SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Parecoxib 40 mg powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40 mg parecoxib (as 42.36 mg parecoxib sodium). After reconstitution, the concentration of parecoxib is 20 mg/ml. Each 2 ml of reconstituted powder contains 40 mg of parecoxib.

Excipient with known effect

This medicinal product contains less than 1 mmol (23 mg) sodium per dose.

When reconstituted in sodium chloride 9 mg/ml (0.9%) solution, Parecoxib contains approximately 0.44 mmol of sodium per vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

White to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term treatment of postoperative pain in adults.

The decision to prescribe a selective cyclooxygenase-2 (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

Posology

The recommended dose is 40 mg administered intravenously (IV) or intramuscularly (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day.

As the cardiovascular risk of COX-2 specific inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. There is limited clinical experience with Parecoxib treatment beyond three days (see section 5.1).

Concomitant use with opioid analgesics

Opioid analgesics can be used concurrently with parecoxib, dosing as described in the paragraph above. In all clinical assessments parecoxib was administered at a fixed time interval whereas the opioids were administered on as needed basis.

Elderly

No dose adjustment is generally necessary in elderly patients (≥65 years). However, for elderly patients weighing less than 50 kg, treatment should be initiated with half the usual recommended dose of Parecoxib and reduce the maximum daily dose to 40 mg (see section 5.2).

Hepatic impairment

There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score ≥10), therefore its use is contraindicated in these patients (see sections 4.3 and 5.2). No dosage adjustment is generally necessary in patients with mild hepatic impairment (Child-Pugh score 5-6). Parecoxib should be introduced with caution and at half the usual recommended dose in patients with moderate hepatic impairment (Child Pugh score 7-9) and the maximum daily dose should be reduced to 40 mg.

Renal impairment

In patients with severe renal impairment (creatinine clearance <30 ml/min.) or patients who may be predisposed to fluid retention, parecoxib should be initiated at the lowest recommended dose (20 mg) and the patient's kidney function should be closely monitored (see sections 4.4 and 5.2). On the basis of pharmacokinetics, no dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance of 30-80 ml/min.).

Paediatric population

The safety and efficacy of parecoxib in children under 18 years old have not been established. No data are available. Therefore, parecoxib is not recommended in these patients.

Method of administration

The IV bolus injection may be given rapidly and directly into a vein or into an existing IV line. The IM injection should be given slowly and deeply into the muscle.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

Precipitation may occur when Parecoxib is combined in solution with other medicinal products and therefore Parecoxib must not be mixed with any other medicinal product, either during reconstitution or injection. In those patients where the same IV line is to be used to inject another medicinal product, the line must be adequately flushed prior to and after Parecoxib injection with a solution of known compatibility.

After reconstitution with acceptable solvents, Parecoxib may **only** be injected IV or IM, or into IV lines delivering the following:

- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion;
- glucose 50 mg/ml (5%) solution for infusion;
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion.

Injection into an IV line delivering glucose 50 mg/ml (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed above, is **not** recommended as this may cause precipitation from solution.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

History of previous serious allergic drug reaction of any type, especially cutaneous reactions such as Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms syndrome (DRESS syndrome), toxic epidermal necrolysis, erythema multiforme or patients with known hypersensitivity to sulfonamides (see sections 4.4 and 4.8).

Active peptic ulceration or gastrointestinal (GI) bleeding.

Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or other allergic-type reactions after taking acetylsalicylic acid or NSAIDs including COX-2 (cyclooxygenase-2) inhibitors.

The third trimester of pregnancy and breast-feeding (see sections 4.6 and 5.3).

Severe hepatic impairment (serum albumin <25 g/l or Child-Pugh score ≥ 10).

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

Treatment of post-operative pain following coronary artery bypass graft (CABG)

surgery (see sections 4.8 and 5.1).

Established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

Parecoxib has been studied in dental, orthopaedic, gynaecologic (principally hysterectomy) and coronary artery bypass graft surgery. There is little experience in other types of surgery, for example gastrointestinal or urological surgery (see section 5.1).

Modes of administration other than IV or IM (e.g. intra-articular, intrathecal) have not been studied and should not be used.

Because of the possibility for increased adverse reactions at higher doses of parecoxib, other COX-2 inhibitors and NSAIDs, patients treated with parecoxib should be reviewed following dose increase and, in the absence of an increase in efficacy, other therapeutic options should be considered (see section 4.2). There is limited clinical experience with Parecoxib treatment beyond three days (see section 5.1).

