumiracoxib doses up to 200 mg…'

**And to add the following paragraphs under a heading of 'Safety' after the paragraphs about Efficacy:**

*The Therapeutic lumiracoxib Arthritis Research and Gastrointestinal Event Trial (TARGET)*

TARGET, a double-blind, phase III study included 18,325 OA patients randomized to lumiracoxib 400 mg o.d. (two to four times the recommended OA dose), naproxen 500 mg b.i.d or ibuprofen 800 mg t.i.d. TARGET prospectively included patients taking low-dose ASA (75-100 mg daily) for primary or secondary prevention of coronary heart disease. Randomization was stratified by low-dose ASA use (24 % of patients in the overall study population) and age.

Gastrointestinal Effect

The primary endpoint was time to event distribution of definite or probable upper gastrointestinal tract ulcer (UGIT) complications (POBs) in patients not receiving low-dose ASA and in the overall population. The results are shown in Table 1 below. In the low dose ASA group a lower incidence of GI events was observed with lumiracoxib compared to both NSAIDs (21%), however the study was not powered to show a difference in this group and it did not reach statistical significance.

**Table 1: TARGET: symptomatic and complicated upper GI tract ulcers (POBs, PUBs)**

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| **Upper GI tract ulcer complications (POBs)** | | | | | |
| **No low-dose aspirin** | | | | | |
| **Study 0117** | | | | | |
| **Lumiracoxib** | **3549** | **9 (0.25)** | **0.24** | **0.12 - 0.50** | **0.0001** |
| **Naproxen** | **3537** | **36 (1.02)** | | | |
| **Study 2332** | | | | | |
| **Lumiracoxib** | **3401** | **5 (0.15)** | **0.17** | **0.07 - 0.45** | **0.0003** |
| **Ibuprofen** | **3431** | **28 (0.82)** | | | |
| **Overall population** | | | | | |
| **Study 0117** | | | | | |
| **Lumiracoxib** | **4741** | **19 (0.40)** | **0.37** | **0.22 - 0.63** | **0.0002** |
| **Naproxen** | **4730** | **50 (1.06)** | | | |
| **Study 2332** | | | | | |
| **Lumiracoxib** | **4376** | **10 (0.23)** | **0.29** | **0.14 - 0.59** | **0.0006** |
| **Ibuprofen** | **4397** | **33 (0.75)** | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Upper GI tract ulcer complications or symptomatic ulcers (PUBs)** | | | | | |
| **No low-dose aspirin** | | | | | |
| **Study 0117** | | | | | |
| **Lumiracoxib** | **3549** | **34 (0.96)** | **0.39** | **0.26 - 0.58** | **<0.0001** |
| **Naproxen** | **3537** | **85 (2.40)** | | | |
| **Study 2332** | | | | | |
| **Lumiracoxib** | **3401** | **21 (0.62)** | **0.36** | **0.22 - 0.60** | **<0.0001** |
| **Ibuprofen** | **3431** | **57 (1.66)** | | | |
| **Overall population** | | | | | |
| **Study 0117** | | | | | |
| **Lumiracoxib** | **4741** | **54 (1.14)** | **0.46** | **0.33 - 0.64** | **<0.0001** |
| **Naproxen** | **4730** | **116 (2.45)** | | | |
| **Study 2332** | | | | | |
| **Lumiracoxib** | **4376** | **34 (0.78)** | **0.47** | **0.31 - 0.70** | **0.0003** |
| **Ibuprofen** | **4397** | **71 (1.61)** | | | |

Cardiovascular Effect

The primary cardiovascular (CV) endpoint studied was the Antiplatelet Trialists' Collaboration (APTC) endpoint: confirmed or probable myocardial infarction (clinical or silent), stroke (ischemic or haemorrhagic) and CV death. There were no significant differences in the total number of patients with confirmed or probable APTC events between lumiracoxib (59 patients, 0.65%) and NSAIDs (50 patients, 0.55 %) (See the results in Table 2).

There was no statistically significant difference between lumiracoxib and NSAIDs for any individual CV endpoint (MI, stroke, CV death, transient ischaemic attacks, deep vein thrombosis and pulmonary embolism). For systolic blood pressure, mean change from baseline were +0.4 mmHg for lumiracoxib and +2.1 mmHg for NSAIDs ($p<0.0001$). For diastolic blood pressure, mean change from baseline were -0.1 mmHg for lumiracoxib and +0.5 mmHg for NSAIDs ($p<0.0001$).

Table 2: TARGET: Confirmed or probably CV events: CV deaths, MIs, strokes (APTC endpoint)

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value |
|---|---|---|---|---|---|
| **Overall population** | | | | | |
| **Study 0117** | | | | | |
| **Lumiracoxib** | **4741** | **40 (0.84)** | **1.46** | **0.89 - 2.37** | **0.1313** |
| **Naproxen** | **4730** | **27 (0.57)** | | | |
| **Study 2332** | | | | | |
| **Lumiracoxib** | **4376** | **19 (0.43)** | **0.76** | **0.41 - 1.40** | **0.3775** |
| **Ibuprofen** | **4397** | **23 (0.52)** | | | |
| **No low-dose aspirin** | | | | | |
| **Study 0117** | | | | | |
| **Lumiracoxib** | **3549** | **22 (0.62)** | **1.49** | **0.76 - 2.92** | **0.2417** |
| **Naproxen** | **3537** | **14 (0.40)** | | | |
| **Study 2332** | | | | | |
| **Lumiracoxib** | **3401** | **13 (0.38)** | **0.94** | **0.44 - 2.04** | **0.8842** |
| **Ibuprofen** | **3431** | **13 (0.38)** | | | |
| **Low-dose aspirin** | | | | | |
| **Study 0117** | | | | | |
| **Lumiracoxib** | **1192** | **18 (1.51)** | **1.42** | **0.70 - 2.90** | **0.3368** |
| **Naproxen** | **1193** | **13 (1.09)** | | | |
| **Study 2332** | | | | | |
| **Lumiracoxib** | **975** | **6 (0.62)** | **0.56** | **0.20 - 1.54** | **0.2603** |
| **Ibuprofen** | **966** | **10 (1.04)** | | | |

**BACKGROUND**

Following a European-wide Article 31 referral, a number of core changes to be made to the SmPC for all COX-2 selective inhibitors were agreed by members of the CHMP. Available evidence suggests that use of any selective COX-2 inhibitor may increase risk of thrombotic events (e.g. myocardial infarction and stroke) compared with placebo and some NSAIDs. This risk may increase with dose and duration of exposure. The MA holder for each COX-2 selective inhibitor has been asked to submit a type II variation to update the SmPC and PIL for their COX-2 inhibitor to include these core changes.

The following changes that each MA holder has been asked to be include in the SmPC:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see sections 4.3, 4.4).

4.2 Posology and method of administration

As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (4.3, 4.4, 4.8 and 5.1).

4.3 Contra-indications

*Congestive heart failure (NYHA II-IV)*

Established ischaemic heart disease and/or cerebrovascular disease

Section 4.4 Special Warnings and Precautions

*Gastrointestinal effects*

Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with lumiracoxib.

Caution is advised with treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, patients using any other NSAID or acetylsalicylic acid concomitantly or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding.

There is a ~~an~~ further increase~~d~~ in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) ~~for lumiracoxib, other COX-2 inhibitors and NSAIDs,~~ when lumiracoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid *vs*. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 5.1).

*Cardiovascular effects*

~~Caution should be exercised in patients with a medical history of ischemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above.~~

~~Appropriate measures should be taken and discontinuation of etoricoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients.~~

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs. As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis (4.2, 4.3, 4.8 and 5.1).

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with lumiracoxib after careful consideration (see 5.1).

COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effect. Therefore antiplatelet therapies should not be discontinued.~~on platelets function. Because etoricoxib does not inhibit platelet aggregation, antiplatelet therapies (eg. acetylsalicylic acid) should not be discontinued. and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (prior history of MI, angina, ischemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary bypass graft surgery or peripheral vascular surgery)~~ (see above, 4.5 and 5.1.).

~~Caution should be exercised in patients with a medical history of ischaemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above.~~

~~Appropriate measures should be taken and discontinuation of lumiracoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients~~.

*General*

If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of etoricoxib therapy should be considered.

No changes to other sections of the SPC are proposed at this stage
Section 5.1 will require updating in the type II variation to follow the procedure (TARGET study).

The Patient Information Leaflet (PIL) is to be updated to include the following:

**Patient information leaflet [subject to user-testing]**

**Do not take <coxib>:**
- If your doctor has diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain) or if you have had a heart attack, stroke or mini stroke (TIA or transient ischaemic attack)

<coxib> may slightly increase your risk of heart attack and stroke and this is why it should not be used by people who have already had heart problems or stroke.

You should discuss with your doctor whether <coxib> is suitable for you if you have conditions which increase your risk of heart disease such as high blood pressure, diabetes, high cholesterol or if you smoke.

***Whilst taking <coxib>***
Your doctor will want to discuss your treatment from time to time. It is important that you use the lowest dose that controls your pain and you should not take <coxib> for longer than necessary. This is because the risk of heart attacks and strokes might increase after prolonged treatment, especially with high doses.

If any of the following symptoms: **shortness of breath, chest pains or ankle swelling** appear or worsen, stop your treatment with <coxib> and consult a doctor, as soon as is practical.

In December 2003, the PhVWP agreed that Section 4.5 (Interaction with medicinal products and other forms of interaction) of the SmPC for all NSAIDs (including COX-2 inhibitors) should be updated to include a possible interaction with angiotensin II antagonists (AIIAs), leading to impaired renal function. The agreed wording is as follows:

**Section 4.5 (Interaction with medicinal products and other forms of interaction)**
*Diuretics, ACE inhibitors and Angiotensin II Antagonists:* NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking lumiracoxib concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

**SUPPORTING EVIDENCE**
The MA holder has supplied amended SmPCs for Prexige 100mg lumiracoxib, Prexige 200 mg lumiracoxib and Prexige 400 mg lumiracoxib. They have also supplied an updated PIL which applies to all 3 lumiracoxib products, as well as summary tables which detail where the

SmPC has changed for 100 mg and 200 mg lumiracoxib (same changes apply to both concentrations), and for 400 mg.

This is a bulk variation which also deals with the duplicate products Stellige, Exforge and Frexocel.

**EVALUATION**
**CHANGES TO THE SmPC**
**Section 4.1 (Therapeutic indications)**
The added wording is exactly as requested by the CHMP.

**Section 4.2 (Posology and method of administration)**

**Assessor's comment:** The MA holder has added details of clinical experience with regard to maximum duration of use for each licensed indication It has included the following statement under Section 4.4 (subheading 'Cardiovascular Effects'):

*'Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with a risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAID's. As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used. The patients need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.'*

This statement relates to cardiovascular effects, and it is therefore appropriate to include this statement in section 4.4. However, the statement also relates to Posology and the MA holder is therefore requested to add the following statement to section 4.2 in support of the information provided about maximum clinical experience for duration of use for licensed indications:

'As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used. The patients need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.'

**Section 4.3 (Contra-indications)**
The changed wording regarding heart failure is exactly as requested by the CHMP, as is the wording to add established ischaemic heart disease and/or cerebrovascular disease

**Section 4.4 (Special warnings and precautions)**
**Gastrointestinal effects**
The core SmPC wording agreed by the CHMP has not been exactly adopted by the MA holder in this section of the amended SmPC. The underlined words in the paragraphs below illustrate where extra words have been added, whereas those in triangular brackets indicate words that have been omitted from the agreed core SmPC:

*'Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], <u>potentially</u> <some of them> resulting in a fatal outcome, have <u>rarely</u> occurred in patients treated with lumiracoxib.*

*There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) <u>for lumiracoxib, other COX-2 inhibitors and NSAIDs</u> when <lumiracoxib is> taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors +*

*acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 5.1).'*

**Assessor's comment:** The core changes to the wording of the SmPC apply to all selective COX-2 inhibitors, with the intention of having identical warnings across the class. The MA holder is requested to remove the underlined words in the sentences above unless it has absolutely no fatal cases of perforations, ulcers or bleeds recorded as suspected adverse events in association with lumiracoxib. If any such reactions are reported in future, the MA holder will be required to submit a fee-paying variation to bring the SmPC in line with the rest of the class for gastrointestinal effects. The MA holder is also requested to add the words in triangular brackets in the paragraph above so that it is in line with the agreed core SmPC changes.

**Cardiovascular effects**
The changed or added wording is exactly as requested by the CHMP.

**General**
The MA holder has added the required sentence, which differs only from the agreed core SmPC changes in that the underlined word below should be 'considered' and not 'discontinued':

*'If during treatment, patients deteriorate in any of the organ system functions described above, appropriate measures should be taken and discontinuation of lumiracoxib therapy should be discontinued.'*

**Assessor's comments:** The MA holder is requested to change the above underlined 'discontinued' to 'considered' to bring it in line with agreed core changes to the SmPC.

**Section 4.5 (Interaction with medicinal products and other forms of interaction)**
The MA holder has amended the body of the text about Diuretics, ACE inhibitors and Angiotensin II Antagonists exactly as requested by the PhVWP. The subheading used by the MA holder, however, is *'Diuretics and antihypertensive drugs'*. The subheading requested by the PhVWP is 'Diuretics, ACE inhibitors and Angiotensin II Antagonists'

**Assessor's comments:** The MA holder is requested to change the heading 'Diuretics and antihypertensive drugs' to 'Diuretics, ACE inhibitors and Angiotensin II Antagonists' to bring it in line with agreed core changes to the SmPC.

The MA holder has also removed the subheading 'The effect of lumiracoxib on the PK of other drugs'.

**Assessor's comment:** This change is acceptable.

**Section 5.1 (Pharmacodynamic properties)**
The MA holder has updated this section of the SmPC under the subheading 'Mode of action'. The sentence about expression of COX-1 has been omitted and the following information about COX-2 has been added:

*'COX-2 is also involved in ovulation, implantation and closure of the ductus arteriosus, regulation of renal function, and central nervous system functions (fever induction, pain perception and cognitive function). It may also play a role in ulcer healing. COX-2 has been identified in tissue around gastric ulcers in man but its relevance to ulcer healing has not been established.*

*The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thrombo-embolic reactions. COX-2 selective inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.'*

**Assessor's comment:** This added information brings the SmPC for lumiracoxib in line with SmPCs for other COX-2 selective inhibitors.

The MA holder has inserted a subheading of '*Efficacy*' before the sentence which starts '*In patients with osteoarthritis, lumiracoxib doses up to 200 mg once daily…*'

**Assessor's comment:** This subheading is acceptable.

The MA holder has included data from the TARGET study under a subheading of 'Safety: the Therapeutic lumiracoxib Arthritis Research and Gastrointestinal Event Trial (TARGET)'. The information included is as follows:

*'TARGET, a double-blind, phase III study included 18,325 OA patients randomized to lumiracoxib 400 mg o.d. (two to four times the recommended OA dose), naproxen 500 mg b.i.d or ibuprofen 800 mg t.i.d. TARGET prospectively included patients taking low-dose ASA (75-100 mg daily) for primary or secondary prevention of coronary heart disease. Randomization was stratified by low-dose ASA use (24 % of patients in the overall study population) and age.*

*<u>Gastrointestinal Effect</u>*
*The primary endpoint was time to event distribution of definite or probable upper gastrointestinal tract ulcer (UGIT) complications (POBs) in patients not receiving low-dose ASA and in the overall population. The results are shown in Table 1 below. In the low dose ASA group a lower incidence of GI events was observed with lumiracoxib compared to both NSAIDs (21%), however the study was not powered to show a difference in this group and it did not reach statistical significance.*

*Table 1: TARGET: symptomatic and complicated upper GI tract ulcers (POBs, PUBs)*

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value* |
|---|---|---|---|---|---|
| ***Upper GI tract ulcer complications (POBs)*** | | | | | |
| ***No low-dose aspirin*** | | | | | |
| ***Study 0117*** | | | | | |
| ***Lumiracoxib*** | ***3549*** | ***9 (0.25)*** | ***0.24*** | ***0.12 - 0.50*** | ***0.0001*** |
| ***Naproxen*** | ***3537*** | ***36 (1.02)*** | | | |
| ***Study 2332*** | | | | | |
| ***Lumiracoxib*** | ***3401*** | ***5 (0.15)*** | ***0.17*** | ***0.07 - 0.45*** | ***0.0003*** |
| ***Ibuprofen*** | ***3431*** | ***28 (0.82)*** | | | |
| ***Overall population*** | | | | | |
| ***Study 0117*** | | | | | |
| ***Lumiracoxib*** | ***4741*** | ***19 (0.40)*** | ***0.37*** | ***0.22 - 0.63*** | ***0.0002*** |
| ***Naproxen*** | ***4730*** | ***50 (1.06)*** | | | |
| ***Study 2332*** | | | | | |
| ***Lumiracoxib*** | ***4376*** | ***10 (0.23)*** | ***0.29*** | ***0.14 - 0.59*** | ***0.0006*** |
| ***Ibuprofen*** | ***4397*** | ***33 (0.75)*** | | | |
| ***Upper GI tract ulcer complications or symptomatic ulcers (PUBs)*** | | | | | |
| ***No low-dose aspirin*** | | | | | |
| ***Study 0117*** | | | | | |
| ***Lumiracoxib*** | ***3549*** | ***34 (0.96)*** | ***0.39*** | ***0.26 - 0.58*** | ***<0.0001*** |
| ***Naproxen*** | ***3537*** | ***85 (2.40)*** | | | |
| ***Study 2332*** | | | | | |
| ***Lumiracoxib*** | ***3401*** | ***21 (0.62)*** | ***0.36*** | ***0.22 - 0.60*** | ***<0.0001*** |
| ***Ibuprofen*** | ***3431*** | ***57 (1.66)*** | | | |
| ***Overall population*** | | | | | |
| ***Study 0117*** | | | | | |
| ***Lumiracoxib*** | ***4741*** | ***54 (1.14)*** | ***0.46*** | ***0.33 - 0.64*** | ***<0.0001*** |
| ***Naproxen*** | ***4730*** | ***116 (2.45)*** | | | |
| ***Study 2332*** | | | | | |
| ***Lumiracoxib*** | ***4376*** | ***34 (0.78)*** | ***0.47*** | ***0.31 - 0.70*** | ***0.0003*** |
| ***Ibuprofen*** | ***4397*** | ***71 (1.61)*** | | | |

*Cardiovascular Effect*

*The primary cardiovascular (CV) endpoint studied was the Antiplatelet Trialists' Collaboration (APTC) endpoint: confirmed or probable myocardial infarction (clinical or silent), stroke (ischemic or haemorrhagic) and CV death. There were no significant differences in the total number of patients with confirmed or probable APTC events between lumiracoxib (59 patients, 0.65%) and NSAIDs (50 patients, 0.55 %) (See the results in Table 2).*

*There was no statistically significant difference between lumiracoxib and NSAIDs for any individual CV endpoint (MI, stroke, CV death, transient ischaemic attacks, deep vein thrombosis and pulmonary embolism). For systolic blood pressure, mean change from baseline were +0.4 mmHg for lumiracoxib and +2.1 mmHg for NSAIDs (p<0.0001). For diastolic blood pressure, mean change from baseline were -0.1 mmHg for lumiracoxib and +0.5 mmHg for NSAIDs (p<0.0001).*

*Table 2: TARGET: Confirmed or probably CV events: CV deaths, MIs, strokes (APTC endpoint)*

| | Number at risk | Number (%) with events | Hazard ratio | 95% CI | p-value |
|---|---|---|---|---|---|
| ***Overall population*** | | | | | |
| ***Study 0117*** | | | | | |
| ***Lumiracoxib*** | ***4741*** | ***40 (0.84)*** | ***1.46*** | ***0.89 - 2.37*** | ***0.1313*** |
| ***Naproxen*** | ***4730*** | ***27 (0.57)*** | | | |
| ***Study 2332*** | | | | | |
| ***Lumiracoxib*** | ***4376*** | ***19 (0.43)*** | ***0.76*** | ***0.41 - 1.40*** | ***0.3775*** |
| ***Ibuprofen*** | ***4397*** | ***23 (0.52)*** | | | |
| ***No low-dose aspirin*** | | | | | |
| ***Study 0117*** | | | | | |
| ***Lumiracoxib*** | ***3549*** | ***22 (0.62)*** | ***1.49*** | ***0.76 - 2.92*** | ***0.2417*** |
| ***Naproxen*** | ***3537*** | ***14 (0.40)*** | | | |
| ***Study 2332*** | | | | | |
| ***Lumiracoxib*** | ***3401*** | ***13 (0.38)*** | ***0.94*** | ***0.44 - 2.04*** | ***0.8842*** |
| ***Ibuprofen*** | ***3431*** | ***13 (0.38)*** | | | |
| ***Low-dose aspirin*** | | | | | |
| ***Study 0117*** | | | | | |
| ***Lumiracoxib*** | ***1192*** | ***18 (1.51)*** | ***1.42*** | ***0.70 - 2.90*** | ***0.3368*** |
| ***Naproxen*** | ***1193*** | ***13 (1.09)*** | | | |
| ***Study 2332*** | | | | | |
| ***Lumiracoxib*** | ***975*** | ***6 (0.62)*** | ***0.56*** | ***0.20 - 1.54*** | ***0.2603*** |
| ***Ibuprofen*** | ***966*** | ***10 (1.04)*** | | | |

**Assessor's comment:**
The information provided by the MA holder giving the main characteristics of the patient population is acceptable.

