

# **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1 NAME OF THE MEDICINAL PRODUCT**

Naproxen Tablets BP 250 mg

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 250 mg Naproxen.

Excipient(s) with known effect

Each tablet contains 63.00mg of lactose.

For the full list of excipients, see section 6.1.

## **3 PHARMACEUTICAL FORM**

Pale yellow uncoated tablets

Pale yellow, round flat tablets with bevelled edge, marked 'NAPROXEN 250' on one side with a break line on the other side.

## **4 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Adults:

Naproxen is used in the treatment of rheumatoid arthritis, osteoarthritis (degenerative arthritis), acute musculoskeletal disorders, Ankylosing spondylitis, dysmenorrhoea, and acute gout.

Children:

Naproxen is effective in the treatment of juvenile rheumatoid arthritis in children over 5 years of age.

## 4.2 Posology and method of administration

### Posology

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

#### *Adults:*

#### ***Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis***

500mg to 1g taken in 2 doses at 12-hour intervals or alternatively, as a single administration. In the following cases a loading dose of 750mg or 1g per day for the acute phase is recommended:

- a) In patients reporting severe night-time pain/or morning stiffness.
- b) In patients being switched to Naproxen from a high dose of another anti-rheumatic compound.
- c) In osteoarthritis where pain is the predominant symptom.

#### ***Acute gout***

In acute gout, an initial dose of 750 mg followed by 250 mg every 8 hours until the attack has passed.

#### ***Acute musculoskeletal disorders and dysmenorrhoea***

The recommended dose is 500 mg initially followed by 250 mg at 6-8 hour intervals as needed, with a maximum daily dose after the first day of 1250 mg.

#### *Paediatric population*

#### ***For juvenile rheumatoid arthritis:***

A dose of 10 mg per kg body weight daily in two divided doses taken in children at 12-hour intervals over 5 years of age with juvenile rheumatoid arthritis.

Naproxen is not recommended for use in any other indication in children under 16 years of age.

#### *Elderly:*

The elderly are at increased risk of the serious consequences of adverse reactions. The patient should be monitored regularly for GI bleeding during NSAID therapy. Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. The implication of this finding for naproxen dosing is unknown. As with other drugs used in the elderly it is prudent to use the lowest effective dose and for the shortest duration possible as older people are more prone to adverse events. For the effect of reduced elimination in the elderly refer to Section 4.4.

#### **Renal/hepatic impairment**

A reduction in dosage may be necessary if there is impaired renal or hepatic function. (see section 4.4). Naproxen is contraindicated in patients with baseline creatinine clearance less than 30 ml/minute because accumulation of naproxen metabolites has been seen in patients with severe renal failure or those on dialysis (see section 4.3).

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

### Method of administration

For oral administration, preferably with or after food.

### **4.3 Contraindications**

NSAIDs are contraindicated in patients who have:

- Hypersensitivity to Naproxen, Naproxen sodium formulations or to any of the excipients listed in section 6.1.
- Patients with active gastrointestinal bleeding.
- Active or history of recurrent peptic ulceration / haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- NSAID's contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, nasal polyps, angioedema or urticaria). Since the potential exists for cross-sensitivity reactions, in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs. These reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.
- Severe hepatic, renal and cardiac failure (see section 4.4).
- A history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- During the last trimester of pregnancy (see section 4.6).

### **4.4 Special warnings and precautions for use**

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below). Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

Older people and/or debilitated patients are particularly susceptible to the adverse effects of NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal. Prolonged use of NSAIDs in these patients is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

The antipyretic and anti-inflammatory activities of Naproxen may reduce fever and inflammation, thereby diminishing their utility as diagnostic signs. Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

As with other non-steroidal anti-inflammatory drugs, elevations of one or more liver function tests may occur. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. Severe hepatic reactions, including jaundice and hepatitis (some cases of hepatitis have been fatal) have been reported with this drug as with other non-steroidal anti-inflammatory drugs. Cross reactivity has been reported. Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

Although sodium retention has not been reported in metabolic studies, it is possible that patients with questionable or compromised cardiac function may be at a greater risk when taking Naproxen.

***Gastrointestinal bleeding, ulceration and perforation:***

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in older people. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see section 4.5).

Patients with a history of GI toxicity, particularly when older, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroid, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see Section 4.5). When GI bleeding or ulceration occurs in patients receiving Naproxen, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see Section 4.8).

***Renal Effects***

There have been reports of impaired renal function, renal failure, acute interstitial nephritis, haematuria, proteinuria, renal papillary necrosis and occasionally nephrotic syndrome associated with naproxen.

