

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Naproxen 250mg Tablets

Naproxen 500mg Tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg Naproxen BP

Excipients with known effect: Also contains 120.00 mg of lactose and 0.017 mg of sunset yellow (E110)

Each tablet contains 500mg Naproxen BP

Excipients with known effect: Also contains 98.979 mg of lactose and 0.027 mg of sunset yellow (E110)

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Tablet.

Pale yellow, flat bevelled edge tablets with N breakline 250 on one side and BL on the other.

Pale yellow, oblong tablets with N breakline 500 on one side and BL on the other

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

##### *Adults*

Naproxen is indicated for the treatment of rheumatoid arthritis, osteoarthritis (degenerative arthritis), ankylosing spondylitis, acute gout, acute musculoskeletal disorders and dysmenorrhoea.

##### *Children*

Juvenile rheumatoid arthritis

#### 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**

The usual dose is 500mg to 1g per day taken in two 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 antirheumatic compound.
- c) In osteoarthritis where pain is the predominant symptom.

**Acute gout**

The recommended dosage is 750mg at once then 250mg every eight hours until the attack has passed.

**Acute musculoskeletal disorders and dysmenorrhoea**

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

***Loading dose***

As a single administration of two tablets, morning or evening, in the following cases a loading dose of 750mg -1g per day for the acute phase is recommended:

1. In patients reporting severe night-time pain and / or morning stiffness.
2. In patients being switched to naproxen from a high dose of another antirheumatic compound.
3. In osteoarthritis where pain is the predominant symptom.

***Elderly***

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. If an NSAIDs is considered necessary, the lowest effective dose should be used and for the shortest duration possible as elderly patients are more prone to adverse events. The patient should be monitored regularly for GI bleeding during NSAID therapy. For the effect of reduced elimination in the elderly refer to Section 4.4.

Dosage should be reduced in the elderly where there is an impairment of renal function (see section 4.4).

***Children (over 5 years)***

For juvenile rheumatoid arthritis: 10mg/kg/day taken in 2 doses at 12-hour intervals.

***Renal/hepatic impairment***

A lower dose should be considered in patients with renal or hepatic impairment. 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.

To be taken preferably with or after food.

**4.3 Contraindications**

- Hypersensitivity to naproxen, naproxen sodium, or any of the excipients listed in section 6.1.
- Patients with active gastrointestinal bleeding or peptic ulceration
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Severe heart failure, hepatic failure and renal failure (see section 4.4)
- During the third 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.

***Elderly and/ or debilitated patients***

Elderly patients 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.

Mild peripheral oedema has been observed in a few patients receiving naproxen. 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.

### ***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 (1000 mg 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 diseases (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

### ***Respiratory disorders***

Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

### ***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)

- in the elderly
- when used with alcohol
- in smoking.

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 below and section 4.5).

Patients with a history of GI toxicity, particularly when elderly, 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 corticosteroids, 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.

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking esomeprazole and naproxen containing products and may occur at any point during naproxen therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Naproxen should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

### ***Renal failure linked to reduced prostaglandin production - cardiovascular, renal and hepatic impairment***

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 the elderly.

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, because of 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 elderly patients 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. The product should be used with caution in patients with a history of, or in those with impaired liver function.

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.

***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 angioedema, 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 papilledema, 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.

### ***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 reaction (SCARs)***

Serious skin reactions, including exfoliative dermatitis, 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 the use of NSAIDs (see section 4.8). 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. 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.

### ***Haematological***

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

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 anticoagulation therapy (e.g. heparin or dicoumarol derivatives) may be at increased risk of bleeding if given naproxen-containing products concurrently (see section 4.5).

### ***Impaired female fertility***

The use of Naproxen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Naproxen should be considered.

### ***Combination with other NSAIDs***

The combination of naproxen-containing products and other NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided because of the cumulative risks of inducing serious NSAID-related adverse events. (see section 4.5).