The European Commission guidelines on the Summary of Product Characteristics state that statements in sections 5.1 – 5.3 should be brief and concise. The data provided in table form are lengthy and not all the data are strictly relevant to the prescriber. The MA holder is requested to remove the tables from section 5.1 and to replace them with a concise textual description of the main findings. A suggested draft description of the TARGET data is included in Annex 1.

The MA holder has defined the primary endpoint of TARGET as 'time to event distribution of definite or probable upper gastrointestinal tract ulcer (UGIT) complications (POBs) in patients not receiving low-dose ASA and in the overall population.' According to the TARGET data published by Schnitzer et al, Lancet 364, 665, the primary endpoint was 'time-to-event distribution of definite or probable upper gastrointestinal ulcer complications (clinically significant bleeding, perforation, or obstruction from erosive or ulcer disease)' with no distinction made between users or non-users of low-dose aspirin. The MA holder is requested to include data from the TARGET trial for users of low-dose aspirin for GI events. It is important that prescribers are aware of the GI outcome in patients using low-dose aspirin, who constitute a significant proportion of the OA population.
Additionally, it is only necessary to describe POB GI events and not also PUB events.

The MA holder is requested to describe data for the APTC endpoint. The MA holder is

also requested to include a textual description of MI events as part of the cardiovascular data. For all cardiovascular events, the MA holder is asked to include data for users and non-users of low-dose aspirin as well as the overall patient population.

The MA is requested to place blood pressure results under a subheading of 'Cardiorenal effect'.

**PATIENT INFORMATION LEAFLET**

The MA holder has incorporated all of the updates requested by the CHMP in its amended PIL. In addition, it has included a statement under the headings 'How to take Prexige tablets; Period pain, acute pain or orthopaedic surgery' of:
*'You should not take more than this or use Prexige for longer than 5 days'*

**Assessor's comment:** These PIL updates are acceptable, and are exactly as requested by the CHMP.

**CONCLUSION AND RECOMMENDATIONS**

The MA has provided updated SmPCs and PILs following the CHMP's request for core changes to the SmPC. In order to comply with the CHMP's changes fully, the MA holder is requested to make the following further changes:

- To add the following statement to section 4.2:
  *'As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used. The patients need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.'*
- To remove the underlined words in the paragraph in section 4.4. under the subheading 'gastrointestinal effects' and to insert the words in triangular brackets:

  *'Upper gastrointestinal complications [perforations, ulcers or bleedings (PUBs)], potentially <some of them> resulting in a fatal outcome, have rarely occurred in patients treated with lumiracoxib.*

  …

  *There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for lumiracoxib, other COX-2 inhibitors and NSAIDs when <lumiracoxib is> taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials (see 5.1).'*
- To replace the underlined word 'discontinued' in section 4.4. under the subheading 'general' with the word 'considered':
- To change the heading 'Diuretics and antihypertensive drugs' to 'Diuretics, ACE inhibitors and Angiotensin II Antagonists' in section 4.5
- To remove the tables from section 5.1 and to replace them with a concise textual description of the main findings. This concise description should describe data from TARGET on:
  - POB GI events
  - APTC endpoint
  - MI events

Data for users and non-users of low-dose aspirin should be included, in addition to data for the overall population. Blood pressure data should be placed under a subheading of 'Cardiorenal effects'. A suggested draft description of the TARGET data is included in Annex 1.

**DECISION –**
This variation is approved on the condition that the MAH incorporate all the requested changes to the SPC.

**DATE :-** 23 March 2005

ANNEX – 1
SUGGESTED WORDING FOR TARGET DATA IN SECTION 5.1

***Safety: TARGET***

*'TARGET, a 12-month, double-blind, phase III study included 18,325 OA patients randomized to lumiracoxib 400 mg o.d. (two to four times the recommended OA dose), naproxen 500 mg b.i.d or ibuprofen 800 mg t.i.d. TARGET included patients taking low-dose ASA (75-100 mg daily) for primary or secondary prevention of coronary heart disease. Randomization was stratified by low-dose ASA use (24 % of patients in the overall study population) and age.*

*Gastrointestinal Effect in TARGET (12-month study)*

*The primary endpoint was time to event distribution of definite or probable upper gastrointestinal tract ulcer (UGIT) complications (POBs).*

- *In the low dose ASA group the incidence of POBs was 15/2167 patients (0.69%) for lumiracoxib versus 19/2159 patients (0.88%) for NSAIDs, with a hazard ratio (HR) of 0.79 (not statistically significant).*
- *In the population not using low-dose aspirin, the incidence of POBs was 14/6950 patients (0.2%) for lumiracoxib versus 64/6968 patients (0.92%) for NSAIDs, with a HR of 0.21 (p<0·0001).*
- *In the overall population, the incidence of POBs was 29/9117 patients (0.32%) for lumiracoxib versus 83/9127 patients (0.91%) for NSAIDs, with a HR of 0.34 (p<0·0001).*

*Cardiovascular Effect in TARGET (12-month study)*

***Thrombotic events***

*The primary cardiovascular (CV) endpoint studied was the Antiplatelet Trialists' Collaboration (APTC) endpoint; confirmed or probable myocardial infarction (MI, clinical or silent), stroke (ischemic or haemorrhagic) and CV death. There was no statistically significant difference between lumiracoxib and NSAIDs for incidence of APTC events, however, the APTC event rate was higher for lumiracoxib than for naproxen.*

- *In the low-dose ASA group, the incidence of APTC events was 24/2167 patients (1.11 %) for lumiracoxib versus 23/2159 patients (1.07%) for NSAIDs, with a hazard ratio (HR) of 1.04.*
- *In the population not using low-dose aspirin, the incidence of APTC events was 35/6950 patients (0.5%) for lumiracoxib versus 27/6968 patients (0.39%) for NSAIDs, with a HR of 1.22.*
- *In the overall population, the incidence of APTC events was 59/9117 patients (0.65 %) for lumiracoxib versus 50/9127 patients (0.55%) for NSAIDs, with a HR of 1.14.*

***MI events***

*Overall incidence of MI in TARGET combined clinical MI with silent MI (detected via ECG). There was no statistically significant difference between lumiracoxib and NSAIDs for incidence of MI.*

- *In the low-dose ASA group, the incidence of MI events was 9/2167 patients (0.57 events per 100 patient years) for lumiracoxib versus 8/2159 patients (0.51 events per 100 patient years) for NSAIDs, with a HR of 1.14.*

- *In the population not using low-dose aspirin, the incidence of MI events was 14/6950 patients (0.26 events per 100 patient years) for lumiracoxib versus 9/6968 patients (0.18 events per 100 patient years) for NSAIDs, with a HR of 1.47.*
- *In the overall population, the incidence of thrombotic events was 23/9117 patients (0.33 events per 100 patient years) for lumiracoxib versus 17/9127 patients (0.26 events per 100 patient years) for NSAIDs, with a HR of 1.31.*

*The cardiovascular safety of lumiracoxib beyond 1 year of use has not been established.*

*Cardiorenal effect in TARGET (12-month study)*

*For systolic blood pressure, mean changes from baseline were +0.4 mmHg for lumiracoxib and +2.1 mmHg for NSAIDs ($p<0.0001$). For diastolic blood pressure, mean changes from baseline were -0.1 mmHg for lumiracoxib and +0.5 mmHg for NSAIDs ($p<0.0001$). The number of discontinuations in TARGET due to oedema was not significantly different between lumiracoxib (43) and NSAIDs (55). The number of discontinuations due to hypertension-related events was also not significantly different between lumiracoxib (37) and NSAIDs (52).'*

# APPENDIX II

## Variation 3 Assessment Report

# PREXIGE 100mg TABLETS (LUMIRACOXIB) PL 00101/0677

# VARIATION 3 ASSESSMENT REPORT

| VARIATION<br>National<br><br>. |
|---|

| | |
|---|---|
| Product:<br>Prexige, Exforge, Stellige, Frexocel Tablets 100mg, 200mg and 400mg.<br><br>MA numbers:<br>PL 00101/0677, 0668, 0669, 0692, 0693, 0694, 0695, 0696, 0697, 0698, 0699, 0700<br><br>MAH:<br>Novartis Pharmaceuticals UK Ltd<br>Frimley Business Park<br>Frimley, Camberley<br>Surrey GU16 7SR | |
| Active constituent:<br>Lumiracoxib | Previous Assessments: |
| Therapeutic classification:<br>Anti-inflammatory and antirheumatic products, non-steroids, coxibs. | Legal status:<br>POM |

| Reason for the variation:<br>The MAH proposes to change the posology for osteoarthritis from 100mg od with the option of up-titration to 200mg od to 100mg od with no up-titration, and to change the posology for dysmenorrhoea from 400mg od to 200mg od. |
|---|

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AAOS | American Academy of Orthopaedic Surgeons |
| ACR | American College of Rheumatology |
| AE | Adverse event |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/SGPT |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT |
| BUN | Blood urea nitrogen |
| $CL_{CR}$ | Creatinine Clearance |
| COX | Cyclooxygenase |
| CRF | Case Report Form |
| CTEP | Cancer Therapy Evaluation Program, National Institute of Health |
| DSMB | Data Safety Monitoring Board |
| EMEA | European Medicines Evaluation Agency |
| FDA | Food and Drug Administration |
| GGT | Gamma-glutamyl transferase |
| GI | Gastrointestinal |
| ICH | The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| LFT | Liver function tests |
| LLN | Lower limit of normal |
| LOCF | Last Observation Carried Forward |
| MRP | Mutual Recognition Procedure |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOS | Not otherwise specified |
| NSAID | Non-steroidal anti-inflammatory drug |
| OA | Osteoarthritis |
| od | omnia die/once a day |
| $PGE_2$ | Prostaglandin $E_2$ |
| POBs | Perforations, obstructions and bleeds |
| PUBs | perforations, ulcers and bleeding |
| PT | Prothrombin time or post-text (table or listing) |
| SAE | Serious adverse event |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |
| ULN | Upper limit of normal |
| VAS | Visual Analogue Scale |

## EXECUTIVE SUMMARY

- Lumiracoxib is a member of the class of anti-inflammatory drugs known as cyclooxygenase-2 (COX2) inhibitors. Unlike others in the class, lumiracoxib lacks a sulphonyl group and is instead a phenyl acetic acid derivative.
- Lumiracoxib was licensed in the UK in September 2003 and an outgoing MRP application to seek a European licence was initiated in July 2004. This was withdrawn following major public health concerns when the COX2 inhibitor class was referred to the EMEA.
- The current variation application proposes a decrease in the dose of lumiracoxib,
  - In osteoarthritis, from an initial dose of 100mg od, with the option to titrate up to 200mg od to a dose of 100mg od with no up-titration.
  - In dysmenorrhoea, from a dose of 400mg od to a dose of 200mg od for 3 days per menstrual cycle.
- In support of this application the MAH has submitted two pivotal 13-week studies investigating lumiracoxib 100mg od in the treatment of patients with osteoarthritis of the knee, each with an extension study up to 52 weeks, and two pivotal studies investigating lumiracoxib 200mg in the treatment of patients with primary dysmenorrhoea.
  Data from a 52-week safety study (TARGET) are also considered.
- The efficacy of lumiracoxib 100mg od in patients with osteoarthritis of the knee has been shown to be similar to that of lumiracoxib 200mg od and 400mg od with no consistent evidence of a dose response.
- The efficacy of lumiracoxib 100mg od in the treatment of osteoarthritis of the hand has not been adequately demonstrated in the subgroup of patients with OA of the hand in studies 2360 and 2361. A pooled analysis of the AUSCAN data from these studies might reassure.
- The efficacy of lumiracoxib 200mg od in patients with primary dysmenorrhoea has been shown to be similar to that of lumiracoxib 400mg od with no consistent evidence of a dose response. As lower doses of lumiracoxib such as 100mg od have not been studied in patients with primary dysmenorrhoea, it is not possible to conclude that 200mg od is the optimal dose in this indication.
- The safety of lumiracoxib at doses of 100mg od and 400mg od have been studied in the above osteoarthritis studies for up to 52 weeks. The safety profile of lumiracoxib has been shown to be similar to that of non-selective NSAIDs with some advantage in gastrointestinal adverse events over the non-selective NSAIDs in those patients not taking low-dose aspirin. In the TARGET study, however, this advantage was lost in patients taking low-dose aspirin.
- The risk:benefit ratio of lumiracoxib in the treatment of osteoarthritis of the knee and hip and in the treatment of primary dysmenorrhoea remains favourable at the lower doses proposed.

## INTRODUCTION

Lumiracoxib (COX189, Prexige™) is a potent and selective inhibitor of cyclooxygenase-2 (COX-2), and is therefore a member of the non-steroidal anti-inflammatory (NSAID) drug class. Some other inhibitors of COX-2 such as rofecoxib and etoricoxib contain a methyl-sulphonyl group, and both celecoxib and valdecoxib are sulphonamides, but lumiracoxib lacks a sulphonyl group and is instead a phenyl acetic acid derivative. Lumiracoxib is therefore structurally different to other COX-2 inhibitors.

Lumiracoxib has been shown to be as effective as non-selective NSAIDs in relieving signs and symptoms of osteoarthritis (OA), acute pain and dysmenorrhoea while having an improved gastrointestinal tolerability.

Lumiracoxib is currently indicated for symptomatic relief in the treatment of osteoarthritis (OA) and for the short-term relief of moderate to severe acute pain associated with: primary dysmenorrhoea, dental surgery and orthopaedic surgery.

## Change proposed

Changes are proposed to section 4.2 Posology to reduce the dose in OA from 100mg daily with the option of up-titration to 200mg daily to 100mg daily with no up-titration, and for dysmenorrhoea from 400mg daily to 200mg daily. Consequential changes are also proposed to Sections 4.4, 4.8, 4.9, 5.1, 5.2 and Section 6 (see proposed SPC with comments at Annex I).

Main change:

**4.2 Posology and method of administration**

*(Additions in bold and deletions crossed through)*

PREXIGE® tablets are administered orally and may be taken with or without food.

Osteoarthritis

The recommended ~~starting~~ dose is 100mg once daily. ~~In patients who fail to respond, the dose may be increased to 200mg daily in one or two divided doses.~~

Patients should not exceed this dose. ~~The clinical experience was restricted to 12 months.~~ **The maximum treatment duration in clinical studies was 12 months.**

**Relief of pain due to primary dysmenorrhoea**

**The recommended dose is 200mg once daily. Patients should not exceed this dose. The maximum treatment duration in clinical studies was 3 days.**

Acute pain

The recommended dose is 400mg once daily. Patients should not exceed this dose ~~and the treatment duration should not exceed 5 days.~~

~~Relief of acute pain due to dental surgery~~: The maximum treatment duration in clinical studies was 24 hours **(dental surgery pain) and 5 days**

~~Relief of acute pain due to~~ (orthopaedic surgery **pain)** ~~the maximum treatment duration in clinical studies was 5 days.~~

~~Relief of pain due to primary dysmenorrhoea: the maximum treatment duration in clinical studies was 3 days.~~

As the cardiovascular risks of lumiracoxib may increase with dose and duration of exposure, the shortest duration and the lowest effective daily dose should be used.

The patients need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.

*Ethnic differences*: Dosing recommendations are the same for Asians, Blacks and Caucasians. (see 5.2 Pharmacokinetic properties).

*Elderly:* As with other drugs ~~used in the elderly, it is prudent to initiate treatment with the lower recommended dose. C~~caution should be exercised in elderly ~~osteoarthritis~~ patients ~~when increasing from a 100 mg to a 200 mg daily dose.~~ (4.4 Special warning and precautions for use and 5.2 Pharmacokinetic properties).

*CYP2C9 poor metabolisers:* No dose adjustment is necessary in patients known to be CYP2C9 poor metabolisers. (see 5.2 Pharmacokinetic properties).

*Hepatic impairment:* No dose adjustment is necessary for patients with mild (Child-Pugh 5-6) to moderate (Child-Pugh 7-8) hepatic impairment. ~~However, it is prudent to initiate treatment at the lower recommended dose in such patients.~~ (See 4.3 Contraindications, 4.4 Special warning and precautions for use and 5.2 Pharmacokinetic properties).

*Renal insufficiency:* No dose adjustment is necessary for patients with creatinine clearance ≥50 ml/min. Lumiracoxib is contraindicated in patients with moderate to severe renal impairment (estimated creatinine clearance <50 ml/min). (See 4.3 Contraindications **and** 4.4 Special warning and precautions for use ~~and 5.2 Pharmacokinetic properties~~).

*Paediatric use:* PREXIGE® has not been studied in children and thus is contraindicated in children under 18 years of age.

## REGULATORY BACKGROUND

The original application for marketing lumiracoxib was made in 2002, and approval was granted in the UK in 2003. During the Mutual Recognition Process (MRP) in 2004, other Member States expressed Major Health Concerns and the application was voluntarily withdrawn because of these and safety concerns with the COX-2 inhibitor class. An Article 31 procedure was initiated by the European Medicines Agency (EMEA) regarding these class safety concerns.
Following completion of the Article 31 procedure, Novartis has modified the Summary of Product Characteristics (SPC) to take into account the Article 31 conclusions as well as data from recently completed clinical trials, in order to resume the MRP process. To support these changes, an addendum to the previous dossier has been prepared.

### Guidelines relevant to this application

**CPMP/EWP/784/97:** Points to consider on Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis.
**CPMP/EWP/612/00:** Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain.

## SUPPORTING DATA

The applicant has submitted the following documents:

- Clinical Overviews
- Summary of Clinical Pharmacology Studies – Addendum
- Summary of Clinical Efficacy in Osteoarthritis – Addendum
- Summary of Clinical Efficacy Addendum in acute pain (post-surgical dental pain or post-orthopaedic surgery pain) and primary dysmenorrhoea
- Summary of Clinical Safety – Addendum

The authors are Novartis employees.

The following table summarises the clinical efficacy studies submitted in support of this application showing which are new studies in osteoarthritis and dysmenorrhoea.

| Study No. | Study objective, duration, population | Lumiracoxib doses (n) | Active comparators Placebo | No. of Patients |
|---|---|---|---|---|
| **Osteoarthritis studies** | | | | |
| 2360 / 2360E *(new)* | 13 week efficacy / safety study in OA of knee, with OL ext. | 100 mg o d.<br>200 mg o.d. (2 wks) then 100 mg o.d. | celecoxib 200 mg o.d.<br>placebo | 1551 |
| 2361 / 2361E *(new)* | 13 week efficacy/safety study in OA of knee, with blinded ext. | 100 mg o.d.<br>200 mg o.d. (2 wks) then 100 mg o.d. | celecoxib 200 mg o.d.<br>placebo | 1684 |
| **Post-surgical dental pain** | | | | |
| 0115 *(old)* | 24 hour single dose efficacy / safety study in dental pain | 200 mg<br>400 mg<br>800 mg | rofecoxib 50 mg<br>placebo | 259 |
| 2302 *(old)* | 24 hour single dose, efficacy / safety study in dental pain | 400 mg | rofecoxib 50 mg<br>celecoxib 200 mg<br>placebo | 355 |
| **Post-orthopedic surgery pain** | | | | |
| 0131 *(old)* | 5 day acute & multiple dose efficacy / safety study in orthopedic pain | 400 mg o.d. | naproxen 500 mg b.i.d.<br>placebo | 180 |
| 0132 *(old)* | 19* day acute & multiple dose efficacy / safety study in orthopedic pain | 400 mg o.d.<br>800 mg o.d. | oxycodone 20 mg q12h<br>placebo | 240 |
| **Primary dysmenorrhea** | | | | |
| 2353 *(new)* | 3 day efficacy / safety cross-over study in dysmenorrhea | 200 mg o.d.<br>200 mg o.d. + 200 mg re-dose | naproxen 500 mg b.i.d.<br>placebo | 144 |
| 2358 *(new)* | 3 day efficacy / safety cross-over study in dysmenorrhea | 200 mg o.d.<br>200 mg o.d. + 200 mg re-dose | placebo | 132 |

Note: other studies are presented in the SCS
OL ext = open-label extension, 200 mg re-dose = optional re-dose on Day 1 only
* Following a 5-day in-patient phase, patients entered a 14-day out-patient phase

In addition the following studies investigated the appropriate dose for knee and hip OA. These were also submitted in the original dossier.

| Study No. | Study Design | Planned Patients | Treatment Duration | Medication dose/day | Primary Efficacy Variables |
|---|---|---|---|---|---|
| **0104** | Parallel group, efficacy/safety study in knee and hip OA versus placebo and diclofenac | 510 | 4 weeks | LUM 50 mg bid<br>LUM 100 mg bid<br>LUM 200 mg bid<br>LUM 400 mg od<br>Diclofenac 75 mg bid<br>Placebo | -OA pain intensity (VAS)<br>-disease activity (PatGA)<br>-WOMAC pain |
| **2316** | Parallel group, efficacy/safety study in knee and hip OA versus placebo | 200 | 4 weeks | LUM 100 mg od<br>Placebo | -OA pain intensity (VAS)<br>-disease activity (PatGA)<br>-WOMAC pain |

VAS = visual analog scale, PatGA = Patient's global assessment of disease activity (VAS)

# EVALUATION

## Clinical Pharmacology

### Study 2320

A new study is presented in which steady state pharmacokinetics of lumiracoxib were characterised over 7 days in OA patients following multiple oral administration of lumiracoxib at doses of 400mg and 800mg od.