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

This medicine contains less than 1 mmol sodium (23 mg) per ml, and is that is to say essentially ‘sodium-free’.

Cardiovascular

COX-2 inhibitors have been associated with increased risk of cardiovascular and thrombotic adverse events when taken long term. The exact magnitude of the risk associated with a single dose has not been determined, nor has the exact duration of therapy associated with increased risk.

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

Appropriate measures should be taken and discontinuation of parecoxib therapy should be considered if there is clinical evidence of deterioration in the condition of specific clinical symptoms in these patients. Parecoxib has not been studied in cardiovascular revascularization procedures other than CABG (coronary artery bypass graft procedures). Studies in types of surgery other than CABG procedures included patients with ASA (American Society of Anaesthesiology) Physical Status Class I-III only.

Acetylsalicylic acid and other NSAIDs

COX-2 inhibitors are not a substitute for acetylsalicylic acid for prophylaxis of cardiovascular thrombo-embolic diseases because of their lack of antiplatelet effects. Therefore, antiplatelet therapies should not be discontinued (see section 5.1). Caution should be exercised when co-administering Parecoxib with warfarin and other oral anticoagulants (see section 4.5). The concomitant use of parecoxib with other non-acetylsalicylic acid NSAIDs should be avoided.

Parecoxib may mask fever and other signs of inflammation (see section 5.1). In isolated cases, an aggravation of soft tissue infections has been described in connection with the use of NSAIDs and in nonclinical studies with Parecoxib (see section 5.3). Caution should be exercised with respect to monitoring the incision for signs of infection in surgical patients receiving Parecoxib.

Gastrointestinal

Upper gastrointestinal (GI) complications [perforations, ulcers or bleedings (PUBs)], some of them resulting in fatal outcome, have occurred in patients treated with parecoxib. Caution is advised in the treatment of patients most at risk of developing a gastrointestinal complication with NSAIDs; the elderly, or patients with a prior history of gastrointestinal disease, such as ulceration and GI bleeding, or patients using acetylsalicylic acid concomitantly. The NASIDs class is also associated with increased GI complications when co-administered with glucocorticoids, selective serotonin reuptake inhibitors, other antiplatelet drugs, other NSAIDs or patients ingesting alcohol. There is further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when parecoxib is taken concomitantly with acetylsalicylic acid (even at low doses).

Skin reactions

Serious skin reactions, including erythema multiforme, exfoliative dermatitis and Stevens-Johnson syndrome (some of them fatal) have been reported through post-marketing surveillance in patients receiving parecoxib. Additionally, fatal reports of toxic epidermal necrolysis have been reported through post-marketing surveillance in patients receiving valdecoxib (the active metabolite of parecoxib) and cannot be ruled out for parecoxib (see section 4.8). DRESS syndrome may occur with parecoxib exposure based on other serious skin reactions reported with celecoxib and valdecoxib exposure. Patients appear to be at highest risk for these reactions early in the course of therapy; the onset of the reaction occurring in the majority of cases within the first month of treatment.

Appropriate measures should be taken by physicians to monitor for any serious skin reactions with therapy, e.g. additional patient consultations. Patients should be advised to immediately report any emergent skin condition to their physician.

Parecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Serious skin reactions are known to occur with NSAIDs including COX-2 selective inhibitors as well as other medicinal products. However, the reported rate of serious skin events appears to be greater for valdecoxib (the active metabolite of parecoxib) as compared to other COX-2 selective inhibitors. Patients with a history of sulfonamide allergy may be at greater risk of skin reactions (see section 4.3). Patients without a history of sulfonamide allergy may also be at risk for serious skin reactions.

Hypersensitivity

Hypersensitivity reactions (anaphylaxis and angioedema) have been reported in post-marketing experience with valdecoxib and parecoxib (see section 4.8). Some of these reactions have occurred in patients with a history of allergic-type reactions to sulfonamides (see section 4.3). Parecoxib should be discontinued at the first sign of hypersensitivity.

Cases of severe hypotension shortly following parecoxib administration have been reported in postmarketing experience with parecoxib. Some of these cases have occurred without other signs of anaphylaxis. The physician should be prepared to treat severe hypotension.

Fluid retention, oedema, renal

As with other medicinal products known to inhibit prostaglandin synthesis, fluid retention and oedema have been observed in some patients taking parecoxib. Therefore, parecoxib should be used with caution in patients with compromised cardiac function, preexisting oedema, or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolemia. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of parecoxib should be taken.