***Renal failure linked to reduced prostaglandin production***

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, angiotensin converting enzyme inhibitors, angiotensin-II receptor antagonists and older people. Renal function should be monitored in these patients (see also Section 4.3).

***Use in patients with impaired renal function***

As naproxen is eliminated to a large extent (95%) by urinary excretion via glomerular filtration, it should be used with great caution in patients with impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised and patients should be adequately hydrated. Naproxen is contraindicated in patients having a baseline creatinine clearance of less than 30ml/minute.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding.

Certain patients, specifically those whose renal blood flow is compromised, such as in extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure, and pre-existing renal disease, should have renal function assessed before and during Naproxen therapy. Some older people in whom impaired renal function may be expected, as well as patients using diuretics, may also fall within this category. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

***Use in patients with impaired liver function***

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for Naproxen dosing is unknown but it is prudent to use the lowest effective dose.

***Haematological***

Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen containing products are administered.

Patients at high risk of bleeding or those on full anti-coagulation therapy (e.g. dicoumarol derivatives) may be at increased risk of bleeding if given naproxen-containing products concurrently.

***Anaphylactic (anaphylactoid) reactions***

Hypersensitivity reactions may occur in susceptible individuals.

Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to aspirin, other non-steroidal anti-inflammatory drugs or naproxen-containing products. They may also occur in individuals with a history of angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

***Steroids***

If steroid dosage is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

***Ocular effects***

Studies have not shown changes in the eye attributable to naproxen administration. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilloedema, have been reported in users of NSAIDs including naproxen, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with naproxen-containing products should have an ophthalmological examination.

***Cardiovascular and cerebrovascular effects***

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000mg daily) may be associated with a lower risk, some risk cannot be excluded.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

***SLE and mixed connective tissue disease***

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see Section 4.8).

***Severe cutaneous adverse reactions (SCARs)***

Exfoliative dermatitis and Stevens Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with Naproxen treatment. If signs and symptoms suggestive of these reactions appear, Naproxen should be withdrawn immediately. If the patient has developed SJS, or TEN or DRESS with the use of Naproxen, treatment with Naproxen must not be restarted and should be permanently discontinued. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reactions occurring in the majority of cases within the first month of treatment. Naproxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

***Combination with other NSAIDs***

The combination of naproxen-containing products and other NSAIDs, including cyclooxygenase-2 selective inhibitors, is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

**Contains lactose:** Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Concomitant administration of antacid or colestyramine can delay the absorption of naproxen but does not affect its extent.

Concomitant administration of food can delay the absorption of naproxen but does not affect its extent.

It is considered unsafe to take NSAIDs in combination with anti-coagulants such as warfarin or heparin unless under direct medical supervision, as NSAIDs may enhance the effects of anti-coagulants (see Section 4.4).

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase

the risk of adverse effects (see Section 4.4).

#### Acetylsalicylic acid

Clinical pharmacodynamic data suggest that concomitant naproxen usage for more than one day consecutively may inhibit the effect of low-dose acetylsalicylic acid on platelet activity and this inhibition may persist for up to several days after stopping naproxen therapy. The clinical relevance of this interaction is not known.

Due to the high plasma protein binding of naproxen, patients simultaneously receiving hydantoins, anticoagulants, other NSAIDs, aspirin or a highly protein-bound sulfonamide should be observed for signs of overdosage of these drugs. Patients simultaneously receiving Naproxen and a hydantoin, sulfonamide or sulfonamide should be observed for adjustment of dose if required. No interactions have been observed in clinical studies with naproxen and anticoagulants or sulfonamides, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

Caution is advised when Naproxen is co-administered with diuretics as there can be a decreased diuretic effect. The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported.

Naproxen and other non-steroidal anti-inflammatory drugs can reduce the antihypertensive effect of anti-hypertensives. Concomitant use of NSAIDs with ACE inhibitors or angiotensin-II receptor antagonists may increase the risk of renal impairment, especially in patients with pre-existing poor renal function (See Section 4.4).

Probenecid given concurrently increases naproxen plasma levels and extends its half-life considerably.

Caution is advised where methotrexate is given concurrently because of possible enhancement of its toxicity, since naproxen, among other nonsteroidal anti-inflammatory drugs, has been reported to reduce the tubular secretion of methotrexate in an animal model.

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.

As with all NSAIDs caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.

NSAIDs should not be used for 8 - 12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

As with all NSAIDs, caution should be taken when co-administering with corticosteroids because of the increased risk of gastrointestinal ulceration or bleeding.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking quinolones may have an increased risk of developing convulsions.