**1. Steady state pharmacokinetics in OA patients after 7 days of dosing**

| | 400 mg | | 800 mg | |
|---|---|---|---|---|
| Parameters | Day 1 | Day 7 | Day 1 | Day 7 |
| $C_{max}$ (ng/ml) | 10500 ± 3447 | 10413 ± 4958 | 19056 ± 7793 | 21098 ± 9177 |
| $t_{max}$ (h) | 2.0 (1.9:4.0) | 2.0 (1.7:4.0) | 2.0 (1.9:2.3) | 2.0 (1.7:3.9) |
| $C_{oh}$ (ng/ml) | 0 | 108 ± 96 | 0 | 292 ± 270 |
| AUCτ (ng h/ml) | 40004 ± 12223 | 38107 ± 12238 | 81795 ± 23216 | 78665 ± 19004 |

Mean ± SD values are given except for $t_{max}$ which is given as median (min:max), $C_{0h}$= pre dose value,

The pharmacokinetic data after 7 days dosing were consistent with data obtained in OA patients at 100, 200 and 400mg after 28 days and 91 days of dosing presented in the original dossier.

**2. Steady state pharmacokinetics in OA patients after 28 and 91 days of dosing (from studies 0112 and 2316 – previously submitted)**

| | 100 mg o.d | 200 mg o.d | | | 400 mg o.d. | | |
|---|---|---|---|---|---|---|---|
| Parameter | Day 28 | Day 0 | Day 28 | Day 91 | Day 0 | Day 28 | Day 91 |
| $C_{max}$ (ng/ml) | 3312 ± 876 | 6517 ± 4435 | 6289 ± 4136 | 6617 ± 4874 | 9289 ± 4874 | 8914 ± 3921 | 8519 ± 3518 |
| $t_{max}$ (h) | 1.1 (0.5:3.5) | 2.0 (0.5:6.0) | 2.0 (0.5:6.3) | 2.0 (1.0:3.0) | 2.0 (0.5:3.1) | 2.0 (0.5:4.0) | 2.0 (0.5:3.0) |
| $C_{oh}$ (ng/ml) | 37 ± 15 | 0 | 85 ± 228 | 119 ± 182 | 0 | 117± 251 | 333 ± 1065 |
| $AUC_{0-6}$ (ng h/ml) | 8346 ± 1775 | 15284 ± 8751 | 13004 ± 7022 | 14377 ± 7410 | 24974 ± 11940 | 23106 ± 9683 | 20782 ± 8011 |
| AUCτ (ng h/ml) | 11107 ± 2486 | - | 17077 ± 9403 | 19123 ± 9419 | - | 31171 ± 13316 | 28803 ± 16519 |

Mean ± SD values are given except for $t_{max}$ which is given as median (min:max). 200 and 400 mg data are from [CP study 0112] and 100 mg data from [CP study 2316]. Day 0= first dose

There was no evidence of accumulation from the first dose compared to doses on days 7, 28 and 91.

*Assessor's comments:*
Study 2320 has been completed since the previous submission but contributes little information relevant to this variation application. With the results of studies 0112 and 2316, it does give some reassurance regarding the chronic use of lumiracoxib 100mg od as higher doses show no evidence of accumulation over 7, 28 and 91 days.

## Clinical Efficacy

### Osteoarthritis

*Dose-finding studies*
The choice of dose was based largely on the results of two dose-finding studies that were submitted in the original dossier:

**Study 0104**
A double blind, randomised, parallel group, international multicentre, double-dummy and placebo-controlled study investigated the following dosing regimens:
- Placebo
- Lumiracoxib 50mg bd, 100mg bd, 200mg bd and 400mg od
- Diclofenac 75mg bd, as extended-release tablet.

**Study 2316**
A double blind, randomised, parallel groups, international multicentre, double-dummy and placebo-controlled study further evaluated the efficacy of lumiracoxib 100mg od compared to placebo.

**3. Mean change from baseline in overall OA pain intensity (VAS mm) in dose selection studies 0104 and 2316 (ITT LOCF)**

| | Baseline | Mean (mean change from baseline) mm | | |
|---|---|---|---|---|
| Treatment groups | Mean mm | Week 1 | Week 2 | Week 4 |
| **Study 0104** | | | | |
| LUM 50 mg bid (N=96) | 66.9 | 47.4 (-19.5)*** | 44.4 (-22.6)** | 38.3 (-28.6)** |
| LUM 100 mg bid (N=95) | 64.7 | 45.5 (-19.2)*** | 43.5 (-21.2)** | 38.4 (-26.3)** |
| LUM 200 mg bid (N=96) | 67.0 | 45.0 (-22.0)*** | 42.9 (-24.1)*** | 37.4 (-29.6)*** |
| LUM 400 mg od (N=98) | 66.9 | 41.3 (-26.0)***,a,b | 39.3 (-27.5)*** | 33.7 (-33.2)*** |
| diclofenac 75 mg bid (N=94) | 66.1 | 38.2 (-27.9)***,a,b,c | 35.7 (-30.4)***,a,b,c | 34.3 (-31.8)*** |
| placebo (N=96) | 67.9 | 58.4 (-9.7) | 54.5 (-13.7) | 50.2 (-17.7) |
| **Study 2316** | | | | |
| LUM 100 mg od (N=122) | 64.8 | 51.3 (-13.4)* | 45.7 (-19.1)* | 40.2 (-24.6)** |
| placebo (N=122) | 65.5 | 56.2 (-9.3) | 50.9 (-14.6) | 48.7 (-16.8) |

ANCOVA *** p<0.001 vs. placebo, ** p<0.01 vs. placebo, * p<0.05 vs. placebo at timepoint;
a = p<0.05 vs. LUM 50 mg bid; b = p<0.05 vs. LUM 100 mg bid; c = p<0.05 vs. LUM 200 mg bid

All doses of lumiracoxib evaluated in study 0104 were found to be superior to placebo. The treatment effect of lumiracoxib when compared with placebo and diclofenac, and the results of PK/PD analyses led to the decision to use 200 mg od and 400 mg od in the first phase III efficacy studies conducted.
Subsequently, because of safety concerns with the COX-2 inhibitor class, the lowest dose tested, 100 mg daily, was further evaluated in later major efficacy studies which provide the data relevant to this application.

*Assessor's comments:*
In study 0104 the 100mg od dose was not studied, but 50mg bd could be considered equivalent. This dose did show efficacy compared to placebo but had a slower onset of action than the highest dose of lumiracoxib or diclofenac.
The efficacy of lumiracoxib 100mg od compared to placebo after 4 weeks treatment was confirmed in study 2316, though the treatment effect was small.

*Efficacy Studies*

**Study 2360 and Study 2361**

These two studies were 13-week, multicentre, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel group trials of 2 different dose regimens of lumiracoxib (lumiracoxib 100mg od and lumiracoxib 200 mg od initial dose for two weeks followed by 100 mg od) in patients with primary knee osteoarthritis.

Main inclusion criteria:
- Male and female outpatients ≥18 years of age, with a documented diagnosis of primary knee OA (confirmed according to ACR criteria) and symptoms for at least 3 months.
- Receiving NSAID or other simple analgesic therapy or expected to require NSAID treatment for at least 3 months in the opinion of the investigator.
- With a pain intensity at baseline of at least 40 mm (0-100 mm VAS) in the affected target joint during the last 24 hours.

In addition, spine/hand/shoulder/hip/foot or other primary OA, present for at least 3 months was documented if present.

Main exclusion criteria:
- secondary OA and /or a history and/or any evidence in the potential target joint of significant diseases.
- Open knee surgery within the last year, or observational arthroscopy, arthroscopic surgery or lavage within the last 180 days.
- Significant medical problems including: peptic ulceration, GI bleeding, fibromyalgia, rheumatoid arthritis, adult juvenile chronic arthritis and history of malignancy.
- Evidence of: hepatic (ALT or AST > 1.5 x upper normal limit [ULN], bilirubin > 1.2 x ULN), renal (serum creatinine > 1.25 x ULN), or blood coagulation disorder or anaemia (haemoglobin more than 20 g/L below the lower limit of normal).

A total of 1551 (Study 2360) and 1684 (Study 2361) patients were randomised to the following treatment groups:
- Lumiracoxib 100mg od.
- Lumiracoxib 200 mg od initial dose for two weeks followed by 100 mg od.
- Celecoxib 200 mg od.
- Placebo.

**Primary efficacy variables**

The following co-primary variables were used:

1. OA pain intensity in the target joint at 13 weeks (0-100 mm VAS)
2. Patient's global assessment (PatGA) of disease activity at 13 weeks (0-100 mm VAS)
3. WOMAC© LK3.1 Total score at 13 weeks

**4. Efficacy at the target joint after 13 weeks (ITT, LOCF)**

[Table compiled by assessor].

| | *Lumiracoxib 100mg OD* | *Lumiracoxib 200mg OD ID* | *Celecoxib 200mg OD* | *Placebo* |
|---|---|---|---|---|
| **OA Pain VAS Score** | | | | |
| **Study 2361** | | | | |
| Baseline | 64.1 | 64.4 | 64.8 | 63.8 |
| Change at 13 weeks | - 26.8 | - 26.2 | - 26.6 | - 21.4 |
| **Study 2360** | | | | |
| Baseline | 66.4 | 65.4 | 66.4 | 66.2 |
| Change at 13 weeks | -25.1 | -25.9 | -24.1 | -18.1 |
| **Patient global assessment** | | | | |
| **Study 2361** | | | | |
| Baseline | 63.1 | 61.6 | 62.9 | 62.9 |
| Change at 13 weeks | - 25.1 | - 21.9 | - 22.9 | - 18.9 |
| **Study 2360** | | | | |
| Baseline | 63.1 | 63.8 | 61.7 | 62.5 |
| Change at 13 weeks | -23.2 | -24.6 | -19.5 | -13.4 |
| **WOMAC Total score** | | | | |
| **Study 2361** | | | | |
| Baseline | 49.2 | 49.7 | 50.5 | 49.7 |
| Change at 13 weeks | - 15.18 | - 14.82 | - 14.69 | - 11.32 |
| **Study 2360** | | | | |
| Baseline | 52.9 | 52.9 | 52.6 | 53.1 |
| Change at 13 weeks | -16.9 | -17.2 | -15.6 | -9.5 |

ID – Initial dose.

There was no statistically significant difference between either lumiracoxib 100mg or lumiracoxib 200mg ID and celecoxib 200mg od, or between the two lumiracoxib dosing regimens.

The two lumiracoxib groups were pooled to form an 'all lumiracoxib 100mg od group', which was claimed to be statistically superior to placebo and non-inferior to celecoxib 200 mg od in all the primary analyses of OA pain, patient's assessment of disease activity and WOMAC total score *(but see p5 of the Statistical Assessment of Efficacy at Annex II.)*. Also, lumiracoxib was significantly superior to celecoxib for patient's assessment of disease activity in study 2360 and in the pooled analysis.

**Secondary efficacy variables**

- Overall OA pain intensity (on a 0-100 mm VAS) by visit.
- Patient's global assessment of disease activity by visit.
- Physician's global assessment of disease activity by visit.
- Response to treatment according to OARSI criteria by visit.

- Standardized AUC of OA pain.
- Patient's health status using the SF-36 and WOMAC© 3.1LK sub-scale scores and total score by visit.
- Usage of rescue medication by visit.

In a sub-group of patients who also had OA in other joints:
- Patient's global assessment of disease activity by visit at 13 weeks.
- Physician's global assessment of disease activity by visit at 13 weeks.
- AUSCAN© questionnaire (only for patients with hand OA) at 13 weeks.

**Key secondary efficacy variables results**

**WOMAC total score by visit (ITT Population LOCF) –**
There was no statistically significant difference between the two lumiracoxib dose groups at 2 weeks or at any later visit. Lumiracoxib 100mg od, lumiracoxib 200mg od ID and celecoxib 200mg od were all significantly more effective than placebo ($p<0.001$) at weeks 2, 8 and 13.

**Response by OMERACT-OARSI criteria**
As defined by the consensus group, OMERACT 6, 2002 a patient was defined as a responder if:
1. There was a reduction of >50% from baseline and an absolute reduction of >20 either in OA pain or in the WOMAC© LK3.1 (DPDA sub-scale score, re-standardized on to a scale of 0 - 100), or if
2. There was a reduction of >20% from baseline and an absolute reduction of >10 in at least two of the three variables: OA pain, the WOMAC© LK3.1 (DPDA sub-scale score re-standardized on to a scale of 0 - 100), or the patient's global assessment of disease activity.

Response to treatment by OMERACT-OARSI criteria at week 13 is summarized in the table below:

**5. Response to treatment by OARSI criteria at week 13 in pooled major efficacy studies 2360 and 2361 (ITT LOCF)**

| | Pooled 2360 + 2361 | | |
|---|---|---|---|
| Response at Week 13 | All LUM 100 mg od | Cel 200 mg od | Placebo |
| **OARSI Response** | | | |
| N | 1616 | 812 | 804 |
| **Responders – n (%)** | **1104 (68.3)** | **528 (65.0)** | **433 (53.9)** |
| Odds ratio vs. placebo | 1.86 | 1.60 | na |
| CI | 1.56, 2.21 | 1.31, 1.95 | na |
| p-value † | <0.001 | <0.001 | na |
| Odds ratio vs. celecoxib | 1.16 | na | na |
| CI | 0.97, 1.39 | na | na |
| p-value † | 0.098 | na | na |

† Multiple logistic regression model with pooled country, treatment and baseline OA pain value as main effects.
Pairwise comparisons tested at the two-sided 5% significance level unadjusted for multiplicity.
All LUM in the pooled analysis is the effect of the combined lumiracoxib treatment groups.
na = not applicable

Both lumiracoxib groups in the separate studies and the combined lumiracoxib group in the pooled dataset were superior to placebo and comparable to celecoxib at all time points.

**Subgroup analyses of patients with OA in joints other than the knee.**
The presence of OA in other joints had no effect on the efficacy of the active treatments as measured by the patient's global assessment of disease activity or by the physician's global assessment of disease activity, as lumiracoxib 100mg od, lumiracoxib 200mg od ID, and celecoxib 200mg od were all significantly superior to placebo (all, $p \leq 0.001$). No statistically significant difference could be detected between either lumiracoxib 100mg or lumiracoxib 200mg ID and celecoxib, or between the two lumiracoxib dose groups.

**Subgroup analyses of patients with no other OA joint**
At Week 13, both lumiracoxib 100mg od and lumiracoxib 200mg od ID were significantly more effective than placebo for both the patient's and physician's global assessment of disease activity. However, celecoxib 200mg did not reach significance at Week 13 in the patient's or physician's global assessment of disease activity, which may be a result of the small number of patients with no other OA joint in this group. The active treatments did not reach significance at some other time points. In the patient's global assessment of disease activity lumiracoxib 100mg od did not reach significance at Week 2. None of the treatments reached significance at Weeks 4 and 8. In the physician's global assessment of disease activity none of the treatments reached significance at Week 4. Only lumiracoxib 100mg od was significant at Week 8.

**Patients with OA of the hand**
The effect of treatment on OA of the hand was assessed using the AUSCAN questionnaire in those patients who reported OA of the hand at the baseline visit. No statistically significant difference in AUSCAN total scores was detected for any between-treatment comparison in patients with OA of the hand. Similar results were seen for the AUSCAN pain, stiffness, and physical function sub-scale scores. There was no stratification for hand OA, which was self reported.

**6. AUSCAN (Total score) in patients with hand OA (ITT LOCF) – after 13 weeks treatment.**

| | *Change from baseline* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Treatment** | Study 2360 | | | | Study 2361 | | | |
| | Mean | s.d. | min | max | Mean | s.d. | min | max |
| Lumiracoxib 100mg od | -5.08 | 9.855 | -36.0 | 25.0 | -2.29 | 11.014 | -53.0 | 38.0 |
| Lumiracoxib 200mg ID | -4.75 | 10.607 | -43.0 | 30.0 | -2.42 | 11.301 | -32.0 | 25.0 |
| Celecoxib 200mg od | -4.93 | 11.046 | -52.0 | 19.0 | -3.75 | 9.052 | -29.0 | 22.0 |
| Placebo | -3.73 | 9.691 | -35.0 | 27.0 | -2.78 | 11.488 | -38.0 | 20.0 |

**Clinical relevance of results**
The minimal perceptible clinical improvement (MPCI) criterion based on the WOMAC pain subscale is based on the estimate published in Ehrich 2000 for knee OA and consists of an Absolute decrease from baseline of at least 9.7 mm in the WOMAC (0-100 mm VAS) pain subscale score (corresponding to a decrease of at least 2 out of 20 points on the WOMAC© LK3.1 pain subscale)

Lumiracoxib 100 mg od was superior to placebo and comparable to celecoxib 200 mg od according to the MPCI criterion at all time points. The majority of patients receiving either of the active treatments perceived a decrease in their pain by week 2, and at least 67% had less pain by week 8 and week 13.
A similar concept is the criterion for minimal clinically important improvement (MCII), published by Tubach et al (2005).

**7. Summary of lumiracoxib changes from baseline compared with published definitions of minimum clinically important or perceptible change (mm).**

| | Week | Pooled studies Pooled regimens (placebo) | Study 2360 Pure 100 mg od (placebo) | Study 2361 Pure 100 mg od (placebo) |
|---|---|---|---|---|
| OA Pain<br>MCII Criterion [1]= **19.9** | 2 | 20.5 † (12.1) | 22.7 (13.0) | 17.6 (11.3) |
| | 13 | 26.0 (19.8) | 25.1 (18.1) | 26.8 (21.4) |
| Disease activity - Patient's global assessment<br>MCII Criterion [1] = **18.3** | 2 | 18.7 † (9.5) | 20.8 (9.7) | 16.3 (9.2) |
| | 13 | 23.7 (16.3) | 23.2 (13.4) | 25.1 (18.9) |
| WOMAC DPDA (Function) 0-100 VAS ††<br>MCII Criterion [1] = **9.1**<br>MPCI Criterion [2] = **9.3** | 2 | 12.94 † (6.03) | 15.32 (7.29) | 10.46 (4.96) |
| | 13 | 16.47 (10.59) | 17.46 (9.29) | 15.46 (11.72) |
| WOMAC Pain 0-100 VAS ††<br>MPCI criterion [2] = **9.7** | 2 | 14.0 † (7.0) | 16.1 (9.05) | 11.75 (5.35) |
| | 13 | 17.5 (12.0) | 17.8 (11.25) | 16.85 ( 12.3) |

MCII is defined as the minimal improvement where 75% of patients recorded "good" on the Likert 5-point scale
MPCI is diff. from baseline in mean change of WOMAC total score in patients with no or poor global response to therapy

† pooled regimens at week 2 comprise groups on 100 mg od and 200 mg od., †† data from studies 2360 and 361 were re-scaled to a 1-100 point scale
Source [1] Tubach F, Ravaud P, Baron G et al., 2005a, [2] Ehraich EW, Davies GM, Watson DJ, et al., 2000.

*Assessor's comments on Studies 2360 and 2361:*
The design of these two studies was appropriate with the appropriate doses of comparator used. Comparison with celecoxib is helpful as another COX2 inhibitor but a comparison with paracetamol, an analgesic commonly used in OA might have given more helpful information regarding the risk:benefit ratio.
Generally patients were well balanced across the groups for age, sex, race, disease duration and prior NSAID use.
In study 2360 approximately 10% of patients in each group were aged >75 years. In study 2361 there were fewer patients aged >75 years in the lumiracoxib 100mg group (8.6%) compared to the lumiracoxib 200mg ID (11.2%), celecoxib (13.1%) and placebo (10.6%) groups but this appears to be balanced by an inverse trend in the ≥65- <75 years age group.
In these two pivotal studies, lumiracoxib at a dose of 100mg od has demonstrated a statistically significant improvement over placebo and similar efficacy to celecoxib 200mg od, in the treatment of OA of the knee. Generally the treatment effects are small (5-7mm on the pain VAS compared to placebo) with a responder rate of 14.4% greater than placebo. The results from the primary efficacy variables are mainly supported by the secondary efficacy variables.