Acute renal failure has been reported through post-marketing surveillance in patients receiving parecoxib (see section 4.8). Since prostaglandin synthesis inhibition may result in deterioration of renal function and fluid retention, caution should be observed when administering Parecoxib in patients with impaired renal function (see section 4.2) or hypertension, or in patients with compromised cardiac or hepatic function or other conditions predisposing to fluid retention.

Caution should be used when initiating treatment with Parecoxib in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with Parecoxib.

Hypertension

As with all NSAIDs, parecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events.

Parecoxib should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with parecoxib and throughout the course of therapy. If blood pressure rises significantly, alternative treatment should be considered.

Hepatic impairment

Parecoxib should be used with caution in patients with moderate hepatic impairment (Child-Pugh score 7-9) (see section 4.2).

Use with oral anticoagulants

The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban) (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Anticoagulant therapy should be monitored, particularly during the first few days after initiating Parecoxib therapy in patients receiving warfarin or other anticoagulants, since these patients have an increased risk of bleeding complications. Therefore, patients receiving oral anticoagulants should be closely monitored for their prothrombin time INR, particularly in the first few days when therapy with parecoxib is initiated or the dose of parecoxib is changed (see section 4.4).

Parecoxib had no effect on acetylsalicylic acid-mediated inhibition of platelet aggregation or bleeding times. Clinical trials indicate that Parecoxib can be given with low dose acetylsalicylic acid (≤ 325 mg). In the submitted studies, as with other NSAIDs, an increased risk of gastrointestinal ulceration or other gastrointestinal complications compared to use of parecoxib alone was shown for concomitant administration of low-dose acetylsalicylic acid (see section 5.1).

Co-administration of parecoxib and heparin did not affect the pharmacodynamics of heparin (activated partial thromboplastin time) compared to heparin alone.

Inhibition of prostaglandins by NSAIDs, including COX-2 inhibitors, may diminish the effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, beta-blockers and diuretics. This interaction should be given consideration in patients receiving parecoxib concomitantly with ACE-inhibitors, angiotensin II antagonists, beta-blockers and diuretics.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors or Angiotensin-II antagonists, may result in further deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

Therefore, the concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.

Co-administration of NSAIDs and ciclosporin or tacrolimus has been suggested to increase the nephrotoxic effect of ciclosporin and tacrolimus because of NSAID effects on renal prostaglandins. Renal function should be monitored when parecoxib and any of these medicinal products are co-administered.

Parecoxib may be co-administered with opioid analgesics. In clinical trials, the daily requirement for PRN opioids was significantly reduced when co-administered with parecoxib.

Effects of other medicinal products on the pharmacokinetics of parecoxib (or its active metabolite valdecoxib)

Parecoxib is rapidly hydrolysed to the active metabolite valdecoxib. In humans, studies demonstrated that valdecoxib metabolism is predominantly mediated via CYP3A4 and 2C9 isozymes.

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (62% and 19%, respectively) when co-administered with fluconazole (predominantly a CYP2C9 inhibitor), indicating that the dose of parecoxib should be reduced in those patients who are receiving fluconazole therapy.

Plasma exposure (AUC and C_{max}) to valdecoxib was increased (38% and 24%, respectively) when co-administered with ketoconazole (CYP3A4 inhibitor), however, a dosage adjustment should not generally be necessary for patients receiving ketoconazole.

The effect of enzyme induction has not been studied. The metabolism of valdecoxib may increase when co-administered with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone.

Effect of parecoxib (or its active metabolite valdecoxib) on the pharmacokinetics of other medicinal products

Treatment with valdecoxib (40 mg twice daily for 7 days) produced a 3-fold increase in plasma concentrations of dextromethorphan (CYP2D6 substrate). Therefore, caution should be observed when co-administering Parecoxib and medicinal products that are predominantly metabolised by CYP2D6 and which have narrow therapeutic margins (e.g. flecainide, propafenone, metoprolol).

Plasma exposure of omeprazole (CYP 2C19 substrate) 40 mg once daily was increased by 46% following administration of valdecoxib 40 mg twice daily for 7 days, while the plasma exposure to valdecoxib was unaffected. These results indicate that although valdecoxib is not metabolised by CYP2C19, it may be an inhibitor of this isoenzyme. Therefore, caution should be observed when administering Parecoxib with medicinal products known to be substrates of CYP2C19 (e.g. phenytoin, diazepam, or imipramine).