There is an increased risk of gastrointestinal bleeding (see Section 4.4) when anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.

There is an increased risk of haematological toxicity when NSAIDs are given with

zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

It is suggested that Naproxen therapy be temporarily discontinued 48 hours before adrenal function tests are performed, because naproxen may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxyindoleacetic acid.

## 4.6 Fertility, Pregnancy and lactation

### *Pregnancy:*

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are in low frequency and do not appear to follow any discernible pattern. As with other drugs of this type, naproxen produces delay in parturition in animals and also affects the human foetal cardiovascular system (risk of closure of ductus arteriosus).

From the 20th week of pregnancy onward, Naproxen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Naproxen should not be given unless clearly necessary.

If Naproxen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Naproxen for several days from gestational week 20 onward. Naproxen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

Good medical practice indicates minimal drug usage in pregnancy and the use of this class of therapeutic agent requires cautious balancing of possible benefit against potential risk to mother and foetus, especially in the first two trimesters of pregnancy.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction (see above)

the mother and the neonate, at the end of pregnancy, to

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Naproxen is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

### *Breast-feeding*

Naproxen has been found in the milk of lactating women. The use of Naproxen

should be avoided in patients who are breast-feeding.

#### *Fertility*

The use of naproxen as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women to conceive. In woman who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of naproxen should be considered.

### **4.7 Effects on ability to drive and use machines**

Some patients may experience drowsiness, dizziness, vertigo, insomnia, fatigue, visual disturbances or depression with the use of Naproxen. If patients experience these or similar undesirable effects, they should not drive or operate machinery

### **4.8 Undesirable effects**

The following adverse events have been reported with NSAIDs and with naproxen *Gastrointestinal disorders:* The most commonly observed adverse events are gastrointestinal in nature. Heartburn, nausea, vomiting, constipation, diarrhoea, flatulence, dyspepsia, abdominal discomfort and epigastric distress.

More serious reactions which may occur are gastro-intestinal bleeding, which is sometimes fatal, particularly in older people (see section 4.4), inflammation, ulceration, perforation, and obstruction of the upper and lower gastrointestinal tract, melaena, haematemesis, stomatitis, exacerbation of ulcerative colitis and Crohn's disease (see section 4.4), oesophagitis, gastritis and pancreatitis.

*Blood and lymphatic system disorders:* Neutropenia, thrombocytopenia, granulocytopenia including agranulocytosis, eosinophilia, leucopenia, aplastic anaemia and haemolytic anaemia.

*Immune system disorders:* Hypersensitivity reactions have been reported following treatment with NSAIDs in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs. These may consist of (a) nonspecific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angio-oedema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

*Metabolic and nutrition disorders:* hyperkalaemia.

*Psychiatric disorders:* Insomnia, dream abnormalities, depression, confusion and hallucinations.

*Nervous system disorders:* Convulsions, dizziness, headache, lightheadedness, drowsiness, paraesthesia, retrobulbar optic neuritis, inability to concentrate and cognitive dysfunction have been reported.

Aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

*Eye Disorders:* Visual disturbances, corneal opacity, papillitis and papilloedema. *Ear and Labyrinth disorders:* Tinnitus, hearing disturbances including impairment and vertigo.

*Cardiac disorders:* Oedema, palpitations, cardiac failure and congestive heart failure have been reported.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

*Vascular disorders:* Hypertension, vasculitis.

*Respiratory, thoracic and mediastinal disorders:* Dyspnoea, asthma, eosinophilic pneumonitis and pulmonary oedema.

*Hepatobiliary disorders:* Jaundice, fatal hepatitis and abnormal liver function tests.

*Skin and subcutaneous tissue disorders:* Skin rashes including, itching (pruritus), urticaria, ecchymoses, purpura, sweating. Alopecia, erythema multiforme, Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis, very rarely toxic epidermal necrolysis, photosensitivity reactions (including cases in which skin resembles porphyria cutanea tarda “pseudoporphyria”) or epidermolysis bullosa-like reactions which may occur rarely.

If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Frequency: Not known - fixed drug eruption, drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

*Musculoskeletal and connective tissue disorders:* Myalgia and muscle weakness. *Renal and urinary disorders:* Including, but not limited to, glomerular nephritis, interstitial nephritis, nephrotic syndrome, haematuria, raised serum creatinine, renal papillary necrosis and renal failure.

*Reproductive system and breast disorders:* Female infertility.

*General disorders and administration site conditions:* Thirst, pyrexia, fatigue and malaise.