*Extrapolation of results to other OA joints*:
According to the CPMP Guidelines it is the responsibility of the applicant to demonstrate that efficacy in one major joint can be extrapolated to other joints. "Due to the pathophysiological differences in osteoarthritis of the knee or hip and osteoarthritis of the hand, extrapolation of results obtained in the lower limbs to the hand [or vice versa] is highly questionable."
AUSCAN questionnaire: The results for the active treatments were very similar to those for placebo. In fact at some time points, placebo appears more effective than lumiracoxib. Although these studies were not powered to show a statistically significant difference, it is of concern that lumiracoxib 100mg od seems to show little efficacy in OA of the hand.
In the subgroup analyses of patients with or without OA in other joints, the treatment effects of the active treatments did not reach statistical significance in patients with no other OA joint. However the actual change from baseline compared to placebo, seen in these patients was similar to that seen in patients with other OA joints. The lack of statistical significance may be due to the smaller numbers in the group with no other OA joint.

*Comparisons across studies*
**Studies 0112 and 0109**
Studies 0112 and 0109, submitted in the original dossier, were similar in design and comparator to studies 2360 and 2361. Study 0112 was a 13-week multicentre randomised double blind, double dummy, placebo-controlled, parallel group trial in patients with primary osteoarthritis of the knee using celecoxib as a comparator.
The primary objective of this trial was to determine if lumiracoxib (200 or 400mg od) was effective in osteoarthritis as compared with placebo. Comparison of efficacy with celecoxib 200mg od was a secondary objective.
The following table shows the change from baseline in efficacy variables for lumiracoxib 200mg od and lumiracoxib 400mg od compared to lumiracoxib 100mg od:

**8. Change from baseline at week 13 of efficacy variables – comparison across studies.** (Table compiled by assessor)

| Efficacy variable | Lumiracoxib 200mg od | | Lumiracoxib 400mg od | | Lumiracoxib 100mg od | Lumiracoxib 100mg od |
|---|---|---|---|---|---|---|
| | Study 0112 | Study 0109 | Study 0112 | Study 0109 | Study 2360 | Study 2361 |
| OA Pain VAS Score | - 26.0 | -28.7 | - 27.4 | -29.7 | -25.1 | -26.8 |
| Patient global assessment | -23.2 | -25.3 | -24.1 | -25.8 | -23.2 | -25.1 |
| Response rate (OARSI criterion) | 64.3% | 69.7% | 69.5% | 71.5% | 64.7% | 73.6% |

*Assessor's comments:*
The absence of a study directly comparing lumiracoxib 100mg od with 200mg od is unfortunate as comparison of results across studies is problematical, even though these studies had similar designs and inclusion/exclusion criteria. The results are of

the same order for all the doses of lumiracoxib with no evidence of a decrease in efficacy with the 100mg od dose. There is, however, no evidence of a dose response of lumiracoxib in the treatment of OA of the knee.

*Long Term Efficacy*
Two extension studies were performed following each of the two pivotal studies 2360 and 2361. All patients completing the core studies were eligible to enter the extension studies.

**Study 2361E1**
A 39-week, double-blind, active-controlled extension to COX189A2361, in patients with primary knee osteoarthritis, using celecoxib (200 mg od) as a comparator.
Of the 1684 randomised patients in Study 2361, 1310 entered the extension study. At Visit 6 of the core study (Day 91), all patients from the core study placebo arm consenting to enter the extension study were randomised (1:1) to receive either lumiracoxib 100 mg od. or celecoxib 200 mg od. All other patients continuing in the extension study remained on their respective treatment regimen. Therefore 853 patients (176 from the placebo arm) received lumiracoxib 100mg od and 457 patients (130 from the placebo arm) received celecoxib 200mg od.

*Primary objective*
To determine if lumiracoxib 100 mg od was effective in treating osteoarthritis (OA) in the target knee as compared to celecoxib 200 mg od with respect to:
- Overall OA pain intensity in the target knee on a 0-100 mm Visual Analogue Scale (VAS) at 26 weeks.
- Patient's global assessment of disease activity on a 0-100 mm VAS at 26 weeks.
- Patient's functional status using the WOMAC© total score at 26 weeks.

*Secondary objectives*
- To assess the safety and tolerability of lumiracoxib compared to celecoxib. For the purpose of assessing long term safety a protocol amendment was made extending the study to 52 weeks (including the 13-week core study).
- Secondary efficacy objectives as in the core study 2361.

*Patient disposition*
A quarter of the patients withdrew before the end of the extension phase (27.3% in the lumiracoxib arm and 21.4% in the celecoxib arm), 'patient withdrew consent' being the most common reason (9.6% and 8.3% respectively). However unsatisfactory therapeutic effect was the second most common reason with 7.6% of patients in the lumiracoxib arm and 5.5% of patients in the celecoxib arm withdrawing for this reason. Adverse events were given as the reason for withdrawal in 5.6% of patients (lumiracoxib) and 4.4% of patients (celecoxib).

*Efficacy results*
The results of the analyses in the main efficacy ITTCA population (LOCF) for the three joint primary efficacy variables are summarized in the table below:

**9. Efficacy results after 26 weeks treatment.**

| | | | Contrast lumiracoxib – celecoxib | | |
|---|---|---|---|---|---|
| Treatment | n | LS Mean | Estimated difference | 95% CI of difference | p-value |
| **OA pain intensity in target joint (VAS) treatment comparison after 26 weeks (ITTCA,LOCF)** | | | | | |
| Lumiracoxib 100mg od | 840 | 38.98 | 0.66 | -1.87, 3.20 | 0.608 |
| Celecoxib 200mg od | 419 | 38.32 | -- | -- | -- |
| **Patient's global assessment of pain (VAS) treatment comparison after 26 weeks (ITTCA, LOCF)** | | | | | |
| Lumiracoxib 100mg od | 840 | 40.52 | 0.05 | -2.52, 2.61 | 0.971 |
| Celecoxib 200mg od | 420 | 40.47 | -- | -- | -- |
| **WOMAC (total score) treatment comparisons after 26 week (ITTCA, LOCF)** | | | | | |
| Lumiracoxib 100mg od | 835 | 34.76 | -0.19 | -2.02, 1.64 | 0.837 |
| Celecoxib 200mg od | 418 | 34.95 | -- | -- | -- |

For each of the three primary efficacy variables specified in the protocol, no differences between lumiracoxib 100 mg od and celecoxib 200 mg od were seen in the main efficacy population (ITTCA).
The comparability of the two treatments is further supported by the observation that there was no difference between the two groups with respect to the consumption of rescue medication.

*Safety results*
The long term safety of lumiracoxib will be discussed below in section 5.3 Clinical Safety.

*Assessor's comments:*
This 52-week study comparing lumiracoxib 100mg od with celecoxib 200mg od demonstrated comparable efficacy. Although the primary efficacy endpoints were analysed after 26 weeks, data were collected up to 52 weeks (LOCF) and showed that similar efficacy persisted with no evidence of tachyphylaxis.
Throughout the extension study approximately 50% of patients reported taking rescue medication (paracetamol), the majority (30-40%) taking >0-1 tablet per day. Fewer than 5% of patients reported taking >2 tablet of rescue medication per day. This use of rescue medication is not excessive and is similar in the two groups.

**Study 2360E1**
This was an open-label extension to the 13-week Study 2360 and all patients who entered the extension study received lumiracoxib 100mg od. It was therefore primarily a safety study but some efficacy data were also collected as secondary endpoints.
Efficacy results are summarized below according to lumiracoxib exposure regimens in months (LOCF).

**10. Summaries by months of exposure of the three main efficacy parameters (LOCF, n=827)**

| lumiracoxib 100 mg o.d. | Overall OA pain intensity (VAS mm) | | Patient's global assessment of disease activity (VAS mm) | | Physician's global assessment of disease activity (VAS mm) | |
|---|---|---|---|---|---|---|
| Exposure[1] | Mean (SD) | Mean diff.[2] (SD) | Mean (SD) | Mean diff.[2] (SD) | Mean (SD) | Mean diff.[2] (SD) |
| 3 months* | 36.1 (23.5) | -16.3 (28.7) | 35.1 (22.8) | -16.1 (27.7) | 31.4 (20.8) | -18.3 (28.0) |
| 6 months | 37.1 (24.4) | -15.4 (29.7) | 37.1 (24.1) | -14.2 (28.6) | 33.1 (22.0) | -16.6 (28.8) |
| 9 months | 37.0 (24.7) | -15.4 (29.3) | 37.8 (24.2) | -13.5 (28.1) | 34.0 (23.0) | -15.6 (28.6) |
| 12 months** | 37.9 (24.7) | -14.5 (28.7) | 38.3 (24.8) | -13.0 (28.3) | 34.4 (23.4) | -15.3 (28.8) |

[1] Exposure = Months of lumiracoxib treatment from initiation (either in the core or in the extension phase depending on initial treatment allocation).

[2] Mean difference from baseline. Baseline is Visit 2 for patients who continued on lumiracoxib 100 mg o.d., and Visit 6 for patients who switched from celecoxib 200 mg o.d. or placebo.

* Note that the efficacy results for month 3 (visit 6 of the core study) do not match those for the core study lumiracoxib group because the current summary does not differentiate between the two core-phase lumiracoxib groups (lumiracoxib 100 mg o.d. and lumiracoxib 200 mg initial dose) and also includes patients who switched from celecoxib and placebo.

** up to 9 months for patients who switched to lumiracoxib 100 mg o.d. in the extension phase

Discontinuation due to unsatisfactory therapeutic effect was also considered an efficacy endpoint. In this extension study unsatisfactory therapeutic effect was the most common reason for withdrawal with 12.6% of patients discontinuing for this reason.

*Assessor's comments:*
The results from patients who took both regimens of lumiracoxib in the core study are pooled with those of patients who commenced lumiracoxib in the extension study, having taken celecoxib or placebo in the core study. Thus the changes seen in the extension study cannot be compared with those seen in the core study and it is difficult to draw any conclusions.
In general the treatment effect shows a trend to decrease over the course of the 9 month extension phase of this study.

**Dysmenorrhoea**

**Study 2353**

This was a randomised, double-blind, active- and placebo-controlled, complete-block crossover study comparing the efficacy of lumiracoxib 200 mg od, lumiracoxib 200 mg with a 200 mg re-dose if needed on day 1 (re-dose could be taken between 1 to 12 hours after the initial dose) followed by 200 mg od on two subsequent days, naproxen 500 mg bd and placebo in women with primary dysmenorrhoea. Patients were randomized to one of four treatment sequences, thus receiving the four treatments in four different menstrual cycles. Study medication was administered for up to 3 days starting at the onset of moderate to severe menstrual pain. Rescue medication (acetaminophen/paracetamol 500 mg, up to a maximum of 4000 mg within any given 24-hour period) was allowed, but not until at least one hour after the first dose of study medication (after the 60 minute pain assessment) in each treatment period and after taking the re-dose medication.

Pain assessments were collected up to 12 hours after the first dose on the first day of each treatment period. Thereafter, patients were allowed to take study medication for up to 3 days, if needed.

A patient global assessment of treatment was performed 72 hours (3 days) after the initial dose in each treatment period or at premature discontinuation

The primary efficacy variable was the Summed (time-weighted) Pain Intensity Difference based on the categorical scale calculated over the 0 to 8 hour time period (SPID-8) on day 1 of a treatment period.

Secondary efficacy variables consisted of the following:

- Time-specific pain intensity difference (PID) based on the categorical scale at time points up to 12 hours after dosing on day 1 of a treatment period.
- Time-specific pain relief (PR) based on the categorical scale at time points up to 12 hours after dosing on day 1 of a treatment period.
- Time-specific pain relief intensity difference (PRID) based on the categorical scale at time points up to 12 hours after dosing on day 1 of a treatment period.
- Time-to-onset of analgesia (defined as the earliest time achieving a PID-categorical value ≥1 and maintaining such values for at least 1 hour) up to 8 hours after dosing on day 1 of a treatment period.
- Time-to-first rescue medication use (measured up to 12 hours on day 1 of a treatment period).
- Summed (time-weighted) Pain Intensity Difference based on the categorical scale calculated over the 0 to 12 hour time period (SPID-12) on day 1 of a treatment period.
- Time-specific PID based on the visual analogue scale (VAS) at time points up to 12 hours after dosing on day 1 of a treatment period.
- Total (time-weighted) pain relief from 0 to 8 hours (TOTPAR-8) and from 0 to 12 hours (TOTPAR-12) on day 1 of a treatment period.
- Patient global evaluation (measured at the end of day 3 of a treatment period or at premature discontinuation).

Safety: Safety parameters consisted of adverse events (AEs), laboratory evaluations, and vital sign measurements.

*Patient disposition*

Overall a fifth of patients withdrew from the study. The most common reason for withdrawal was protocol violation.

**11. Patient disposition by treatment sequence based on medication dispensed.**

| | L/Nap/Pla/LR | LR/Pla/Nap/L | Nap/LR/L/Pla | Pla/L/LR/Nap | All regimens |
|---|---|---|---|---|---|
| | N = 36 | N = 36 | N = 36 | N = 36 | N = 144 |
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| **Total no. of patients:** | | | | | |
| completed | 30 (83.3) | 28 (77.8) | 32 (88.9) | 28 (77.8) | 118 (81.9) |
| discontinued | 6 (16.7) | 8 (22.2) | 4 (11.1) | 8 (22.2) | 26 (18.1) |
| **Reasons for discontinuation** | | | | | |
| Adverse event | 0 ( 0.0) | 0 ( 0.0) | 1 ( 2.8) | 1 ( 2.8) | 2 ( 1.4) |
| Protocol violation | 2 ( 5.6) | 3 ( 8.3) | 2 ( 5.6) | 4 (11.1) | 11 ( 7.6) |
| Subject withdrew consent | 2 ( 5.6) | 2 ( 5.6) | 1 ( 2.8) | 2 ( 5.6) | 7 ( 4.9) |
| Lost to follow-up | 2 ( 5.6) | 3 ( 8.3) | 0 ( 0.0) | 1 ( 2.8) | 6 ( 4.2) |

L = lumiracoxib 200 mg o.d.; LR = lumiracoxib 200 mg o.d. with optional 200 mg redose on day 1; Nap = naproxen 500 mg b.i.d.; Pla = placebo.

*Results*

Both the lumiracoxib 200 mg od. and 200 mg / redose (on day one only) treatment groups demonstrated effective, similar relief from pain associated with primary dysmenorrhoea as shown by the results for the primary efficacy variable, SPID-8. Both lumiracoxib treatments were statistically superior to placebo, as was the active comparator naproxen. All of the active treatment groups demonstrated comparable efficacy.

**12. Summed (time weighted) pain intensity difference from 0-8 hours (SPID-8) in dysmenorrhoea versus comparators (ITT population)**

| Population Treatment | N | LSM | Comparisons | Estimated difference | 95% CI | p-value† |
|---|---|---|---|---|---|---|
| **ITT population** | | | | | | |
| **Primary analysis** | | | | | | |
| Lumiracoxib 200 mg o.d. | 126 | 12.07 | - Placebo | 3.85 | 2.83, 4.87 | <0.001‡ |
| Lumiracoxib 200 mg o.d. /redose | 127 | 12.00 | - Placebo | 3.78 | 2.76, 4.80 | <0.001‡ |
| **Other pairwise comparisons** | | | | | | |
| Lumiracoxib 200 mg o.d. | 126 | 12.07 | - Lumiracoxib 200 mg o.d. /redose | 0.06 | -0.96, 1.08 | 0.904 |
| | | | - Naproxen | -0.04 | -1.06, 0.98 | 0.939 |
| Lumiracoxib 200 mg o.d. /redose | 127 | 12.00 | - Naproxen | -0.10 | -1.12, 0.92 | 0.844 |
| Naproxen | 124 | 12.11 | - Placebo | 3.89 | 2.86, 4.92 | <0.001 |
| Placebo | 125 | 8.22 | | | | |

† ANOVA with period, treatment and pain intensity (categorical) at baseline as fixed factors, and patient as a random factor. All tests were performed at the 5% significance level.

‡ Significance for primary analysis were judged using the modified Bonferroni procedure proposed by Hochberg which adjusts for multiplicity.

LSM = least squares mean

All active treatments were also consistently superior to placebo and generally comparable to each other for the time-specific secondary efficacy variables PID (categorical), PID (VAS), PR, and PRID, as well as for SPID-12, TOTPAR-8 and TOTPAR-12.

The median time to onset of analgesia with Miller's adjustment was about 1 hour for both lumiracoxib 200 mg od and naproxen, which was approximately twenty minutes faster than for the placebo group. The analysis using the stratified proportional hazards model resulted in a significant hazard ratio for the naproxen - placebo comparison and a trend in favour of lumiracoxib when compared to placebo.

Within the first 12 hours after the first dose of study drug, a lower percentage of patients required redose medication in the active treatment groups as compared to the

placebo group (31% [naproxen], 35% & 37% [lumiracoxib] vs. 46% [placebo]). A similar pattern was seen for rescue medication use (8 [naproxen] 13% & 14% [lumiracoxib] vs. 23% [placebo]). As less than 50% of patients used redose or rescue within 12 hours in all treatment groups, the median times to redose and rescue medication use were greater than 12 hours in all groups. When comparing the treatments using the proportional hazard model, it was shown that the time to rescue was statistically significant for each active treatment group compared to placebo.

**Study 2358**

This was a randomized, double-blind, placebo-controlled, complete-block crossover study comparing the efficacy of lumiracoxib 200 mg od, lumiracoxib 200 mg with a 200 mg re-dose if needed on day 1 (re-dose could be taken between 1 to 12 hours after the initial dose) followed by 200 mg od. on two subsequent days, and placebo in women with primary dysmenorrhoea. Patients were randomized to one of six treatment sequences, thus receiving each of the three treatments in a different menstrual cycle.

The primary efficacy variable was the Summed (time-weighted) Pain Intensity Difference based on the categorical scale calculated over the 0 to 8 hour time period (SPID-8) on day 1 of a treatment period.
Similarly, the secondary efficacy variables were the same as in study 2353.

*Patient disposition*

In this study nearly a third of patients did not complete the study. The most common cause for withdrawal was withdrawal of consent.

**13. Patient disposition by treatment sequence based on medication dispensed.**

| | L/LR/Pla N = 22 n (%) | L/Pla/LR N = 22 n (%) | LR/L/Pla N = 22 n (%) | LR/Pla/L N = 22 n (%) | Pla/L/LR N = 23 n (%) | Pla/LR/L N = 21 n (%) | All regimens N = 132 n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. of patients:** | | | | | | | |
| Completed | 16 (72.7) | 16 (72.7) | 18 (81.8) | 16 (72.7) | 13 (56.5) | 15 (71.4) | 94 (71.2) |
| Discontinued | 6 (27.3) | 6 (27.3) | 4 (18.2) | 6 (27.3) | 10 (43.5) | 6 (28.6) | 38 (28.8) |
| **Reasons for discontinuation** | | | | | | | |
| Adverse event | 1 ( 4.5) | 1 ( 4.5) | 0 ( 0.0) | 0 ( 0.0) | 2 ( 8.7) | 0 ( 0.0) | 4 ( 3.0) |
| Abnormal lab values | 0 ( 0.0) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 4.5) | 0 ( 0.0) | 0 ( 0.0) | 1 ( 0.8) |
| Protocol violation | 2 ( 9.1) | 1 ( 4.5) | 1 ( 4.5) | 1 ( 4.5) | 3 (13.0) | 2 ( 9.5) | 10 ( 7.6) |
| Withdrawal of consent | 2 ( 9.1) | 2 ( 9.1) | 1 ( 4.5) | 2 ( 9.1) | 3 (13.0) | 3 (14.3) | 13 ( 9.8) |
| Lost to follow-up | 1 ( 4.5) | 2 ( 9.1) | 2 ( 9.1) | 2 ( 9.1) | 2 ( 8.7) | 1 ( 4.8) | 10 ( 7.6) |

L = lumiracoxib 200 mg o.d.; LR = lumiracoxib 200 mg with optional 200 mg redose on day 1; Pla = placebo.

*Results*

Both the lumiracoxib 200 mg od and 200 mg / redose (on day 1 only) treatment groups demonstrated effective, similar relief from pain associated with primary dysmenorrhoea as shown by the results for the primary efficacy variable, SPID-8. Both lumiracoxib treatments demonstrated comparable efficacy and were statistically superior to placebo.