### ***Interference in tests***

Naproxen therapy should be temporarily withdrawn 48 hours before adrenal function tests are performed as it may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxyindoleacetic acid.

Sporadic abnormalities in laboratory tests (e.g. liver function test) have occurred in patients on naproxen therapy, but no definite trend was seen in any test indicating toxicity.

### ***Medication Overuse Headache (MOH)***

After long term treatment with analgesics, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH - medication-overuse headache) should be suspected in patients who have frequent or daily headaches despite (or because of) regular use of analgesics. Patients with medication overuse headache should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

### **Important information regarding the ingredients of this medicine**

**Lactose:** This medicinal product contains Lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Sodium:** This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'

**Sunset yellow:** Naproxen Tablets also contain Sunset yellow, which may cause allergic reactions.



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

- Concomitant administration of antacid or colestyramine delays the absorption of naproxen but does not affect its extent. Naproxen should be taken at least one hour before or four to six hours after colestyramine.
- 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 sulphonamide should be observed for signs of overdosage of these drugs. Patients simultaneously receiving Naproxen and a hydantoin, sulfonamide or sulfonylurea should be observed for adjustment of dose if required. No interactions have been observed in clinical studies with naproxen and anticoagulants or sulfonylureas, 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 risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs. 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. 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. It is recommended that these levels are monitored whenever initiating, adjusting or discontinuing naproxen.
- Naproxen and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of anti-hypertensives. Concomitant use of NSAIDs with beta-

blockers, 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 non-steroidal 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 effect 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 (see section 4.4).
- Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and 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 increased 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 haem arthrosis 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. Sporadic abnormalities in laboratory tests (e.g. liver function test) have occurred in patients on naproxen therapy, but no definite trend was seen in any test indicating toxicity.
- Bisphosphonates: Concomitant use of bisphosphonates and NSAIDs may increase the risk of gastric mucosal damage.

## **4.6 Fertility, Pregnancy and Lactation**

### **Pregnancy**

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

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.

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 last trimester of pregnancy (see section 4.3 and 5.3).

### **Breast-feeding**

In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

### **Fertility**

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

See section 4.4 for use regarding female fertility.

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

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

#### 4.8 Undesirable effects

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (See section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (See section 4.4 - Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

The following adverse events have been reported with NSAIDs and with naproxen.

| <b>System Organ Class</b>                   | <b>Common<br/>(≥ 1/100 &lt; 1/10)</b> | <b>Uncommon<br/>(≥ 1/1000 &lt; 1/100)</b> | <b>Rare<br/>(≥ 1/10,000 &lt; 1/1000)</b>             | <b>Very Rare<br/>(&lt; 1/10,000)</b>                | <b>Frequency not known (cannot be estimated from the available data)</b> |
|---|---------------------------------------|---|--|---|--|
| <b>Blood and lymphatic system disorders</b> |                                       |   | haemolytic anaemia                                   | granulocytopenia, thrombocytopenia, agranulocytosis | aplastic anaemia, neutropenia  |
| <b>Immune system disorders</b>              |                                       |   | allergic and hypersensitivity reactions, anaphylaxis |   |  |
| <b>Metabolism and nutrition disorders</b>   |                                       |   | hyperkalaemia  |   |  |
| <b>Psychiatric disorders</b>                |                                       | depression, cognitive dysfunction,        |  |   | hallucinations   |