In two pharmacokinetic interaction studies in rheumatoid arthritis patients receiving a stable weekly methotrexate dose (5-20 mg/week, as a single oral or intramuscular dose), orally administered valdecoxib (10 mg twice daily or 40 mg twice daily) had little or no effect on the steady-state plasma concentrations of methotrexate. However caution is advised when methotrexate is administered concurrently with NSAIDs, because NSAID administration may result in increased plasma levels of methotrexate. Adequate monitoring of methotrexate-related toxicity should be considered when co-administering parecoxib and methotrexate.

Co-administration of valdecoxib and lithium produced significant decreases in lithium serum clearance (25%) and renal clearance (30%) with a 34% higher serum exposure compared to lithium alone. Lithium serum concentration should be monitored closely when initiating or changing parecoxib therapy in patients receiving lithium.

Co-administration of valdecoxib with glibenclamide (CYP3A4 substrate) did not

affect either the pharmacokinetics (exposure) or the pharmacodynamics (blood glucose and insulin levels) of glibenclamide.

Injectable anaesthetics

Coadministration of IV parecoxib 40 mg with propofol (CYP2C9 substrate) or midazolam (CYP3A4 substrate) did not affect either the pharmacokinetics (metabolism and exposure) or the pharmacodynamics (EEG effects, psychomotor tests and waking from sedation) of IV propofol or IV midazolam. Additionally, coadministration of valdecoxib had no clinically significant effect on the hepatic or intestinal CYP 3A4-mediated metabolism of orally administered midazolam. Administration of IV parecoxib 40 mg had no significant effect on the pharmacokinetics of either IV fentanyl or IV alfentanil (CYP3A4 substrates).

Inhalation anaesthetics

No formal interaction studies have been done. In surgery studies in which parecoxib was administered pre-operatively, no evidence of pharmacodynamic interaction was observed in patients receiving parecoxib and the inhalation anaesthetic agents nitrous oxide and isoflurane (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

Parecoxib is suspected to cause serious birth defects when administered during the last trimester of pregnancy because as with other medicinal products known to inhibit prostaglandin, it may cause premature closure of the ductus arteriosus or uterine inertia (see sections 4.3, 5.1 and 5.3).

NSAID use during the second or third trimester of pregnancy may cause foetal renal dysfunction which may result in reduction of amniotic fluid volume or oligohydramnios in severe cases. Such effects may occur shortly after treatment initiation and are usually reversible. Pregnant women on NSAIDs should be closely monitored for amniotic fluid volume.

Parecoxib is contraindicated in the third trimester of pregnancy (see section 4.3).

There are no adequate data from the use of parecoxib in pregnant women or during labour. However, inhibition of prostaglandin synthesis might adversely affect pregnancy. Data from epidemiological studies suggest an increased risk of miscarriage after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors, including parecoxib, has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality (see sections 5.1 and 5.3). During the first and second trimester of pregnancy, Parecoxib should not be given unless clearly necessary.

Breast-feeding

Administration of a single dose of parecoxib to lactating women following caesarean section resulted in the transfer of a relatively small amount of parecoxib and its active metabolite valdecoxib into human milk, and this resulted in a low relative dose for the infant (approximately 1% of the weight-adjusted maternal dose). Parecoxib must not be administered to women who breast-feed (see section 4.3).

Fertility

The use of Parecoxib, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, is not recommended in women attempting to conceive (see sections 4.3, 5.1 and 5.3).

Based on the mechanism of action, the use of NSAIDs, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including Parecoxib should be considered.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness, vertigo or somnolence after receiving Parecoxib should refrain from driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction for Parecoxib is nausea. The most serious reactions occur uncommonly to rarely, and include cardiovascular events such as myocardial infarction and severe hypotension, as well as hypersensitivity events such as anaphylaxis, angioedema and severe skin reactions. Following coronary artery bypass graft surgery, patients administered Parecoxib have a higher risk of adverse reactions such as: cardiovascular/ thromboembolic events (including myocardial infarction, stroke/TIA, pulmonary embolus, and deep vein thrombosis; see sections 4.3 and 5.1), deep surgical infections, and sternal wound healing complications.