**14. Summed (time weighted) pain intensity difference from 0-8 hours (SPID-8) in dysmenorrhoea versus comparators (ITT population)**

| Population Treatment | N | LSM | Comparisons† | Estimated difference | 95% CI | p-value |
|---|---|---|---|---|---|---|
| ITT population | | | | | | |
| Primary analysis | | | | | | |
| Lumiracoxib 200 mg o.d. | 104 | 10.82 | - placebo | 4.07 | 2.66, 5.47 | <0.001‡ |
| Lumiracoxib200 mg / redose | 103 | 11.71 | - placebo | 4.96 | 3.55, 6.37 | <0.001‡ |
| Other pairwise comparisons | | | | | | |
| Lumiracoxib 200 mg o.d. | 104 | 10.82 | - lumiracoxib 200 mg / redose | -0.89 | -2.30, 0.52 | 0.214 |
| Placebo | 105 | 6.75 | | | | |

† ANOVA with period, treatment and pain intensity (categorical) at baseline as fixed factors, and patient as a random factor.

‡ Significance for primary analysis was judged using the modified Bonferroni procedure proposed by Hochberg which adjusts for multiplicity.

LSM = least squares mean.

The lumiracoxib treatments were also consistently superior to placebo for the time-specific secondary efficacy variables PID (categorical), PID (VAS), PR, and PRID, as well as for the composite secondary efficacy variables SPID-12, TOTPAR-8 and TOTPAR-12. In general, the lumiracoxib 200 mg/ redose group did not have a notable benefit over lumiracoxib 200 mg od, although slight advantages were seen for some of the secondary efficacy variables.
Lumiracoxib showed statistically significantly faster onset than the placebo group. The median time to onset of analgesia (using Miller's adjustment) was 1.35 hours for lumiracoxib 200mg od group and 2.03 hours for the placebo group.

The median time to redose medication use was longer for the lumiracoxib 200 mg / redose regimen (> 12 hours) than for the lumiracoxib 200 mg od regimen (8 hours), due to slightly more than half (56%) the patients in the 200 mg od group taking the redose within the first 12 hours after the first dose of study drug. Redose medication was taken by 46% of patients in the lumiracoxib 200mg/ redose group and 76% of patients in the placebo group.

*Assessor's comments:*
The design of these two studies is similar with study 2353 including an active comparator in addition to placebo.
Each subject took all treatments in random sequence for subsequent menstrual cycles. As the severity of dysmenorrhoea can be very variable between subjects, this design is appropriate to help to decrease inter-subject variability. There was, however, a high dropout rate, particularly in study 2358.
In the primary efficacy variable the active treatments demonstrated superior efficacy to placebo and there was little difference between the two lumiracoxib doses or between lumiracoxib and naproxen (study 2353).
These results are largely supported by the results of the secondary efficacy variables, though the rate of redose and the amount of rescue medication taken shows a trend towards greater efficacy from naproxen 500mg bd. The pain intensity difference on the categorical scale (PIDcat) over 0-24 hours did show an attenuation of effect between 12 and 24 hours *(see p 29 Summary of Clinical Efficacy – Dysmenorrhoea at Annex V)*, which may suggest that the effect of 100mg lumiracoxib in dysmenorrhoea may not last the full 24 hours.

*Comparison across studies*
The results obtained in the two new studies show a similar efficacy for lumiracoxib 200mg od in dysmenorrhoea as that shown in the two previous studies using lumiracoxib 400mg od as shown in the table below. There is a distinct lack of a dose response and lower doses of lumiracoxib have not been investigated in the treatment of dysmenorrhoea.

**15. Summed (time weighted) pain intensity difference from 0-8 hours (SPID-8) in dysmenorrhoea (ITT population).** (Table compiled by assessor)

| Treatment | | Study 2353 | Study 2358 | Study 0129 | Study 0130 |
|---|---|---|---|---|---|
| **Lumiracoxib 200mg od** | N<br>LS Mean<br>Dif –placebo<br>95% CI | 126<br>**12.07**<br>**3.85**<br>2.83, 4.87 | 104<br>**10.82**<br>**4.07**<br>2.66, 5.47 | - | - |
| **Lumiracoxib 200mg + 200mg redose (optional)** | N<br>LS Mean<br>Dif –placebo<br>95% CI | 127<br>**12.0**<br>**3.78**<br>2.76, 4.80 | 103<br>**11.71**<br>**4.96**<br>3.55, 6.37 | - | - |
| **Lumiracoxib 400mg od** | N<br>LS Mean<br>Dif –placebo<br>95% CI | - | - | 78<br>**11.32**<br>**4.66**<br>2.81, 6.51 | **81**<br>9.86-<br>3.38<br>**1.73, 5.04** |
| **Naproxen 500mg bd** | N<br>LS Mean<br>Dif –placebo<br>95% CI | 124<br>**12.11**<br>**3.89**<br>2.86, 4.92 | -<br><br>-<br> | -<br><br>-<br> | **88**<br>11.04<br>4.57<br>**2.95, 6.18** |
| **Rofecoxib 50mg od** | N<br>LS Mean<br>Dif –placebo<br>95% CI | - | - | 80<br>**11.31-**<br>**4.65**<br>2.81, 6.48 | - |
| **Placebo** | N<br>LS Mean | 125<br>**8.22** | 105<br>**6.75** | 78<br>**6.66** | **88**<br>6.47 |

LS – Least Square
CI – Confidence Interval

*Assessor's comments:*
No study directly comparing the 400mg od dose of lumiracoxib with the proposed 200mg od dose has been conducted in dysmenorrhoea. However from the comparison across studies as in the table above, the effect seen with the 200mg od dose is similar to that demonstrated by the 400mg od dose. Both doses have shown similar efficacy to the comparators.
Lower doses of lumiracoxib have not been studied in dysmenorrhoea so it is not possible to know whether 200mg od is the optimal dose or whether a lower dose might also offer similar efficacy.

*Long term efficacy*
No long term studies have been performed as dysmenorrhoea is a short term indication.

## Clinical Safety

The safety and tolerability of lumiracoxib has been evaluated in healthy volunteers and in patients with the targeted disorders, acute pain (postoperative dental and post-surgical orthopaedic), dysmenorrhoea, osteoarthritis and rheumatoid arthritis.
The applicant has provided data on the safety populations from all studies to date, many of which have been previously assessed.
For the purposes of this report, this assessor will concentrate on the safety data from 'new' efficacy studies in osteoarthritis and dysmenorrhoea and long term safety data.

### Short term safety (dysmenorrhoea)

**Study 2353**

Approximately 20% of patients in the lumiracoxib groups had adverse events (AEs), compared to 23% in the naproxen group and 13% in the placebo group. There were no relevant differences between the groups for AEs by primary system-organ class with the exception of gastrointestinal disorders, which were more frequent in the lumiracoxib 200 mg / redose and naproxen groups (approximately 7% of patients in each group) compared to the lumiracoxib 200 mg od and placebo groups (approximately 2% of patients in each group).
The incidence of AEs suspected to be study drug related was highest in the lumiracoxib 200 mg / redose group (about 7%), followed by the naproxen, placebo and lumiracoxib 200 mg od groups (about 5%, 2%, and 2% respectively). The main reason for this imbalance was a higher frequency of suspected related gastrointestinal disorders (mainly nausea) and nervous system disorders (mainly dizziness) in the lumiracoxib 200 mg / redose group compared to the other groups.
*Deaths and SAEs*
There were no deaths reported in this study. Two patients had SAEs, one in the lumiracoxib 200 mg / redose group (intervertebral disc herniation) and one in the naproxen group (ankle fracture). Neither was suspected to be related to study drug; both were severe events.

**Study 2358**

Overall, AEs were less frequent in the lumiracoxib 200 mg od group (approximately 24% of patients) than in the lumiracoxib 200 mg / redose (33%) and placebo groups (36%). There were no relevant differences between the groups for AEs by primary system-organ class with the exception of nervous system disorders, which were more frequent in the lumiracoxib 200 mg od and 200 mg / redose groups (about 11% and 13% respectively) compared to the placebo group (8%). This difference is mainly due to a higher incidence of headache and dizziness in the lumiracoxib groups compared to placebo to the lumiracoxib groups.
The incidence of AEs suspected to be study drug-related was higher in the placebo group (about 11%) than in the lumiracoxib 200 mg od and 200 mg / redose groups (about 5% and 3% respectively). The main reason for this imbalance was a higher frequency of study drug related gastrointestinal disorders (mainly nausea and vomiting) in the placebo group compared
*Deaths and SAEs*
There were no deaths reported during this study. Two patients had SAEs, one in the lumiracoxib 200 mg od group (road traffic accident) and one in the lumiracoxib 200

mg / redose group (renal colic). Neither was suspected to be related to study drug; both were severe events.

**Prespecified adverse events**

In addition the occurrence of prespecified adverse events: gastrointestinal events (excluding ulcers), gastrointestinal ulcers, peripheral oedema and cardiovascular events (both including and excluding chest pain) were noted. No events were reported in the "gastrointestinal ulcers", "cardiovascular events", or "peripheral oedema" prespecified event categories.

**16. Patients with prespecified adverse events (AEs)**

| Patients studied | Lumiracoxib 200mg od n=105 n (%) | | Lumiracoxib 200mg od/ redose n=103 n (%) | | Naproxen 500mg bd n=124 n (%) | Placebo n=105 n (%) | |
|---|---|---|---|---|---|---|---|
| | Study 2353 | Study 2358 | Study 2353 | Study 2358 | Study 2353 | Study 2353 | Study 2358 |
| Total no. with prespecified AEs | 2 (1.6) | 7 (6.7) | 8 (6.3) | 6 (5.8) | 7 (5.6) | 2 (1.6) | 7 (6.7) |
| **Prespecified event category** | | | | | | | |
| Gastrointestinal events (excluding ulcers) | 2 (1.6) | 7 (6.7) | 8 (6.3) | 6 (5.8) | 7 (5.6) | 2 (1.6) | 7 (6.7) |
| Chest pain | | | 1 (0.8) | | | | |

*Assessor's comments:*

The adverse events seen in these short-term studies are the same as have been seen in earlier studies and are already listed in section 4.8 of the SPC. There is no clear dose response as regards overall adverse events, although in study 2358, the lumiracoxib 200mg od group did have a lower incidence than the lumiracoxib 200mg/redose group In study 2353, gastrointestinal adverse events were less frequent in the lumiracoxib 200mg od group compared to the lumiracoxib 200mg/ redose and naproxen groups.

**Long term Safety Studies (osteoarthritis)**

*Studies ≤13 weeks*

**Studies 2360**

Overall 62% of patients in this study experienced adverse events, a similar number in the two lumiracoxib groups (64.7% and 67%) and fewer in the celecoxib and placebo groups (58.8% and 54% respectively).

**17. AEs overall and by primary system organ class (greater than or equal to 2.0% for any group) (safety population)**

| | Lumiracoxib 100mg od | Lumiracoxib 200mg od ID | Celecoxib 200mg od | Placebo |
|---|---|---|---|---|
| **Patients studied** | n (%) | n (%) | n (%) | n (%) |
| Total no. of patients | 391 (100) | 385 (100) | 393 (100) | 382 (100) |
| Total no. with AEs | 253 (64.7) | 258 (67.0) | 231 (58.8) | 223 (58.4) |
| **Primary system organ class affected** | | | | |
| Infections and infestations | 130 (33.2) | 117 (30.4) | 91 (23.2) | 115 (30.1) |
| Gastrointestinal disorders | 69 (17.6) | 76 (19.7) | 65 (16.5) | 56 (14.7) |
| Nervous system disorders | 56 (14.3) | 65 (16.9) | 63 (16.0) | 60 (15.7) |
| Musculoskeletal and connective tissue disorders | 55 (14.1) | 46 (11.9) | 54 (13.7) | 56 (14.7) |
| Respiratory, thoracic and mediastinal disorders | 35 (9.0) | 39 (10.1) | 39 (9.9) | 21 (5.5) |
| Injury, poisoning and procedural complications | 22 (5.6) | 30 (7.8) | 26 (6.6) | 22 (5.8) |
| General disorders and admin. site conditions | 27 (6.9) | 20 (5.2) | 24 (6.1) | 19 (5.0) |
| Psychiatric disorders | 8 (2.0) | 16 (4.2) | 8 (2.0) | 11 (2.9) |
| Investigations | 21 (5.4) | 15 (3.9) | 9 (2.3) | 13 (3.4) |
| Skin and subcutaneous tissue disorders | 17 (4.3) | 13 (3.4) | 9 (2.3) | 8 (2.1) |
| Ear and labyrinth disorders | 2 (0.5) | 9 (2.3) | 7 (1.8) | 2 (0.5) |
| Vascular disorders | 6 (1.5) | 9 (2.3) | 15 (3.8) | 10 (2.6) |
| Metabolism and nutrition disorders | 9 (2.3) | 4 (1.0) | 4 (1.0) | 0 (0.0) |

Frequency of AEs by Primary system organ class is presented in descending order for the Lumiracoxib 200mg od ID treatment group.

*Deaths and SAEs*

One death occurred during the study. A 65-year-old white male in the lumiracoxib 200mg od ID group died of a myocardial infarction. The patient had a medical history that included coronary heart disease, hypertension and hypercholesterolemia. The event was not suspected to be related to study medication.

The percentage of patients with non-fatal SAEs was similar for all treatment groups; 1.5% for lumiracoxib 100mg od, 1.0% for lumiracoxib 200mg ID, 0.8% for celecoxib and 1.6% for placebo. There were no differences between treatment groups for the body systems affected.

Only 3 SAEs were suspected by the investigators of being study drug related:

| Treatment | Patient | SAE | Outcome |
|---|---|---|---|
| Lumiracoxib 100mg od | 0527-00007 | Abdominal pain lower | Discontinued, concomitant medication, resolved 6 March 2004 |
| Celecoxib 200mg od | 0572-00006 | Deep vein thrombosis | Discontinued, concomitant medication, hospitalized, ongoing at follow up |
| Placebo | 0605-00006 | Hypertension | Study drug adjusted/temporarily interrupted, concomitant medication, hospitalized, resolved 1 December 2003 |

*Prespecified adverse events*

Prespecified AEs as defined in the analysis plan comprised five major categories of events; gastrointestinal events (excluding ulcers), gastrointestinal ulcers, oedema, chest pain, and cardiovascular events. These AEs occurred more often in the lumiracoxib 200mg ID group (16.9% patients) than in the lumiracoxib 100mg (14.3% patients), celecoxib 200mg (14.2% patients), and placebo (12.8% patients) groups. The majority of the prespecified AEs were gastrointestinal events.

**Study 2361**

Approximately 45% of patients in the study experienced an adverse event. The proportion of patients with AEs was similar in the two lumiracoxib treatment groups and lower in both the celecoxib and placebo groups.

**18. AEs overall and by primary system organ class (greater than or equal to 2.0% for any group) (safety population)**

| | Lumiracoxib 100mg od | Lumiracoxib 200mg od ID | Celecoxib 200mg od | Placebo |
|---|---|---|---|---|
| **Patients studied** | n (%) | n (%) | n (%) | n (%) |
| Total no. of patients | 420 (100) | 420 (100) | 420 (100) | 424 (100) |
| Total no. with AEs | 200 (47.6) | 204 (48.6) | 180 (42.9) | 178 (42.0) |
| **Primary system organ class affected** | | | | |
| Infections and infestations | 87 (20.7) | 70 (16.7) | 64 (15.2) | 81 (19.1) |
| Gastrointestinal disorders | 70 (16.7) | 68 (16.2) | 66 (15.7) | 48 (11.3) |
| Nervous system disorders | 38 ( 9.0) | 44 (10.5) | 38 ( 9.0) | 36 ( 8.5) |
| Musculoskeletal and connective tissue disorders | 30 ( 7.1) | 28 ( 6.7) | 31 ( 7.4) | 31 ( 7.3) |
| Vascular disorders | 14 (3.3) | 18 (4.3) | 9 (2.1) | 18 (4.2) |
| General disorders and admin. site conditions | 11 (2.6) | 17 (4.0) | 20 (4.8) | 14 (3.3) |
| Respiratory, thoracic and mediastinal disorders | 20 (4.8) | 16 (3.8) | 10 (2.4) | 14 (3.3) |
| Investigations | 16 (3.8) | 14 (3.3) | 5 (1.2) | 7 (1.7) |
| Injury, poisoning and procedural complications | 13 (3.1) | 13 (3.1) | 8 (1.9) | 10 (2.4) |
| Skin and subcutaneous tissue disorders | 9 (2.1) | 13 (3.1) | 14 (3.3) | 18 (4.2) |
| Ear and labyrinth disorders | 13 (3.1) | 10 (2.4) | 6 (1.4) | 7 (1.7) |
| Psychiatric disorders | 6 (1.4) | 9 (2.1) | 12 (2.9) | 7 (1.7) |

Frequency of AEs by Primary system organ class is presented in descending order for the Lumiracoxib 200mg od ID treatment group.

*Deaths and SAEs*

One death occurred during the study. A 66-year-old white female in the lumiracoxib 100 mg group experienced sudden death while skiing. The patient had a history of hypertension and obesity. The event was not suspected to be related to study medication. This event matched one of the preferred terms pre-specified to identify and report suspected significant vascular events. As a consequence, the case was forwarded to the Cardiovascular Safety Committee, who adjudicated it as a probable CV death.

The percentage of patients with non-fatal SAEs was similar for all treatment groups, 1.2% for lumiracoxib 100mg od, 1.7% for lumiracoxib 200mg ID, 1.4% for celecoxib and 1.7% for placebo.. There were no differences between treatment groups for the body systems affected.

As in study 2360, three SAEs were suspected of being related to study medication.

| Treatment | Patient | SAE | Outcome |
|---|---|---|---|
| Lumiracoxib 200mg od ID | 0196-00022 | Anaphylactic reaction | Discontinued, concomitant medication, hospitalized |
| Celecoxib 200mg od | 0234-00011 | Hypersensitivity | Discontinued, concomitant medication |
| Placebo | 0206-00014 | Coronary artery atherosclerosis | Study drug adjusted/temporarily interrupted; discontinued, concomitant medication. |
| | | Angina pectoris | Concomitant medication, non-drug therapy, hospitalized |

*Prespecified adverse events*

These AEs occurred more often in the active treatment groups [51 (12.1 %), 55 (13.1 %), and 57 (13.6 %) patients in the lumiracoxib 100 mg, lumiracoxib 200 mg ID, and celecoxib 200 mg group] compared with placebo [40 patients (9.4 %)]. The majority of the prespecified AEs were gastrointestinal events. There were no cases of GI ulcers.

*Assessor's comments:*

The adverse events experienced by patients during these studies were not unexpected, but do show a trend towards a dose response, being marginally higher in the lumiracoxib 200mg ID group. However the short time during which patients took the 200mg dose (two weeks) throws doubt on the likelihood of this being a true dose response. Of some concern are the two cardiac deaths, one in the lumiracoxib 100mg group and one in the lumiracoxib 200mg ID group. Although there were pre-existing risk factors and the deaths were not thought to be related to study medication, in the light of concerns over the cardiovascular safety of the COX2 inhibitor class causality cannot be ruled out.

*Studies >13 weeks to 52 weeks.*

**Study 2360E1**

This was a 39-week open-label extension to the 13-week Study 2360.

Of the 1551 patients randomised in Study 2360, 834 consented to enter into the extension study. Patients who entered into the extension phase from the core study lumiracoxib group received lumiracoxib treatment for up to one year. Those who switched from celecoxib or placebo in the core study, received lumiracoxib treatment for up to 9 months.

The primary objective was to assess long-term safety and tolerability of lumiracoxib in patients who participated in the core study for 13 weeks.

The secondary objectives were to assess long-term efficacy of lumiracoxib in patients with knee OA who participated in the core study for 13 weeks with respect to:

- Overall OA pain intensity (Target knee) by visit.
- Patient's global assessment of disease activity by visit.
- Physician's global assessment of disease activity by visit.
- Discontinuation due to unsatisfactory therapeutic effect.

*Patient disposition*

Over the long term, unsatisfactory therapeutic effect was the primary reason for withdrawing from the study (12.6%), though 9.2% withdrew due to adverse events.

**19. Patient disposition in extension study 2360E1**

| Total number of patients studied | lumiracoxib 100 mg o.d. N = 834 |
|---|---|
| Completed | 559 (67.0) |
| Discontinued | 275 (33.0) |
| Reason for discontinuation – n (%) | |
| Adverse Event(s)* | 77 (9.2) |
| Abnormal Laboratory Value(s) | 5 (0.6) |
| Unsatisfactory Therapeutic Effect | 105 (12.6) |
| Patient's Condition No Longer Requires Study Drug | 2 (0.2) |
| Protocol Violation | 21 (2.5) |
| Patient Withdrew Consent | 39 (4.7) |
| Lost to Follow-Up | 14 (1.7) |
| Administrative Problems | 12 (1.4) |

*Adverse events*

Approximately 70% of patients in the extension safety population experienced an AE. A similar frequency was observed for the total safety population.