#### **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 website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## **4.9 Overdose**

### *Symptoms*

Significant overdosage may be characterised by:

Headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, dizziness, tinnitus, fainting, occasionally convulsions, drowsiness, heartburn, indigestion. In cases of significant poisoning acute renal failure and liver damage are possible.

Respiratory depression and coma may occur after the ingestion of NSAIDs but are rare.

In one case of naproxen overdose, transient prolongation of the prothrombin time due to hypofibrinogenemia may have been due to selective inhibition of the synthesis of vitamin-K dependent clotting factors.

A few patients have experienced seizures, but it is not known whether these were naproxen-related or not. It is not known what dose of naproxen will be life threatening.

#### Management

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal may be given. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured. Renal and liver function should be closely monitored. In renal failure haemodialysis may be appropriate. Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding. However, haemodialysis may still be appropriate in a patient with renal failure who has taken naproxen.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids. Propionic acid derivatives.

ATC code: M01AE02

Naproxen has analgesic, anti-inflammatory and anti-pyretic actions.

Naproxen is a non-steroidal anti-inflammatory analgesic compound with antipyretic properties as has been demonstrated in classical animal test systems. Naproxen exhibits its anti-inflammatory effect even in adrenalectomised animals, indicating that its action is not mediated through the pituitary-adrenal axis.

Naproxen inhibits prostaglandin synthetase (as do other NSAIDs). As with other NSAIDs, however, the exact mechanism of its anti-inflammatory action is not known.

## 5.2 Pharmacokinetic properties

### Absorption

Naproxen is readily absorbed from the gastro intestinal tract.

### Distribution

Peak plasma levels are reached in 2 to 4 hours after ingestion. Naproxen is present in the blood mainly as unchanged drug, extensively bound to plasma proteins and has a half-life in between 12 and 15 hours, enabling a steady state to be achieved within 3 days of initiation of therapy on a twice daily dose regimen. The degree of re-absorption is not significantly affected by either foods or most antacids.

### Elimination

Excretion is almost entirely via urine as naproxen and 6-O-desmethylnaproxen and their conjugates.

### Biotransformation

Metabolism in children is similar to that in adults. Chronic alcoholic liver disease reduces the total plasma concentration of naproxen but the concentration of unbound naproxen increases. In older people, the unbound plasma concentration of naproxen is increased although total plasma concentration is unchanged.

## 5.3 Preclinical safety data

### *Carcinogenicity*

Naproxen was administered with food to Sprague-Dawley rats for 24 months at doses of 8, 16 and 24mg/kg/day. Naproxen was not carcinogenic in rats.

### *Mutagenicity*

Mutagenicity was not seen in *Salmonella typhimurium* (5 cell lines), *Sachharomyces cerevisisae* (1 cell line), and mouse lymphoma tests.

### *Fertility*

Naproxen did not affect the fertility of rats when administered orally at doses of 30mg/kg/day to males and 20mg/kg/day to females.

### *Teratogenicity*

Naproxen was not teratogenic when administered orally at dose of 20mg/kg/day during organogenesis to rats and rabbits.

### *Perinatal/Postnatal Reproduction*

Oral administration of naproxen to pregnant rats at doses of 2, 10 and 20mg/kg/day during the third trimester of pregnancy resulted in difficult labour. These are known

effects of this class of compounds and were demonstrated in pregnant rats with aspirin and indometacin.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose

Starch (Maize)

Polyvinylpyrrolidone

Sodium Starch Glycollate

Magnesium Stearate

Quinoline Yellow E104

Isopropyl Alcohol

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

Containers - 36 months. Blister packs – 36 months

### **6.4 Special precautions for storage**

Keep the tablets in the original container tightly closed, or in the same outer carton, in a dry place. Do not store above 25°C. Protect from light.

### **6.5 Nature and contents of container**

Securitainer or securitainers type containers (i.e. polypropylene/polythene containers opaque to light with tamper evident lid).

Pack sizes: 1000, 500, 250, 100, 84, 70, 56, 42, 28, 21, 15, 14

Blister pack strips composed of aluminium foil and PVC film.

Pack sizes: 84, 70, 56, 42, 28, 21, 15, 14

## **6.6 Special precautions for disposal**

No special requirements for disposal

## **7 MARKETING AUTHORISATION HOLDER**

Hualan Pharmaceuticals Limited

16/17 College Green

Dublin

D02 V078

Ireland

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 52104/0019

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first Authorisation: 19 April 2000

Date of last renewal: 03 March 2009

## **10 DATE OF REVISION OF THE TEXT**

13/08/2024