Tabulated list of adverse reactions

The following adverse reactions were reported for patients who received parecoxib (N=5,402) in 28 placebo-controlled clinical trials. Reports from post-marketing experience have been listed as “frequency not known” because the respective frequencies cannot be estimated from the available data. Within each frequency grouping, adverse reactions are listed using MedDRA terminology and presented in order of decreasing seriousness.

Adverse Drug Reaction Frequency

Very Common (≥1/10)	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1,000 to <1/100*	*Rare (≥1/10,000 to <1/1,000)*	*Not Known*
Infections and infestations				
	Pharyngitis, alveolar osteitis (dry socket)	Abnormal sternal serous wound drainage, wound infection		
Blood and lymphatic system disorders				
	Anaemia postoperative	Thrombocytopenia		
Immune System Disorders				
			Anaphylactoid reaction	
Metabolism and nutrition disorders				
	Hypokalaemia	Hyperglycaemia, anorexia		
Psychiatric disorders				
	Agitation, insomnia			
Nervous system disorders				
	Hypoaesthesia, dizziness	Cerebrovascular disorder		
Ear and labyrinth disorders				
		Ear pain		
Cardiac disorders				
		Myocardial infarction, bradycardia		Circulatory collapse, congestive heart failure, tachycardia
Vascular disorders				
	Hypertension, hypotension	Hypertension (aggravated), orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders				
	Respiratory insufficiency	Pulmonary embolism		Dyspnoea
Gastrointestinal disorders				
Nausea	Abdominal pain, vomiting, constipation, dyspepsia, flatulence	Gastroduodenal ulceration, gastrooesophageal reflux disease, dry mouth, gastrointestinal sounds abnormal	Pancreatitis, oesophagitis, oedema mouth (perioral swelling)	
Skin and subcutaneous tissue disorders				
	Pruritus, hyperhidrosis	Ecchymosis, rash, urticaria		Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis

Adverse Drug Reaction Frequency				
Very Common (≥1/10)	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1,000 to <1/100*	*Rare (≥1/10,000 to <1/1,000)*	*Not Known*
Musculoskeletal and connective tissue disorders				
	Back pain	Arthralgia		
Renal and urinary disorders				
	Oliguria		Renal failure acute	Renal failure
General disorders and administration site conditions				
	Oedema peripheral	Asthenia, injection site pain, injection site reaction		Hypersensitivity reactions including anaphylaxis and angiodema
Investigations				
	Blood creatinine increased	Blood CPK increased, blood LDH increased, SGOT increased, SGPT increased, BUN increased.		
Injury, poisoning and procedural complications				
		Post procedural complication (skin)		

Description of selected adverse reactions

In post-marketing experience, toxic epidermal necrolysis has been reported in association with the use of valdecoxib, and cannot be ruled out for parecoxib (see section 4.4). In addition, the following rare, serious adverse reactions have been reported in association with the use of NSAIDs and cannot be ruled out for Parecoxib: bronchospasm and hepatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store).

4.9 Overdose

Reporting of overdose with parecoxib has been associated with adverse reactions which have also been described with recommended doses of parecoxib.

In case of overdose, patients should be managed by symptomatic and supportive care. Valdecoxib is not removed by haemodialysis. Diuresis or alkalisation of urine may not be useful due to high protein binding of valdecoxib.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, Coxibs,

ATC code: M01AH04

Parecoxib is a prodrug of valdecoxib. Valdecoxib is a 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 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.

The efficacy of Parecoxib was established in studies of dental, gynaecologic (hysterectomy), orthopaedic (knee and hip replacement), and coronary artery bypass graft surgical pain. The first perceptible analgesic effect occurred in 7 -13 minutes, with clinically meaningful analgesia demonstrated in 23-39 minutes and a peak effect within 2 hours following administration of single doses of 40 mg IV or IM Parecoxib. The magnitude of analgesic effect of the 40 mg dose was comparable with that of ketorolac 60 mg IM or ketorolac 30 mg IV. After a single dose, the duration of analgesia was dose and clinical pain model dependent, and ranged from 6 to greater than 12 hours.