**20. Number (%) of patients with AEs overall and by system organ class in the extension phase and total (extension and core) safety populations (incidence of at least 2.0% in the extension safety population)**

| lumiracoxib 100 mg o.d. | Extension safety population | Total safety population |
|---|---|---|
| No. (%) of patients studied | 834 (100) | 1181 (100) |
| No. (%) of patients with AEs | 580 (69.5) | 866 (73.3) |
| **Primary system organ class affected – n (%)** | | |
| Infections and infestations | 239 (28.7) | 430 (36.4) |
| Musculoskeletal and connective tissue disorders | 223 (26.7) | 305 (25.8) |
| Nervous system disorders | 159 (19.1) | 251 (21.3) |
| Gastrointestinal disorders | 144 (17.3) | 265 (22.4) |
| Injury, poisoning & procedural complications | 98 (11.8) | 143 (12.1) |
| Respiratory, thoracic and mediastinal disorders | 79 (9.5) | 143 (12.1) |
| General disorders & administration site conditions | 78 (9.4) | 118 (10.0) |
| Investigations | 52 (6.2) | 87 (7.4) |
| Skin and subcutaneous tissue disorders | 39 (4.7) | 70 (5.9) |
| Renal and urinary disorders | 31 (3.7) | 44 (3.7) |
| Psychiatric disorders | 29 (3.5) | 51 (4.3) |
| Metabolism and nutrition disorders | 28 (3.4) | 42 (3.6) |
| Vascular disorders | 24 (2.9) | 40 (3.4) |
| Reproductive system and breast disorders | 22 (2.6) | 32 (2.7) |
| Eye disorders | 19 (2.3) | 30 (2.5) |
| Cardiac disorders | 17 (2.0) | 23 (1.9) |

AEs are listed in order of decreasing frequency in the extension safety population for each primary system organ class

Headache was the most common AE and diarrhoea was the most common AE affecting the GI tract. Generally, there was little difference in the incidence of the individual AEs between the total and extension safety populations.

*Assessor's comments:*

It is reassuring that the incidence of AEs does not appear to increase during the extension study.

*Deaths and Serious Adverse Events*

One death occurred in a patient following withdrawal from the study as a result of an SAE. The 72-year-old Caucasian female was diagnosed on day 363 as having had a cerebrovascular accident. She was hospitalized the same day and immediately withdrawn from the study. She voluntarily discharged herself 8 days later and died the same day. The event was not suspected by the investigator to be related to study medication.

SAEs occurred at a similar rate in both the extension safety population and total safety population (3.7% and 3.5% respectively), and were generally assessed as moderate to severe in intensity.

Three SAEs were considered by the investigator to be related to study medication.

| Patient | SAE | Outcome |
|---|---|---|
| 0238 00062 | Enterocolitis, hemorrhagic | Study drug permanently discontinued, concomitant medication taken, patient hospitalized, ongoing |
| 0671 00010 | Creatinine clearance decreased | Study drug permanently discontinued, ongoing |
| 0527 00019 | Pulmonary embolism | Study drug permanently discontinued, concomitant medication taken, patient hospitalized, resolved after 8 days |

*Prespecified adverse events*

There were 5 major categories of prespecified AEs as defined in the analysis plan: GI events (excluding ulcers), GI ulcers, oedema, chest pain, and cardiovascular events. The incidence of these AES was lower in the extension safety population (15.1%) than in the total safety population (19.6%). In both populations, the majority of the prespecified AEs were GI events.

*Biochemistry*

A number of patients had newly occurring or worsening notable biochemistry abnormalities (by DSMB criteria) during the study. The most common abnormality was a mild/moderate decrease in creatinine clearance and one case was classified as an SAE (see above). In the extension population 8.0% had a >25% decrease over baseline of creatinine clearance compared to 6.4% in the total safety population. Elevated bilirubin and transaminases occurred in similar numbers of patients in the extension population and in the total safety population. A total of 10 patients discontinued as a result of blood chemistry changes

*Assessor's comments:*

The adverse events that occurred during the extension study were not unexpected. Generally the rate of adverse events was not dissimilar from the rate in the overall safety population (core study plus extension) or in the core study alone. The SAEs and biochemical changes that occurred reflected the known adverse events of lumiracoxib.

There is no evidence from this study that the rate of adverse events increases over 52 weeks.

**Study 2361E1**

Approximately 48% of patients in the study experienced an AE in the extension phase only. The proportion of patients with AEs was similar for the lumiracoxib and celecoxib treatment groups.

**21. AEs overall and by primary system organ class (at least 2.0% for any group) (extension safety population) – extension phase only**

| | Lumiracoxib 100 mg o.d. n (%) | Celecoxib 200 mg o.d. n (%) |
|---|---|---|
| **Patients studied** | | |
| Total no. of patients | 853 (100) | 457 (100) |
| Total no. with AEs | 413 (48.4) | 220 (48.1) |
| **Primary system organ class affected** | | |
| Infections and infestations | 170 (19.9) | 84 (18.4) |
| Musculoskeletal and connective tissue disorders | 131 (15.4) | 69 (15.1) |
| Gastrointestinal disorders | 86 (10.1) | 60 (13.1) |
| Nervous system disorders | 82 ( 9.6) | 45 ( 9.8) |
| Injury, poisoning and procedural complications | 44 ( 5.2) | 21 ( 4.6) |
| Vascular disorders | 38 ( 4.5) | 32 ( 7.0) |
| Skin and subcutaneous tissue disorders | 36 ( 4.2) | 12 ( 2.6) |
| Investigations | 33 ( 3.9) | 15 ( 3.3) |
| General disorders and administration site conditions | 28 ( 3.3) | 14 ( 3.1) |
| Respiratory, thoracic and mediastinal disorders | 18 ( 2.1) | 14 ( 3.1) |
| Metabolism and nutrition disorders | 17 ( 2.0) | 12 ( 2.6) |
| Ear and labyrinth disorders | 15 ( 1.8) | 10 ( 2.2) |
| Psychiatric disorders | 13 ( 1.5) | 11 ( 2.4) |
| Eye disorders | 11 ( 1.3) | 12 ( 2.6) |
| Cardiac disorders | 9 ( 1.1) | 10 ( 2.2) |

Frequency of AEs by primary system organ class is presented in descending order for the lumiracoxib 100 mg o.d. treatment group.

Nasopharyngitis and urinary tract infection were both reported with higher frequencies in the lumiracoxib group compared with the celecoxib group. Back pain occurred with a higher frequency in the lumiracoxib group while arthralgia occurred with a higher frequency in the celecoxib group. Dyspepsia and hypertension occurred more frequently with the celecoxib group compared with the lumiracoxib group. Headache occurred with similar frequencies in both treatment groups. All other common AEs occurred with a frequency of $\leq 2.5$ % in either treatment group and showed little differences between the treatment groups.

Similar findings were seen across the combined extension and core phases for the two active treatment groups.

*Deaths and Serious Adverse Events*

No deaths occurred in this extension study. The percentage of patients with non-fatal SAEs in the extension phase only was similar for the lumiracoxib and celecoxib treatment groups (4.5% and 4.9% respectively).

**22. SAEs suspected to be study drug-related (extension safety population)**

| Treatment | Patient | SAE | Outcome |
|---|---|---|---|
| Lumiracoxib 100 mg o.d. | 0001-00005 | Alanine aminotransferase increased | Discontinued |
| Lumiracoxib 100 mg o.d. | 0209-00028 | Diverticulitis | Study drug adjusted/temporarily interrupted; discontinued; hospitalized |
| Lumiracoxib 100 mg o.d. | 0212-00013 | Diverticulitis | Concomitant medication; hospitalized |
| Lumiracoxib 100 mg o.d. | 0091-00019 | Uncontrolled hypertension | Discontinued; concomitant medication; hospitalization |

*Prespecified AEs*
The prespecified AEs occurred in 10.3 % of patients in the lumiracoxib group and 12.5% of patients in the celecoxib group. The majority of the prespecified AEs were gastrointestinal events, which occurred with a higher frequency in the celecoxib group (7.2 % lumiracoxib vs. 9.6 % celecoxib). There was one case of a GI ulcer (gastric) in a celecoxib-treated patient. Across the extension and core phases, the percentages were similar in the two active treatment groups (18.9 % lumiracoxib and 20.0 % celecoxib).

*Assessor's comments:*
Of the prespecified adverse events there was a higher percentage of patients in the celecoxib group with GI adverse events. Cardiovascular events occurred at similar rates in the two groups (0.9% lumiracoxib vs. 1.1% celecoxib). There was little difference between the extension population and the total (core study plus extension) population.

*Biochemistry*
There were two SAEs involving elevated liver enzymes; both occurred in lumiracoxib-treated patients. Both were forwarded to the Liver Safety Committee and adjudicated as hepatocellular liver injury, probably drug-related.
Increase in transaminases >3 x ULN was more frequent with lumiracoxib than celecoxib (0.8% for lumiracoxib and 0.5% for celecoxib). Notable increases in creatinine and notable decreases in creatinine clearance were more frequent in the lumiracoxib group compared with the celecoxib group, with 6.6% of patients in the lumiracoxib group and 1.8% of patients in the celecoxib group having a decrease in creatinine clearance of >25% over baseline. For potassium, the percentage of patients with >5.5 mmol/L was higher in the celecoxib group (6.6%) compared with the lumiracoxib group (5.3%). No other relevant differences were evident between the treatment groups. Similar findings were seen across the combined extension and core phases for the two active treatment groups.

*Assessor's comments:*
The pattern of increases in biochemical parameters seen in study 2360E1 is repeated in this extension study. In this study the presence of a comparator highlights the increased effect that lumiracoxib appears to have on renal function compared to another COX2 inhibitor. The adverse effect on renal function of lumiracoxib has a marked dose response when data from 1-year studies submitted in the original dossier are considered together with the new data:
Percentage of patients with creatinine clearance >25% decrease from baseline;
lumiracoxib 100mg od – 6.4%, 200mg od – 16.6%, 400mg od – 19.3%,
celecoxib 200mg od – 7.2%. From these pooled data lumiracoxib 100mg od has a similar effect to celecoxib 200mg od.

**TARGET study**
This was an international, multicentre, randomised, active-controlled, double-blind, double-dummy, parallel group study stratified by low-dose aspirin use and age, comparing the safety of lumiracoxib 400 mg once daily with the non-selective NSAIDs naproxen and ibuprofen, in patients with osteoarthritis treated for 52 weeks.

The study consisted of two sub-studies with identical designs but using different comparators: Study 0117 used naproxen 500 mg twice daily as a comparator whereas ibuprofen 800 mg thrice daily was used in study 2332.

**Primary objective:**
- To demonstrate that lumiracoxib 400 mg once daily decreases the incidence of predefined complicated ulcers (POBs) of the upper gastrointestinal tract (UGIT) compared to NSAIDs (naproxen 500 mg twice daily and ibuprofen 800 mg thrice daily) in osteoarthritis (OA) patients NOT taking low-dose aspirin.
- To demonstrate that lumiracoxib decreases the incidence of pre-defined complicated ulcers (POBs) of the upper gastrointestinal tract compared to NSAIDs (naproxen 500 mg twice daily and ibuprofen 800 mg thrice daily) in the overall TARGET population.

**Secondary objective:**
- To assess the cardiovascular and renal safety, as well as the overall safety and tolerability profile of lumiracoxib compared to NSAIDs (naproxen 500 mg twice daily and ibuprofen 800 mg thrice daily) in the overall TARGET population.
- To assess the efficacy of lumiracoxib compared to NSAIDs (naproxen 500 mg twice daily and ibuprofen 800 mg thrice daily) in the overall TARGET population.

The results of this study have been previously assessed in an update of the licensing Assessment Report and for the assessment of the cardiovascular safety of lumiracoxib as part of the Article 31 referral of the COX2 inhibitor class (*see Annex III*).
The main conclusions regarding cardiovascular and gastrointestinal safety were:
- There was little evidence of increased thrombotic CV risk over 12 months of use for lumiracoxib compared with ibuprofen, and some evidence to suggest a non-significant increase in CV risk with lumiracoxib compared with naproxen.
- There is some evidence of significantly smaller increases in blood pressure for lumiracoxib compared with naproxen or ibuprofen, with less aggravation of existing hypertension and less de novo hypertension for lumiracoxib compared with ibuprofen.
- Lumiracoxib had a better GI profile than either ibuprofen or naproxen in non-users of low-dose aspirin.
- The GI benefit for patients taking low-dose aspirin has not been demonstrated. Lumiracoxib treatment may not be appropriate for this subset of patients, in terms of GI risk, and particularly since any patients using low-dose aspirin are likely to have existing CV risk factors.

- As the effects of lumiracoxib have not been studied for >12 months in any patient, there would be an argument for not prescribing lumiracoxib for a period of >12 months.

Regarding other safety concerns:
- TARGET confirms the renal safety of lumiracoxib. It is equivalent to other NSAIDs (COX-2 selective and COX-2-non-selective). The safety of 100mg and 200mg doses does not warrant laboratory monitoring of renal function.
- TARGET confirms the hepatic safety of lumiracoxib. The safety of 100mg and 200mg doses does not warrant laboratory monitoring of hepatic function.

*Assessor's comments:*
TARGET was primarily a safety study and was conducted using a dose of 400mg od of lumiracoxib. Compared to the non-selective NSAIDs, lumiracoxib demonstrated a comparable safety profile, though with some excess of CV events compared to Naproxen. Regarding hepatic and renal events, there was a numerical increase in the lumiracoxib group compared to non-selective NSAIDs (46 [0.5%] vs 33 [0.4%] for renal events and 6 [0.1%] vs 3 [0.0%] for hepatic events) but not a statistically significant increase. This was due to an increase in the subgroup of patients not taking low-dose aspirin, an increase that was not seen in the subgroup of patient taking low-dose aspirin.
As this study was conducted at a dose four times that proposed for chronic use in the current variation, overall TARGET is reassuring regarding the hepatic and renal safety of lumiracoxib 100mg od compared to naproxen or ibuprofen.

## DISCUSSION

### Efficacy

#### Osteoarthritis

According to the AAOS clinical guideline on osteoarthritis of the knee acetaminophen/paracetamol has been shown to be as effective a pain reliever as NSAIDs in patients with osteoarthritis (OA) of the knee. From the point of view of assessing the risk:benefit of lumiracoxib in the treatment of osteoarthritis, a comparison with paracetamol would have been helpful.

The efficacy demonstrated by lumiracoxib 100mg od in OA of the knee reached a statistically significant difference compared to placebo. However, it is questionable whether the extra improvement of lumiracoxib over placebo of 5-7mm is clinically meaningful.
The difference over baseline achieved by lumiracoxib 100mg od exceeded the clinically meaningful change of 9.7mm in the WOMAC pain subscale as suggested by Ehrich et al (2000) as being the minimum perceptible clinical improvement (MPCI) and the change over baseline of 19.9mm in OA pain (VAS) as estimated by Tubach et al (2005) as the minimal clinically important improvement (MCII). However these levels were also achieved by placebo *(see Table 7, p15)*.
No studies have been performed that directly compare 100mg od with 200mg od in osteoarthritis but a comparisons across studies, which is not ideal, suggests that the results obtained with 100mg od are similar to those obtained with 200mg od and 400mg od. There is no evidence of a dose response of lumiracoxib in the treatment of

OA of the knee and no evidence that non-responders to the 100mg od dose would benefit from an increase to 200mg od.

*Extrapolation of results*

The effect of lumiracoxib on osteoarthritis of the hip has not been investigated at doses below 400mg, although, there is an ongoing study investigating the safety/efficacy of lumiracoxib 100mg od in patients with primary hip osteoarthritis. While it was reasonable to extrapolate from 400mg to 200mg, it is necessary to extrapolate further to 100mg od for the purposes of this variation application. Of some help in this are the subgroup analyses in studies 2360 and 2361, in which patients who also had OA of the hip showed a similar improvement in patient global assessment of disease activity as the total ITT population. This may suggest that the efficacy of lumiracoxib 100mg od can be extrapolated to OA of the hip.

Extrapolation to the hand is more problematic. The CHMP Guidelines for osteoarthritis state that extrapolation of results obtained in the lower limbs to the hand or vice versa is highly questionable and in the studies submitted with this dossier, in the subgroup of patients with OA in the hand, the results of the AUSCAN questionnaire provide no evidence that lumiracoxib 100mg od has benefit over placebo *(see Table 6, p14)*.

**Dysmenorrhoea**

The two new studies (2353 and 2358) in dysmenorrhoea investigated the efficacy of 200mg od for up to three days in each menstrual cycle compared to placebo. One study also compared the effect of lumiracoxib to naproxen 500mg bd.

Comparable efficacy was demonstrated between active treatments and no advantage was shown to taking a repeat dose of lumiracoxib 200mg in the first day. However no studies directly comparing 200mg od with 400mg od were performed. The efficacy demonstrated in studies 2353 and 2358 was similar to that shown in earlier studies using lumiracoxib 400mg od with no evidence of a dose response *(see table 15, p24)*.

No studies have been performed to investigate lower doses of lumiracoxib, such as 100mg od, in dysmenorrhoea so it is questionable whether the optimal dose for the treatment of dysmenorrhoea has yet been identified. Further studies investigating lower doses might help to answer this question.

**Safety**

The safety of the class of COX2 inhibitors, including lumiracoxib has been the subject of much discussion in the EMEA Article 31 referral. The studies submitted in this application have shown adverse events that are in accordance with those seen in previous studies. There is no evidence from these studies that the rates of adverse events increase over a one-year period and generally the rates are similar to those seen with celecoxib, another COX2 inhibitor.

Regarding the adverse events of particular concern; gastrointestinal, cardiovascular, hepatic and renal, the results neither reassure, nor cause increased concern. In the long term extension study 2361E1, lumiracoxib at a dose of 100mg od appeared to have an increased adverse effect on renal function compared to celecoxib, however in the TARGET study at a dose of 400mg od, lumiracoxib had only slightly greater effect than non-selective NSAIDs in the total population. The numerical increase seen in the TARGET study for hepatic and renal events occurred mainly in the

subgroup of patients not taking low-dose aspirin. When all one-year studies are considered there is a marked dose response effect on creatinine clearance, with lumiracoxib 100mg od showing similar effects to celecoxib 200mg od but much lower effects than lumiracoxib 200mg od or 400mg od.
Unfortunately all the safety data have been collected over a one-year period. No patients have been exposed to lumiracoxib for periods greater than one year. Therefore the safety of lumiracoxib over the longer term cannot be assessed.

**Risk:Benefit Assessment**

The studies submitted with this application have demonstrated efficacy of lumiracoxib in osteoarthritis of the knee and in primary dysmenorrhoea at the proposed doses. Given the safety concerns surrounding the COX2 inhibitors as a class, it is advised that the lowest effective dose should be used for the shortest possible time. Therefore although the data are consistent with the efficacy of the lower doses being slightly reduced, the safety of the lower doses is likely to be better.
Overall the risk:benefit ratio for lumiracoxib at the proposed dose of 100mg remains favourable for osteoarthritis of the knee and hip. The efficacy of lumiracoxib 100mg od in osteoarthritis of the hand is small and therefore the risk:benefit for this indication may be unfavourable.
The risk:benefit ratio for lumiracoxib at the proposed dose of 200mg od remains favourable for the relief of dysmenorrhoea.

## CONCLUSION

The variation application can be granted if the following changes to the Summary of Product Characteristics and Patient Information Leaflet are made:

1. **SPC Changes**

   The following amendment to the SPC should be made before the variation application can be granted

   a. In Section 5.1, Pharmacodynamic properties, a statement should be included that reflects the efficacy of 100mg lumiracoxib in osteoarthritis of the hand. A form of words that may be acceptable is:

   ***Efficacy***

   *In patients with osteoarthritis of the knee, lumiracoxib 100mg once daily provided significant improvements in pain, stiffness, function, and patient assessments of disease status. These beneficial effects were maintained for up to 52 weeks. Increasing the dose to 200mg daily is not recommended, as this does not provide any additional benefit.*

   *The efficacy of lumiracoxib 100mg daily in osteoarthritis of joints other than the knee and the hip has not been confirmed.*

   b. In section 4.2 Posology and Method of Administration, the following amendment should be made:

   *Relief of pain due to primary dysmenorrhoea*

   *……The maximum treatment duration ~~in clinical studies was~~ should not exceed 3 days per menstrual cycle.*

## 2. Patient Information Leaflet

1. The following amendment to the PIL should be made:
   **How to Take Prexige Tablets**
   *Children and adolescents under 18 years of age should **NOT** take Prexige tablets.*

The Applicant has agreed to the above changes to the SPC and PIL and the variation application can now be approved.

**MEDICAL ASSESSOR**
**DATE: 28th November 2005.**

## STATISTICAL ASSESSMENT OF EFFICACY

This assessment considers a proposed variation to the UK license for Prexige (lumiracoxib). The proposed changes are to reduce the recommended doses in both osteoarthritis and primary dysmenorrhea. The application presents a number of studies that have been conducted since the UK license was granted. This assessment will focus on those studies pivotal to the variation proposed.

## OSTEOARTHRITIS

The present license recommends a starting dose of 100mg, which can be increased to 200mg in non-responders. The proposal is to remove the option of increasing to 200mg.

### Summary of the original submission

In the initial application, a number of Phase II studies were conducted, though only one compared multiple doses of lumiracoxib (Study 0104). This study included 100mg per day, albeit administered as 50mg BD. One further study investigated the use of lumiracoxib 100mg once-daily (Study 2316).

Study 0104 was a double blind, double-dummy, randomised, parallel-group, multicentre, placebo- and active-controlled study. A total of 583 patients with OA of the knee or the hip (ACR criteria) for at least 3 months were randomised and dosed for 28 days. The primary efficacy endpoint was the overall joint pain intensity over the previous 24 hours in the most affected joint after 4 weeks on a 100 mm VAS.

**Mean (± SD) results in primary endpoint at baseline and week 4:**

| | N | Baseline | Week 4 | P value vs placebo | Estimated difference | Upper 95% Confidence limit | p |
|---|---|---|---|---|---|---|---|
| **Placebo** | **96** | **67.9 ± 12.74** | **50.2 ± 24.57** | **NA** | **NA** | **NA** | **NA** |
| **Lumiracoxib 50mg BD** | **96** | **66.9 ± 13.97** | **38.3 ± 24.32** | **0.001** | **- 11.0** | **- 3.4** | **= 0.0014** |
| Lumiracoxib 100mg BD | 95 | 64.7 ± 14.31 | 38.4 ± 24.38 | 0.001 | - 8.8 | - 2.1 | = 0.0052 |
| Lumiracoxib 200mg BD | 96 | 67.0 ± 13.00 | 37.4 ± 25.39 | < 0.001 | - 12.1 | - 3.9 | = 0.0009 |
| Lumiracoxib 400mg QD | 98 | 66.9 ± 12.98 | 33.7 ± 23.74 | < 0.001 | - 15.9 | - 7.5 | < 0.0001 |
| Diclofenac 75mg BD | 93 | 66.1 ± 13.73 | 34.3 ± 23.24 | < 0.001 | NA | NA | NA |

*Comment: The evidence for dose-response from Study 0104 is unclear, particularly within the dose-range of interest. It is noted that the difference in efficacy between the 50mg BD dose and the 100mg BD dose (i.e. between 100 and 200 mg per day) is estimated as being small and in favour of the lower dose.*

Study 2316 was a double blind, randomised, parallel-group, multicentre, double-dummy and placebo-controlled study of lumiracoxib 100mg once-daily in 244 patients with OA of the knee or the hip (ACR criteria) for at least 3 months. The primary efficacy endpoint was the overall joint pain intensity over the previous 24 hours in the most affected joint after 4 weeks on a 100 mm VAS.

Mean results (all ITT- LOCF) in primary endpoint at baseline and week 4 were:

| | N = | Baseline | Week 4 | Mean diff (95% CI) p value |
|---|---|---|---|---|
| Placebo | 122 | 65.51 | 47.69 | - 8.41 (-13.97, -2.84) p = 0.003 |
| Lumiracoxib 100mg QD | 122 | 64.79 | 39.29 | |

Mean results on Patient's Global Assessment of Disease Activity:

| | N = | Baseline | Week 4 | Mean diff (95% CI) p value |
|---|---|---|---|---|
| Placebo | 122 | 63.12 | 48.87 | - 8.81 (- 14.11, - 3.52) p = 0.001 |
| Lumiracoxib 100mg QD | 122 | 63.85 | 40.05 | |

In addition to the Phase II studies, three pivotal studies were originally submitted. These examined doses of 200mg once-daily and 400mg once-daily. The proposed dose of 100mg once-daily was not examined and these studies are, therefore, not discussed in detail. The studies offered evidence of efficacy relative to placebo in knee and hip OA at 400mg once-daily and in OA of the knee at 200mg once-daily (efficacy in the hip was extrapolated from the 400mg data). In these same studies, non-inferiority was established compared with celecoxib 200mg once-daily in OA of the knee, but not compared with rofecoxib 50mg in OA of the hip. The non-inferiority margins used were 5mm on the VAS and 0.6 on the WOMAC pain score. OA of the hand was examined in a dedicated trial (2319) and both 200mg once daily and 400mg once-daily were shown to be superior to placebo.

**Summary of the variation application**

**Two further studies are presented in osteoarthritis (2360 and 2361).**

Trial Design

The two studies were identical in design. Both were 13-week, multicentre, randomised, double-blind, double-dummy, placebo- and active- controlled, parallel-group trials of two different dose regimens of lumiracoxib (100mg once-daily for 13 weeks and 200mg once-daily for two weeks followed by 100mg once-daily for 11 weeks) in patients with primary knee osteoarthritis, using celecoxib (200mg once-daily) as an active control.

In Study 2360, a total of 1551 adult patients with symptomatic primary knee osteoarthritis (pain ≥ 40mm VAS at target joint) who required NSAID or other analgesic therapy were randomised, 391 to lumiracoxib 100mg once-daily, 385 to lumiracoxib 200mg / 100mg once-daily, 393 to celecoxib and 382 to placebo. In Study 2361, a total of 1684 adult patients with symptomatic primary knee osteoarthritis who required NSAID or other analgesic therapy were randomised, 420 to lumiracoxib 100mg once-daily, 420 to lumiracoxib 200mg / 100mg once-daily, 420 to celecoxib and 424 to placebo.

The primary efficacy variables in both studies were pain intensity in target joint, patient global assessment of disease activity and functional status (WOMAC) after 13 weeks of therapy. A hierarchical testing strategy was in place to control for the multiple treatment group comparisons on these three primary endpoints. There were a number of secondary efficacy endpoints, including the assessment of hand osteoarthritis in the relevant sub-population (approximately 43% of all randomised patients in 2360 and 20% in 2361). The confirmatory analyses of the primary endpoints were based on ANCOVA allowing for baseline and centre in addition to treatment group. Treatment-by-centre interactions were

separately examined. The primary analyses were based on 'ITT' populations (including all randomised patients who were given - though did not necessarily take - study medication) and used LOCF to impute missing values.

Trial Results

Patient withdrawals were highest from the placebo group in both studies, primarily because of a difference in the number of withdrawals due to unsatisfactory therapeutic effect. Similar proportions of patients were withdrawn from celecoxib and lumiracoxib treatment.

The mean number of rescue tablets taken by patients was higher in the placebo group than in any active treatment group. There was some indication in 2360 of a greater rescue medication use by patients on celecoxib compared with lumiracoxib.

Efficacy results on the primary endpoints (at 13 weeks, ITT (LOCF)) are presented in the table below for 2360:

| | | | | Comparison versus placebo | | |
|---|---|---|---|---|---|---|
| **Variable** | **Treatment** | **Baseline** | **Endpoint LS Mean** | **Estimate of effect** | **95% CI** | **P-value** |
| OA pain intensity (VAS mm) | **Lum 100** | **66.4** | **40.84** | **-6.69** | **(-10.09 , -3.30)** | **<0.001** |
| | Lum 200 / 100 | 65.4 | 39.42 | -8.11 | (-11.52 , -4.71) | <0.001 |
| | Celecoxib 200 | 66.4 | 41.83 | -5.70 | (- 9.09 , -2.32) | <0.001 |
| | **Placebo** | **66.2** | **47.54** | | | |
| Patient assessment of disease activity (VAS mm) | **Lum 100** | **63.1** | **39.62** | **-9.10** | **(-12.41 , -5.80)** | **<0.001** |
| | Lum 200 / 100 | 63.8 | 38.63 | -10.10 | (-13.42 , -6.77) | <0.001 |
| | Celecoxib 200 | 61.7 | 42.06 | -6.66 | (- 9.96 , -3.36) | <0.001 |
| | **Placebo** | **62.5** | **48.72** | | | |
| WOMAC score | **Lum 100** | **52.9** | **35.62** | **-7.42** | **(- 9.75 , -5.09)** | **<0.001** |
| | Lum 200 / 100 | 52.9 | 35.30 | -7.75 | (-10.09 , -5.41) | <0.001 |
| | Celecoxib 200 | 52.6 | 36.70 | -6.35 | (- 8.67 , -4.02) | <0.001 |
| | **Placebo** | **53.1** | **43.05** | | | |

Lum – lumiracoxib. All doses in mg, once daily

Efficacy results on the primary endpoints (at 13 weeks, ITT (LOCF)) are presented in the table below for 2361:

| | | | | Comparison versus placebo | | |
|---|---|---|---|---|---|---|
| **Variable** | **Treatment** | **Baseline** | **Endpoint LS Mean** | **Estimate of effect** | **95% CI** | **P-value** |
| OA pain intensity (VAS mm) | **Lum 100** | **64.1** | **37.05** | **-5.09** | **(-8.04, -2.15)** | **<0.001** |
| | Lum 200 / 100 | 64.4 | 37.81 | -4.33 | (-7.28, -1.39) | 0.004 |
| | Celecoxib 200 | 64.8 | 37.52 | -4.63 | (-7.57, -1.68) | 0.002 |
| | **Placebo** | **63.8** | **42.14** | | | |
| Patient assessment of disease activity (VAS mm) | **Lum 100** | **63.1** | **37.72** | **-5.93** | **(-8.87, -2.99)** | **<0.001** |
| | Lum 200 / 100 | 61.6 | 39.99 | -3.66 | (-6.60, -0.71) | 0.015 |
| | Celecoxib 200 | 62.9 | 39.77 | -3.88 | (-6.82, -0.94) | 0.010 |
| | **Placebo** | **62.9** | **43.65** | | | |
| WOMAC score | **Lum 100** | **49.2** | **34.27** | **-3.92** | **(-5.98, -1.86)** | **<0.001** |
| | Lum 200 / 100 | 49.7 | 34.86 | -3.33 | (-5.40, -1.27) | 0.002 |
| | Celecoxib 200 | 50.5 | 35.24 | -2.95 | (-5.01, -0.89) | 0.005 |
| | **Placebo** | **49.7** | **38.19** | | | |

Lum – lumiracoxib. All doses in mg, once daily

There was a similar pattern of results in both studies. There were statistically significant differences between both regimens of lumiracoxib and placebo. There were no statistically significant differences either between the two regimens of lumiracoxib or between either lumiracoxib regimen and celecoxib, which were declared non-inferior.

*Statistical Assessor's Comments on Methodology and Results*

*The conduct of two pivotal studies for the 100mg once-daily dose is appropriate. The rationale for testing a regimen commencing with 200mg once-daily for 2 weeks prior to continuation with 100mg once-daily is unclear. The primary tests conducted pool the two lumiracoxib regimens. However, this is considered unhelpful for the purposes of this variation. The trials also provide data on the efficacy of two lumiracoxib regimens relative to (i) placebo, (ii) each other and (iii) an active control, celecoxib. Of greatest interest for the purposes of this application are the data comparing the lumiracoxib 100mg group with placebo, as highlighted (in bold) in the tables above.*

*These two trials were designed and analysed in line with CPMP guidance in this area and were consistent with the other osteoarthritis trials in this programme. There are no major methodological concerns affecting the results of the confirmatory statistical tests. In particular, there are no concerns over the definitions of the primary analysis populations, the handling of multiplicity or the use of rescue medication. It is therefore considered that the trials provide statistically significant evidence of efficacy for lumiracoxib 100mg daily versus placebo.*

*The clinical relevance of the results should be considered. The quantity of discontinuations (approximately 24% in 2360 and XX% in 2361) will influence the estimates of treatment effect and therefore complicate the assessment of clinical relevance. The magnitude of the impact on the estimates of effect has not been estimated. It is noted that analyses excluding LOCF from baseline show smaller estimates of effect than those presented here. This is unsurprising and the chosen method of imputation is probably 'fair' given the excess of withdrawals on placebo for unsatisfactory therapeutic effect.*

*For information, a summary of the results from previous pivotal studies in osteoarthritis is presented in the table below. As with all 'across-trial' comparisons, a comparison of the differences to placebo for 100mg in trials 2360 and 2361 with 200mg and 400mg in previous studies should be made with caution.*

| | | | | | Comparison versus placebo | | |
|---|---|---|---|---|---|---|---|
| Variable | Trial | Treatment | Baseline | Endpoint LS Mean | Estimate of effect | 95% CI | P-value |
| OA pain intensity (VAS mm) | 0128 | Lum 400 | 64.0 | 41.32 | -6.35 | (-10.94, -1.76) | 0.007 |
| | | Placebo | 62.5 | 47.66 | | | |
| | 0112 | Lum 200 | 65.5 | 39.07 | -6.33 | (-9.86, -2.80) | <0.001 |
| | | Lum 400 | 65.1 | 37.46 | -7.94 | (-11.47, -4.41) | <0.001 |
| | | Placebo | 65.7 | 45.40 | | | |
| | 0109 | Lum 200 | 66.9 | 37.29 | -7.39 | (-11.38, -3.40) | <0.001 |
| | | Lum 400 | 65.9 | 35.84 | -8.83 | (-12.82, -4.84) | <0.001 |
| | | Placebo | 66.7 | 44.68 | | | |
| Patient assessment of disease activity (VAS mm) | 0128 | Lum 400 | 61.6 | 42.47 | -7.04 | (-11.67, -2.41) | 0.003 |
| | | Placebo | 61.4 | 49.52 | | | |
| | 0112 | Lum 200 | 62.9 | 39.67 | -7.62 | (-11.05, -4.20) | <0.001 |
| | | Lum 400 | 62.6 | 38.56 | -8.73 | (-12.15, -5.31) | <0.001 |
| | | Placebo | 63.2 | 47.29 | | | |
| | 0109 | Lum 200 | 63.6 | 37.41 | -8.55 | (-12.39, -4.70) | <0.001 |
| | | Lum 400 | 62.8 | 36.53 | -9.42 | (-13.26, -5.58) | <0.001 |
| | | Placebo | 62.4 | 45.95 | | | |
| WOMAC score | 0128 | Lum 400 | 47.3 | 35.25 | -3.21 | (-6.21, -0.22) | 0.036 |
| | | Placebo | 47.9 | 36.46 | | | |
| | 0112 | Lum 200 | 49.0 | 34.48 | -4.82 | (-7.14, -2.50) | <0.001 |
| | | Lum 400 | 48.1 | 34.11 | -5.19 | (-7.52, -2.87) | <0.001 |
| | | Placebo | 49.2 | 39.30 | | | |
| | 0109 | Lum 200 | 49.9 | 30.51 | -7.38 | (-9.97, -4.80) | <0.001 |
| | | Lum 400 | 47.2 | 30.41 | -7.48 | (-10.06, -4.91) | <0.001 |
| | | Placebo | 46.7 | 37.89 | | | |

Lum – lumiracoxib. All doses in mg, once daily

*It is concluded that no clear dose-response relationship has been demonstrated. The differences between the efficacy of the 100mg once daily and 200mg once-daily doses appear small.*

*Whilst not the primary hypothesis in these studies, there are some interesting points relating to the tests of non-inferiority between lumiracoxib and celecoxib.*

1. *For each endpoint, delta was defined as half the difference between celecoxib and placebo observed in the study. As a general approach this method can be criticised, as the rationale for including a test for non-inferiority in these studies (which include a placebo control) is to exclude clinically relevant differences between the active treatments. It is not obvious that a definition of 'half of the difference to placebo' will achieve this. In 2361, the effects of active treatment relative to placebo are relatively small (see 2) and the non-inferiority margins defined might be considered reasonable. Because of the larger effect sizes the same conclusion would not be drawn from 2360.*

2. *The non-inferiority margins defined in 2360 and 2361 differ to each other and to those defined in the other studies in this development programme. It is interesting to compare the differences previously defined (and, therefore, thought to be of clinical irrelevance) with differences between active and placebo in the studies. For example, considering pain in the target joint in 2361, a difference of 5mm was previously considered clinically irrelevant and this trial was sized to be adequately powered to detect a difference of 6mm. However, the difference observed in this trial between lumiracoxib (albeit at a different dose with potentially different risks against which to weigh the benefits) and placebo was 4.7mm. The difference between celecoxib and placebo was marginally less. In 2360 there are no similar concerns as the estimated magnitudes of effect were greater*

*and the overall magnitude of benefit for 100mg is consistent with that observed for 200mg and 400mg once-daily elsewhere in the programme.*

3. *Notwithstanding the weak justification for the choice of non-inferiority margin and criticisms of the method for selecting delta (see 1) there are also methodological concerns over the statistical analysis used to conclude non-inferiority.*
4. *The difference between celecoxib and placebo used to define the non-inferiority margin has been incorporated into the statistical model rather than being calculated in advance and considered a constant, which is the preferred method. In technical language, this translates to comparing the contrast of (1/2 1/2 -1/2 -1/2) with zero rather than comparing (1/2 1/2 -1 0). This reduces the variability in the model, which, in turn, increases the likelihood of demonstrating non-inferiority. In 2361 this affects the conclusions of the analysis of pain in target joint, for which a conclusion of non-inferiority has been drawn but, where, by standard criteria (i.e. comparing the confidence interval of the difference between celecoxib and lumiracoxib (-2.65, 2.47) with 2.32) non-inferiority would not have been achieved. Conclusions for the other primary endpoints are not affected.*

*Despite these issues, it is repeated that the assessment of non-inferiority was of secondary importance in these studies, in which evidence of efficacy relative to placebo is clear. Anyway, there is little evidence to indicate that the efficacy of lumiracoxib at the doses proposed is likely to be less than that of celecoxib 200mg. The points highlighted above are, therefore, considered to be of very minor concern.*

OA of the Hand

In neither study was there statistically significant evidence of efficacy from the AUSCAN endpoint in the sub-population of patients with hand osteoarthritis.

**AUSCAN Total Score – Study 2360**

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| **Lumiracoxib 100** | **165** | **24.90** | **Placebo** | **-1.12** | **(-3.24, 1.00)** | **0.301** |
| Lumiracoxib 200 / 100 | 163 | 25.15 | Placebo | -0.87 | (-2.99, 1.25) | 0.421 |
| Celecoxib | 175 | 14.59 | Placebo | -1.43 | (-3.53, 0.68) | 0.184 |
| **Placebo** | **165** | **26.02** | | | | |

**AUSCAN Total Score – Study 2361**

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| **Lumiracoxib 100** | **84** | **27.42** | **Placebo** | **-0.50** | **(-3.66, 2.67)** | **0.758** |
| Lumiracoxib 200 / 100 | 76 | 27.88 | Placebo | -0.03 | (-3.35, 3.29) | 0.986 |
| Celecoxib | 83 | 25.95 | Placebo | -1.96 | (-5.15, 1.22) | 0.226 |
| **Placebo** | **88** | **27.91** | | | | |

*Statistical Assessor's Comments*

*The table below presents the results on AUSCAN total score in 2319, the study from the initial submission in hand OA. It is noted that the effects observed in 2360 and 2361 were smaller than for the higher doses of lumiracoxib examined in 2319. The sponsor argues that the absence of statistical significance in 2360 and 2361 was due to a lack of stratification and reduced patient numbers. However, it can be seen from the width of the confidence*

*intervals generated, that had the effect sizes been similar to those previously observed, statistical significance would probably have been achieved in these studies despite these concerns. Therefore, it is concluded that the primary reason for failing to demonstrate an effect is the reduced effect size compared to those observed in other studies of higher doses. Given the effect on hand OA at 200mg and 400mg it seems unlikely that 100mg has no effect (indeed the estimates of effect are in the right direction). However, from the data presented, the possibility that the effect of the 100mg dose is reduced compared to the higher doses appears likely. The estimated effect sizes should be considered clinically, it might be that the indication for OA of the hand is not supported for lumiracoxib 100mg. A pooled analysis, combining patients with OA of the hand from 2360 and 2361 might be considered.*

**AUSCAN Total Score after 4 weeks**

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg QD | 201 | 26.02 | Placebo | - 3.09 | - 5.12<br>- 1.06 | 0.003 |
| Lumiracoxib 400mg QD | 191 | 24.56 | Placebo | - 4.55 | - 6.59<br>- 2.51 | < 0.001 |
| Placebo | 191 | 29.11 | | | | |

Long-term efficacy

Long-term effects were examined in extension studies to both 2360 and 2361, though only the extension phase to 2361 included a control arm.

Patients from the core phase of 2361 had the option of continuing in this 39-week, double-blind, active-controlled extension phase. Patients on active treatment in the core study, continued with the same active treatment in the extension phase: patients on placebo were randomised 1:1 between lumiracoxib 100mg once-daily and celecoxib 200mg once-daily. A total of 1310 patients entered the extension, 677 on lumiracoxib and 306 on celecoxib.