Use of parecoxib beyond 3 days

Most trials were designed for dosing of parecoxib up to 3 days. Data from 3 randomised placebo-controlled trials, where the protocols allowed treatment of parecoxib for >3 days was pooled and analysed. In the pooled analysis of 676 patients, 318 received placebo and 358 received parecoxib. Of the patients treated with parecoxib, 317 patients received parecoxib for up to 4 days, 32 patients for up to

5 days, while only 8 patients were treated for up to 6 days and 1 patient for 7 or more days. Of the patients treated with placebo, 270 patients received placebo for up to 4 days, 43 patients for up to 5 days, while only 3 patients were treated for up to 6 days and 2 patients for 7 or more days. Both groups had similar demographics. The mean (SD) duration of treatment was 4.1 (0.4) days for parecoxib and 4.2 (0.5) days for placebo, the range was 4-7 days for parecoxib and 4-9 days for placebo. The occurrence of adverse events in patients receiving parecoxib for 4-7 days (median duration 4 days) was low after treatment Day 3 and similar to placebo.

Opioid-sparing effects

In a placebo-controlled, orthopedic and general surgery study (n =1050), patients received Parecoxib at an initial parenteral dose of 40 mg IV followed by 20 mg twice daily for a minimum of 72 hours in addition to receiving standard care including supplemental patient controlled opioids. The reduction in opioid use with Parecoxib treatment on Days 2 and 3 was 7.2 mg and 2.8 mg (37% and 28% respectively). This reduction in opioid use was accompanied by significant reductions in patient reported opioid symptom distress. Added pain relief compared to opioids alone was shown. Additional studies in other surgical settings provided similar observations. There are no data indicating less overall adverse events associated with the use of parecoxib compared to placebo when used in conjunction with opioids.

Gastrointestinal studies

In short-term studies (7 days), the incidence of endoscopically observed gastroduodenal ulcers or erosions in healthy young and elderly (≥ 65 years) subjects administered Parecoxib (5-21%), although higher than placebo (5-12%), was statistically significantly lower than the incidence observed with NSAIDs (66-90%).

CABG post-operative safety studies

In addition to routine adverse event reporting, pre-specified event categories, adjudicated by an independent expert committee, were examined in two placebo-controlled safety studies in which patients received parecoxib for at least 3 days and then were transitioned to oral valdecoxib for a total duration of 10-14 days. All patients received standard of care analgesia during treatment. Patients received low-dose acetylsalicylic acid prior to randomization and throughout the two CABG surgery studies.

The first CABG surgery study evaluated patients treated with IV parecoxib 40 mg bid for a minimum of 3 days, followed by treatment with valdecoxib 40 mg bid (parecoxib/valdecoxib group) (n=311) or placebo/placebo (n=151) in a 14-day, double-blind placebo-controlled study. Nine pre-specified adverse event categories were evaluated (cardiovascular thromboembolic events, pericarditis, new onset or exacerbation of congestive heart failure, renal failure/dysfunction, upper GI ulcer complications, major non-GI bleeds, infections, non-infectious pulmonary complications, and death). There was a significantly ($p<0.05$) greater incidence of cardiovascular/thromboembolic events (myocardial infarction, ischemia, cerebrovascular accident, deep vein thrombosis and pulmonary embolism) detected in the parecoxib/valdecoxib treatment group compared to the placebo/placebo treatment group for the IV dosing period (2.2% and 0.0% respectively) and over the entire study period (4.8% and 1.3% respectively). Surgical wound complications (most involving

the sternal wound) were observed at an increased rate with parecoxib/valdecoxib treatment.

In the second CABG surgery study, four pre-specified event categories were evaluated (cardiovascular/thromboembolic; renal dysfunction/renal failure; upper GI ulcer/bleeding; surgical wound complication). Patients were randomized within 24-hours post-CABG surgery to: parecoxib initial dose of 40 mg IV, then 20 mg IV Q12H for a minimum of 3 days followed by valdecoxib PO (20 mg Q12H) (n=544) for the remainder of a 10 day treatment period; placebo IV followed by valdecoxib PO (n=544); or placebo IV followed by placebo PO (n=548). A significantly (p=0.033) greater incidence of events in the cardiovascular/thromboembolic category was detected in the parecoxib /valdecoxib treatment group (2.0%) compared to the placebo/placebo treatment group (0.5%). Placebo/valdecoxib treatment was also associated with a higher incidence of CV thromboembolic events versus placebo treatment, but this difference did not reach statistical significance. Three of the six cardiovascular thromboembolic events in the placebo/valdecoxib treatment group occurred during the placebo treatment period; these patients did not receive valdecoxib. Pre-specified events that occurred with the highest incidence in all three treatment groups involved the category of surgical wound complications, including deep surgical infections and sternal wound healing events.

There were no significant differences between active treatments and placebo for any of the other prespecified event categories (renal dysfunction/failure, upper GI ulcer complications or surgical wound complications).

General surgery

In a large (N=1050) major orthopedic/general surgery trial, patients received an initial dose of parecoxib 40 mg IV, then 20 mg IV Q12H for a minimum of 3 days followed by valdecoxib PO (20 mg Q12H) (n=525) for the remainder of a 10 day treatment period, or placebo IV followed by placebo PO (n=525). There were no significant differences in the overall safety profile, including the four pre-specified event categories described above for the second CABG surgery study, for parecoxib/valdecoxib compared to placebo treatment in these post-surgical patients.

Platelet studies

In a series of small, multiple dose studies in healthy young and elderly subjects, Parecoxib 20 mg or 40 mg twice daily had no effect on platelet aggregation or bleeding compared to placebo. In young subjects, Parecoxib 40 mg twice daily had no clinically significant effect on acetylsalicylic acid - mediated inhibition of platelet function (see section 4.5).

5.2 Pharmacokinetic properties

Following IV or IM injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver.

Absorption

Exposure of valdecoxib following single doses of Parecoxib, as measured by both the area under the plasma concentration vs. time curve (AUC) and peak concentration (C_{max}), is approximately linear in the range of clinical doses. AUC and C_{max} following twice daily administration is linear up to 50 mg IV and 20 mg IM. Steady state plasma concentrations of valdecoxib were reached within 4 days with twice daily dosing.

Following single IV and IM doses of parecoxib 20 mg, C_{max} of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour, respectively. Exposure to valdecoxib was similar in terms of AUC and C_{max} following IV and IM administration. Exposure to parecoxib was similar after IV or IM administration in terms of AUC. Average C_{max} of parecoxib after IM dosing was lower compared to bolus IV dosing, which is attributed to slower extravascular absorption after IM administration. These decreases were not considered clinically important since C_{max} of valdecoxib is comparable after IM and IV parecoxib administration.

Distribution

The volume of distribution of valdecoxib after its IV administration is approximately 55 litres. Plasma protein binding is approximately 98% over the concentration range achieved with the highest recommended dose, 80 mg/day. Valdecoxib, but not parecoxib, is extensively partitioned into erythrocytes.

Biotransformation

Parecoxib is rapidly and almost completely converted to valdecoxib and propionic acid in vivo with a plasma half-life of approximately 22 minutes. Elimination of valdecoxib is by extensive hepatic metabolism involving multiple pathways, including cytochrome P 450 (CYP) 3A4 and CYP2C9 isoenzymes and glucuronidation (about 20%) of the sulfonamide moiety. A hydroxylated metabolite of valdecoxib (via the CYP pathway) has been identified in human plasma that is active as a COX-2 inhibitor. It represents approximately 10% of the concentration of valdecoxib; because of this metabolite's low concentration, it is not expected to contribute a significant clinical effect after administration of therapeutic doses of parecoxib.

Elimination

Valdecoxib is eliminated via hepatic metabolism with less than 5% unchanged valdecoxib recovered in the urine. No unchanged parecoxib is detected in urine and only trace amounts in the faeces. About 70% of the dose is excreted in the urine as inactive metabolites. Plasma clearance (CLp) for valdecoxib is about 6 l/hr. After IV or IM dosing of parecoxib, the elimination half-life ($t_{1/2}$) of valdecoxib is about 8 hours.

Elderly

Parecoxib has been administered to 335 elderly patients (65-96 years of age) in pharmacokinetic and therapeutic trials. In healthy elderly subjects, the apparent oral clearance of valdecoxib was reduced, resulting in an approximately 40% higher plasma exposure of valdecoxib compared to healthy young subjects. When adjusted

for body weight, steady state plasma exposure of valdecoxib was 16% higher in elderly females compared to elderly males (see section 4.2).

Renal impairment

In patients with varying degrees of renal impairment administered 20 mg IV Parecoxib, parecoxib was rapidly cleared from plasma. Because renal elimination of valdecoxib is not important to its disposition, no changes in valdecoxib clearance were found even in patients with severe renal impairment or in patients undergoing dialysis (see section 4.2).