*Assessor's Comment: Of the patients receiving placebo in the core phase, 176 were randomised to receive lumiracoxib and 130 to receive celecoxib. This is a notable imbalance under 1:1 randomisation. The probability of this occurring is approximately 0.5% (i.e. 1 in every 200). Were this indicative of a flaw in the randomisation process, it would be of concern. If this has occurred due to chance, it is of no concern. Given that this imbalance has occurred on entry to the extension phase, and affects only a proportion of patients entering the extension phase, it is considered unimportant.*

Primary efficacy endpoints were the same as for the core study. Missing data were imputed via LOCF. The study was not designed to demonstrate strict evidence of non-inferiority between lumiracoxib and celecoxib. There were no large differences in the estimated effects in the two treatment groups.

Perhaps equally as informative in the absence of a placebo arm against which to assess the efficacy data is an investigation of the number of withdrawals and the reasons for withdrawal. Patient withdrawals were predominately due to withdrawal of consent, unsatisfactory therapeutic effect and adverse events. Numbers of withdrawals were greater in each of these categories from the lumiracoxib treatment arm. The proportion of withdrawals due to abnormal laboratory values was also higher from lumiracoxib, though absolute numbers were small in both treatment groups, making comparison difficult.

Also informative is the use of rescue medication over the course of the follow-up period. Over half of the patients in both treatment groups attending any given visit used rescue

medication since the previous visit (the majority using 1 tablet per day). Approximately 80% of patients in both treatment arms used rescue medication prior to their final visit.

*Statistical Assessor's Comments*

*Data from the extension phase are difficult to interpret, both due to the absence of a placebo control and due to the number of patient withdrawals. There appear to be no large differences in the effects of celecoxib and lumiracoxib, which is reassuring providing that the licensed active control, celecoxib, is exhibiting efficacy in this study. The proportion of patients using rescue medication may warrant clinical consideration.*

**Statistical Assessor's Overall Conclusions on Studies 2360 and 2361**

These trials in OA of the knee provide clear evidence of statistical superiority to placebo for the 100mg once-daily dose of lumiracoxib. Considering the whole trial programme, there is little evidence that the 200mg once-daily dose will lead to additional efficacy on average and no evidence that non-responders to 100mg will benefit from a dose-increase. Therefore, based on the totality of the data provided, the exclusion of the higher dose seems reasonable.

If 100mg once-daily is to be the only licensed dose, the clinical relevance of the estimated effects should be further considered. This is of particular relevance now that additional studies have been conducted, with greater numbers of patients than were treated with this dose in the initial submission. These considerations should bear in mind that considerable amounts of data are missing due to patient withdrawals and that, whilst this is unlikely to influence the fact that the comparisons to placebo are statistically significant, the influence of the estimates of effect are unknown.

The choices of non-inferiority margins made in the original submission (e.g. 5mm on the VAS) give some guide as to differences originally considered clinically irrelevant.

Assessment of clinical relevance might also consider the estimated effect of celecoxib 200mg. The demonstration of non-inferiority to the active control is not considered reliable. Nevertheless, it is possible to compare the estimated sizes of effect, which are consistent with being similar.

Efficacy in joints other than the knee should also be considered. The 100mg once-daily dose has not been examined in OA of the hip. Furthermore, there are no data confirming a statistically significant effect on OA of the hand for this dose. The applicant's explanation for this, based on reduced patient numbers and a lack of stratification, is not accepted. The primary reason for the absence of statistical significance is considered to be the size of the estimated effect, which is small. It seems likely that this dose is active, given the effects demonstrated on higher doses and the directions of the estimates of effect in studies 2360 and 2361. Nevertheless, the CHMP guideline on osteoarthritis states that for a broad indication of 'treatment of osteoarthritis', effects should be observed for OA of the hand and OA of the knee or hip. The clinical relevance of the estimated effects therefore requires consideration.

Although the comparisons are 'between-trial' and, therefore, not wholly reliable, there is some indication that the effects of 100mg once daily are smaller than those of 200mg once daily in hand OA. This might therefore be a population of patients for whom the exclusion of the higher dose is detrimental for efficacy.

Evidence of long-term efficacy for 100mg once-daily is complicated by withdrawals and the absence of a placebo-control arm or randomised withdrawal phase. There is high-use of rescue medication but no large difference in estimated effect between lumiracoxib and placebo.

## PRIMARY DYSMENORRHEA

The present license recommends a dose of 400mg. The proposal is to decrease the recommended dose to 200mg.

### Summary of the original submission

In the initial application, 2 studies were presented in primary dysmenorrhea (0129 and 0130). These were multicentre, randomised, double-blind, double-dummy, placebo- and active-controlled, complete-block, 3-period crossover trials in women with a self-reported history of primary dysmenorrhea. Patients received lumiracoxib 400 mg, active control (rofecoxib 50mg in 0129 or naproxen 500mg in 0130), or placebo for up to 3 days (if needed) from the onset of moderate to severe menstrual pain, in each of 3 menstrual cycles. Efficacy was assessed using summed (time-weighted) pain intensity difference from hour 0 to hour 8 (SPID-8) on day 1 as the primary variable No dose-finding work was conducted in primary dysmenorrhea. The 400mg dose was selected based on studies using a dental pain model.

Each of the active treatment groups in both trials were statistically significantly more effective than placebo for SPID-8 (see below) and the majority of secondary endpoints.

Trial 0129 - SPID8 (ITT population)

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 400mg QD | 78 | 11.32 | Placebo | 4.66 | 2.81, 6.51 | < 0.001 |
| Rofecoxib 50mg QD | 80 | 11.31 | Lumiracoxib 400mg QD | 0.01 | - 1.82, 1.85 | 0.988 |
| Placebo | 78 | 6.66 | Rofecoxib 50mg QD | 4.65 | 2.81, 6.48 | < 0.001 |

Trial 0130 - SPID8 (ITT population)

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 400mg QD | 81 | 9.86 | Placebo | 3.38 | 1.73, 5.04 | < 0.001 |
| Naproxen 500mg BD | 88 | 11.04 | Lumiracoxib 400mg QD | - 1.18 | - 2.83, 0.47 | 0.159 |
| Placebo | 88 | 6.47 | Naproxen 500mg BD | 4.57 | 2.95, 6.18 | < 0.001 |

### Summary of the variation application

Two further studies are presented (2353 and 2358). These are both multicentre, randomised, double-blind, placebo-controlled, complete-block, crossover trials in women with primary dysmenorrhea. Patients received lumiracoxib 200 mg, lumiracoxib 200mg with optional re-dose after 12 hours or placebo for up to 3 days (if needed) from the onset of moderate to severe menstrual pain, one treatment per menstrual cycle. In 2353, naproxen 500mg twice-daily was included as an active-control. Efficacy was assessed using SPID-8.

The primary analysis was based on the ITT population of all randomised patients who took at least one dose of trial medication. The analysis was based on ANOVA with treatment, period, baseline pain intensity and patient (random factor).

Study 2353 recruited 144 patients to the four treatment sequences. A total of 26 patients failed to complete the study, with 9 withdrawals prior to the first dose, and 6, 9, 2 and 0 withdrawals after dosing in cycles 1-4 respectively. Results on the primary endpoint were as follows:

Trial 2353 - SPID8 (ITT population)

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg | 126 | 12.07 | Placebo | 3.85 | 2.83, 4.87 | <0.001 |
| Lumiracoxib 200mg / re-dose | 127 | 12.00 | Placebo | 3.78 | 2.76, 4.80 | <0.001 |
| Naproxen 500mg QD | 124 | 12.11 | Placebo | 3.89 | 2.86, 4.92 | <0.001 |
| Placebo | 125 | 8.22 | | | | |

Study 2358 recruited 132 patients to the six treatment sequences. A total of 38 patients failed to complete the study, with 15 withdrawals prior to the first dose, and 16, 6 and 1 withdrawals after dosing in cycles 1-3 respectively. Results on the primary endpoint were as follows:

Trial 2358 - SPID8 (ITT population)

| | N | LS Mean | Contrast with | Estimated difference | 95% CI | p |
|---|---|---|---|---|---|---|
| Lumiracoxib 200mg | 104 | 10.82 | Placebo | 4.07 | 2.66, 5.47 | <0.001 |
| Lumiracoxib 200mg / re-dose | 103 | 11.71 | Placebo | 4.96 | 3.55, 6.37 | <0.001 |
| Placebo | 105 | 6.75 | | | | |

In both studies, statistically significant differences were observed on a range of secondary endpoints, including patient global evaluation.

*Statistical Assessor's Comments on Methodology and Results*

*It is unusual to see crossover trials used to demonstrate pivotal evidence of efficacy. Crossover trials have the advantage that treatment comparisons can be made 'within-patient'. This can reduce variability and therefore the number of patients required to test a particular hypothesis. The desirable trial design features for obtaining reliable data from a crossover trial are as follows: that the treated condition should be stable and chronic (so that the patient returns to a 'baseline' state at the start of each treatment period), that the duration of the trial is sufficiently short to avoid large numbers of patient dropouts and that there is no potential for differential carryover (i.e. effects from one period persisting into a later period). These conditions appear to be fulfilled for the two pivotal studies under consideration.*

*These pivotal trials are consistent in design with previous trials designed to test efficacy in this pain model. In particular the endpoints and methods of statistical analysis are appropriate. Crucial issues for these studies are the number of patient withdrawals and the handling of missing data, particularly for data missing due to use of rescue medication. On the former point, the contribution to the efficacy analysis of patients who withdrew during the course of the trial depends on the number of treatment periods completed. A patient completing only two periods will contribute (within-patient) only to the comparison between the two treatments received. A patient completing only one period can offer no within-patient information. This 'loss of information' is to be expected in crossover trials and there appears to be no imputation for this type of missing data, which is appropriate. On the latter point, efficacy data has not been collected following administration of rescue medication. Instead LOCF is applied which will reflect the 'failure' of the treatment received. This seems reasonable, though, as with all imputation procedures, the robustness of the data to the method selected should have been examined.*

*In both trials, a number of patients withdrew prior to receiving a dose of treatment (9 of 26 withdrawals in 2353 and 15 of 38 withdrawals in 2358). These withdrawals are clearly unrelated to treatment in these double-blind trials and are ignorable. In trial 2353, post-dose withdrawals occurred predominately in treatment periods 1 and 2. In trial 2358, post-dose withdrawals occurred predominately in treatment period 1. In both trials, the pattern of withdrawals is consistent with being similar between treatments. There is no reason for concern over the introduction of important bias.*

*The use of rescue medication within the first 12 hours gives some indication itself of efficacy. More patients have used additional medication on placebo than on either active treatment.*

*These are the first data generated at this dose in this indication and, therefore, the clinical relevance of the effect sizes clearly requires consideration. The estimated effects of the 200mg once-daily dose are similar to those of the 400mg once-daily dose (from trials 0129 and 0130), though these comparisons are drawn between trials and are not wholly reliable.*

*It is of interest to note the proportion of patients who used re-dose medication. In 2353 this was 35-37%, and in 2358 this was 46-56% of patients initially taking lumiracoxib 200mg. These were lower proportions than used re-dose medication on placebo. The use of re-dose medication might have been influenced by the design of the trial, i.e. the fact that further medication was available, and doesn't necessarily indicate an insufficient effect in all patients. Nevertheless, the timings of re-dose medication use would be of interest and the relative efficacy of lumiracoxib with and without re-dose from, say, 12-24 hours on day 1 would have been of interest.*

**Statistical Assessor's Overall Conclusions on Studies 2353 and 2358**

There are no major methodological concerns with the design and analysis of these trials. The trials demonstrate that a 200mg once daily dose of lumiracoxib is statistically superior to placebo. The clinical relevance of the effects should be considered. Further investigation of the manner in which patients used the option for re-dose and whether the option to re-dose might be useful in this patient population could be performed.

# APPENDIX III

## Variation 4 Assessment Report

# PREXIGE 100mg TABLETS (LUMIRACOXIB) PL 00101/0677

# VARIATION 4 ASSESSMENT REPORT

**VARIATION ASSESSMENT REPORT**

**PL NUMBER :-**

| | |
|---|---|
| Prexige 100mg (lumiracoxib) tablets | PL 00101/ 0677 (lead) |
| Prexige 200mg tablets | PL 00101/ 0668 |
| Prexige 400mg tablets | PL 00101/ 0669 |

**APPLICATION NUMBER :-** 0028

**PRODUCT NAME: :-** Prexige

**ACTIVE INGREDIENT(S)/LEVEL :-**

lumiracoxib 100 mg
lumiracoxib 200 mg
lumiracoxib 400 mg

**LINKED/RELATED VARIATIONS :-**

| | |
|---|---|
| Exforge 100mg tablets | PL 00101/ 0698 |
| Exforge 200mg tablets | PL 00101/ 0699 |
| Exforge 400mg tablets | PL 00101/ 0700 |
| | |
| Stellige 100mg tablets | PL 00101/ 0695 |
| Stellige 200mg tablets | PL 00101/ 0696 |
| Stellige 400mg tablets | PL 00101/ 0697 |
| | |
| Frexocel 100mg tablets | PL 00101/ 0692 |
| Frexocel 200mg tablets | PL 00101/ 0693 |
| Frexocel 400mg tablets | PL 00101/ 0694 |

**PROPOSED CHANGES**

**BACKGROUND**

Following a European-wide Article 31 referral, a number of core changes are to be made to the SmPC for all COX-2 selective inhibitors, as agreed by members of the CHMP. The final Commission Decision for lumiracoxib (dated 28/11/2005) was circulated on 02/12/2005, and a number of pre-agreed changes to the SPCs for lumiracoxib must be introduced in line with the Commission Decision. These include an additional contradindication in patients with peripheral arterial disease and introduction of a warning regarding skin reactions in section 4.4, plus additional reactions in section 4.8 and other minor changes regarding the format of the SPCs.

## SUPPORTING EVIDENCE

The MA holder has supplied amended SmPCs for Prexige 100mg lumiracoxib, Prexige 200 mg lumiracoxib and Prexige 400 mg lumiracoxib, plus duplicates (Exforge, Stellige and Frexocel). They have also supplied an updated PIL which applies to all 3 lumiracoxib products, and drafts of PILs for duplicate products which will not be marketed in the UK.

## EVALUATION

### CHANGES TO THE SmPC

The following changes are proposed:

Throughout the SPC, all references to other sections of the SPC (i.e. "section 4.8 Undesirable effects") have been truncated to refer just to the section numbers (i.e. "Section 4.8"). An ongoing posology variation has also changed these references in the same way.

Where reference to 'tablets' has been made, 'film-coated' has been inserted in front of 'tablets' in some places. An ongoing posology variation has also included these references to film-coated tablets.

In section 4.3 (Contraindications), the following change is proposed:
**Patients with** ~~E~~established ischaemic heart disease**, peripheral arterial disease** and/or cerebrovascular disease.

This change also involves the following change to section 4.4 (Special warnings and precautions for use):

Patients with significant risk factors for cardiovascular events (eg hypertension, hyperlipidaemia, diabetes mellitus, smoking) ~~or peripheral arterial disease~~ should only be treated with lumiracoxib after careful consideration (see section 5.1).

In section 4.4 (Special warnings and precautions for use), following the paragraphs regarding CV risk, the following text is inserted:
***Skin reactions***
**Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance. Patients appear to be at highest risk for these reactions early in the course of therapy, with the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving lumiracoxib. Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Lumiracoxib, should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.**

In section 4.8 (Undesirable effects) the following changes are proposed:

*Cardiac disorders*
Uncommon: Palpitations, **Myocardial infarction***
Rare: Cardiac failure, Atrioventricular block of first degree~~, Myocardial Infarction~~

*Vascular disorders*
Uncommon: Venous insufficiency, Hypotension, **Cerebrovascular accident***

*General disorders*
Common: Fatigue, oedema (e.g lower limb)
Uncommon: Appetite increased or decreased, Chest pain, Rigors, Thirst
**Rare: Anaphylaxis**

And an additional statement has been added below the list of adverse reaction in section 4.8:
*** Based on analyses of long-term placebo and active controlled clinical trials, some selective COX-2 inhibitors have been associated with an increased risk of serious thrombotic arterial events, including myocardial infarction and stroke. The absolute risk increase for such events is unlikely to exceed 1% per year based on existing data (uncommon).**

In section 5.1 (Pharmacological properties) the following change is proposed:

*MI events in TARGET (12-month study)*
There was no statistically significant difference between lumiracoxib and NSAIDs for incidence of MI (clinical MI ~~with~~**and** silent MI).

Two other changes were included as part of the Commission Decision wording but are being implemented as part of the ongoing posology variation: these were under the heading "The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)" and expand the abbreviations o.d., t.i.d and b.i.d. to once daily, three times daily and twice daily; and a change under the heading of "Gastrointestinal Effect in TARGET (12-month study)" to change the first appearance of 'hazard ratio (HR)' from the second bullet point to the first.

One additional change has been introduced as part of the Commission Decision wording, regarding wording for CYP2C9 metabolism, as follows:

**In section 4.5: Pharmacokinetic Interactions**
~~Lumiracoxib undergoes CYP2C9 dependent metabolism.~~ **The oxidative metabolism of lumiracoxib is mainly CYP2C9 mediated.**

**And in section 5.2, Biotransformation**
~~In humans, lumiracoxib undergoes extensive hepatic metabolism mediated primarily by CYP2C9.~~ **In humans, lumiracoxib undergoes extensive hepatic metabolism. The oxidative metabolism of lumiracoxib is mainly CYP2C9 mediated.**

**PATIENT INFORMATION LEAFLET**
The PIL has been updated to reflect changes from the Article 31 referral.

The 'Before taking Prexige tablets' section has been revised as follows:
Your doctor has diagnosed heart problems including heart failure (moderate or severe types), angina (chest pain), or if you have had a heart attack, stroke or mini stroke (TIA or transient ischaemic attack), **or if you have poor circulation in your legs or feet (peripheral arterial disease).**

Under the section "If you answer 'YES' to any of the following questions, tell your doctor before you start treatment with Prexige. Prexige may not be suitable for you, or you may need to be monitored while taking it", the following bullet point has been added:

**Do you have a history of allergy to other drugs? (Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy).**

Under the 'using other medicines' section, the text has been revised as follows:
"Medicines used to treat ~~heart conditions or~~ high blood pressure **or heart failure**, for example ACE inhibitors **(e.g. enalapril) or angiotensin II antagonists (e.g. losartan)**.

Under the section 'Possible side-effects/ **If you get any of the following STOP taking the tablets immediately and tell your doctor:**', the following two bullets have been added:
**Any sign of skin reactions such as ulcers or blistering**

**Allergic reaction with swelling of the face, lips, tongue or throat (angioedema) which may cause difficulty in breathing or swallowing**

Under the section "Uncommon side-effects, reported in more than 1 person in 1000, but less than 1 in 100 include:", the following has been revised:

- Palpitations (fast or irregular heartbeat), **heart attack**
- Hypotension (low blood pressure), **stroke**

Under the section "Rare side effects, reported in more than 1 person in 10,000, but less than 1 in 1,000 include:" the following has been revised:

- **Shortness of breath, chest pains or ankle swelling (heart failure)** and abnormalities of the heart rhythm
- **Swelling of the face and mouth**
- **Serious allergic reaction with breathing difficulties and low blood pressure or dizziness**

The PIL has also been updated to reflect changes from the posology variation with regard to recommended daily doses, duration of treatment and not being used by patients under 18 years of age.

**CONCLUSION AND RECOMMENDATIONS**
These changes incorporate most of the wording introduced by the Commission Decision of the Article 31 approval and should be approved. The remaining Article 31

wording is being introduced by the ongoing posology variation, which will also be approved.

**DECISION –**
This variation is approved.

**DATE:-** 02 December 2005

# 6. OVERALL CONCLUSION

**QUALITY**
The important quality characteristics of Prexige 100mg Tablets (and duplicates) are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**PRECLINICAL**
The anti-inflammatory, analgesic and anti-pyretic activities of lumiracoxib were investigated and shown to have equivalent activities compared to other COX-2 selective inhibitors and diclofenac. Results of the toxicology studies did not identify any properties likely to cause toxicity in humans when the product is used as directed in the SPC.

**EFFICACY**
The indications approved are for symptomatic relief in the treatment of osteoarthritis of the hip and knee.

Prexige tablets (and duplicates) have been shown to be effective in relieving pain in osteoarthritis of the knee and hip joints and the efficacy is maintained over at least 52 weeks.

No unmanageable clinical safety concerns were identified.

**RISK BENEFIT ASSESSMENT**
The quality of the product is acceptable, no unmanageable preclinical or clinical safety concerns were identified, and a benefit has been shown to be associated with Prexige 100mg Tablets (and duplicates). The benefit risk is therefore considered to be positive, at the recommended dosage levels.