Hepatic impairment

Moderate hepatic impairment did not result in a reduced rate or extent of parecoxib conversion to valdecoxib. In patients with moderate hepatic impairment (Child-Pugh score 7-9), treatment should be initiated with half the usual recommended dose of Parecoxib and the maximum daily dose should be reduced to 40 mg since valdecoxib exposures were more than doubled (130%) in these patients. Patients with severe hepatic impairment have not been studied and therefore the use of Parecoxib in patients with severe hepatic impairment is not recommended (see sections 4.2 and 4.3).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity at 2-fold the maximum human exposure to parecoxib. However, in the repeated dose toxicity studies in dogs and rats, the systemic exposures to valdecoxib (the active metabolite of parecoxib) were approximately 0.8-fold the systemic exposure in elderly human subjects at the maximum recommended therapeutic dose of 80 mg daily. Higher doses were associated with aggravation and delayed healing of skin infections, an effect probably associated with COX-2 inhibition.

In reproduction toxicity tests, the incidence of post-implantation losses, resorptions and foetal body weight retardation occurred at doses not producing maternal toxicity in the rabbit studies. No effects of parecoxib on male or female fertilities were found in rats.

The effects of parecoxib have not been evaluated in late pregnancy or in the pre- and postnatal period.

Parecoxib administered intravenously to lactating rats as a single dose showed concentrations of parecoxib, valdecoxib and a valdecoxib active metabolite in milk similar to that of maternal plasma.

The carcinogenic potential of parecoxib has not been evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium hydrogen phosphate

Phosphoric acid and/or sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6.

Parecoxib and opioids should not be administered together in the same syringe.

Use of Ringer-Lactate solution for injection or glucose 50 mg/ml (5%) in Ringer Lactate solution for injection for reconstitution will cause the parecoxib to precipitate from solution and therefore is **not** recommended.

Use of water for injection is **not** recommended, as the resulting solution is not isotonic.

Parecoxib should not be injected into an IV line delivering any other medicinal product. The IV line must be adequately flushed prior to and after Parecoxib injection with a solution of known compatibility (see section 6.6).

Injection into an IV line delivering glucose 50 mg/ml (5%) in Ringer-Lactate solution for injection, or other IV fluids not listed in section 6.6, is not recommended as this may cause precipitation from solution.

6.3 Shelf life

The shelf life of the un-reconstituted product is 36 months (3 years).

Chemical and physical in-use stability of the reconstituted solution, which should not be refrigerated or frozen, have been demonstrated for up to 24 hours at 25^{o}C. Thus, 24 hours should be considered the maximum shelf life of the reconstituted product. However, due to the importance of microbiological infection risk for injectable products, the reconstituted solution should be used immediately unless reconstitution has taken place in controlled and validated aseptic conditions. Unless such requirements are met, in-storage times and conditions prior to use are the responsibility of the user, and would not normally be longer than 12 hours at 25^{o}C

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions prior to reconstitution.

For storage conditions of the reconstituted the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I colourless glass vials (5 ml) with a bromobutyl rubber stopper, and an aluminium flip off seal.

Parecoxib is available in packs containing 5 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Parecoxib must be reconstituted before use. Parecoxib is preservative free. Aseptic technique is required for its preparation.

Reconstitution solvents

Acceptable solvents for reconstitution of Parecoxib are:

- sodium chloride 9 mg/ml (0.9%) solution for injection/infusion
- glucose 50 mg/ml (5%) solution for infusion
- sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion

Reconstitution process

Use aseptic technique to reconstitute lyophilised parecoxib (as parecoxib).

Remove the purple flip-off cap to expose the central portion of the rubber stopper of the 40 mg parecoxib vial. Withdraw, with a sterile needle and syringe, 2 ml of an acceptable solvent and insert the needle through the central portion of the rubber stopper transferring the solvent into the 40 mg vial. Dissolve the powder completely using a gentle swirling motion and inspect the reconstituted product before use. The entire contents of the vial should be withdrawn for a single administration.

After reconstitution, the liquid should be a clear solution. Parecoxib should be inspected visually for particulate matter and discoloration prior to administration. The solution should not be used if discolored or cloudy, or if particulate matter is observed. Parecoxib should be administered within 24 hours of reconstitution (see section 6.3), or discarded.

The reconstituted product is isotonic.

IV line solution compatibility

After reconstitution with acceptable solvents, Parecoxib may only be injected IV or IM, or into IV lines delivering:

sodium chloride 9 mg/ml (0.9%) solution for injection/infusion;

glucose 50 mg/ml (5%) solution for infusion;

sodium chloride 4.5 mg/ml (0.45%) and glucose 50 mg/ml (5%) solution for injection/infusion.

For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL35533/0141

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/04/2025

10 DATE OF REVISION OF THE TEXT

23/04/2025