|  |   |  |  |   |   |
|--|---|--|--|---|---|
|  |   | insomnia,<br>loss of<br>concentration,<br>abnormal<br>dreams |  |   |   |
| <b>Nervous<br/>system<br/>disorders</b>                            | confusion,<br>dizziness,<br>drowsiness,<br>headache |  |  | convulsions,<br>aseptic<br>meningitis*  | vertigo,<br>paraesthesia,<br>malaise,<br>exacerbation of<br>Parkinson's<br>disease  |
| <b>Eye disorders</b>   | visual<br>disturbances                              |  |  |   | optic neuritis,<br>papilloedema   |
| <b>Ear and<br/>labyrinth<br/>disorders</b>                         | tinnitus  |  | hearing<br>impairment                                |   |   |
| <b>Cardiac<br/>disorders</b>                                       |   | palpitations   |  |   | cardiac failure   |
| <b>Vascular<br/>disorders</b>                                      |   |  | vasculitis   | arterial thrombotic<br>events e.g.<br>myocardial<br>infarction or<br>stroke (see 4.4) | hypertension  |
| <b>Respiratory,<br/>thoracic and<br/>mediastinal<br/>disorders</b> |   |  | aggravated<br>asthma,<br>eosinophilic<br>pneumonitis |   | bronchospasm,<br>dyspnoea,<br>rhinitis,<br>pulmonary<br>oedema  |
| <b>Gastro-<br/>intestinal<br/>disorders</b>                        |   |  |  | pancreatitis  | Thirst, peptic<br>ulcers,<br>perforation or GI<br>bleeding**,<br>nausea, vomiting,<br>diarrhoea,<br>flatulence,<br>constipation,<br>dyspepsia,<br>abdominal pain,<br>melaena,<br>haematemesis,<br>ulcerative<br>stomatitis,<br>exacerbation of<br>colitis and<br>Crohn's disease<br>(see section 4.4),<br>gastritis |
| <b>Hepatobiliary</b>   |   |  | hepatitis<br>(sometimes<br>fatal), jaundice          |   | abnormal liver<br>function  |

|  |                         |                              |                           |   |  |
|--|-------------------------|------------------------------|---------------------------|---|--|
| <b>Skin and subcutaneous tissue disorders</b>                  | rash, pruritus, purpura | urticaria, photo-sensitivity | alopecia, pseudoporphyria | erythema multiforme, Stevens Johnsons syndrome, toxic epidermal necrosis, epidermolysis bullosa   | angiooedema, epidermal necrosis, exfoliative and bullous dermatoses, lichen planus, Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4), fixed drug eruption |
| <b>Musculo-skeletal and connective tissue disorders</b>        |                         |                              | myalgia, muscle weakness  |   |  |
| <b>Renal and urinary disorders</b>                             |                         |                              |                           | glomerular nephritis, haematuria, tubulointerstitial nephritis (with possible progression to renal failure), nephritic syndrome, renal papillary necrosis | renal failure, nephropathy, increase in serum creatinine   |
| <b>Reproductive system and breast disorders</b>                |                         |                              |                           |   | impaired female fertility (see 4.4)  |
| <b>General disorders and administration site complications</b> | fatigue                 |                              |                           |   | mild peripheral oedema, pyrexia  |

\*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 and disorientation.

\*\* sometimes fatal, particularly in the elderly, may occur (See section 4.4).

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

**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**

Symptoms include headache, heartburn, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions/seizures. 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 hypothermia may have been due to selective inhibition of the synthesis of vitamin-K dependent clotting factors.

In cases of significant poisoning acute renal failure and liver damage are possible. It is not known what dose of the drug would be life-threatening.

**Management**

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount activated charcoal should be considered. 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. 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 anti-rheumatic products, non-steroids. Propionic acid derivatives.

ATC code: M01AE02

#### **Mechanism of action:**

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 adrenal-ectomised animals, indicating that its action is not mediated through the pituitary-adrenal axis.

Naproxen reduces the synthesis of prostaglandins primarily by inhibiting the enzyme cyclo-oxygenase. Naproxen has been shown to have anti-inflammatory activity in a number of experimental models. Naproxen inhibits prostaglandin E<sub>2</sub> synthesis *in vitro* by human rheumatoid synovial microsomes. It also inhibits prostaglandin E<sub>2</sub> production by phytohaemagglutinin-stimulated peripheral blood mononuclear cells. At 10<sup>-4</sup> M (23mg.l<sup>-1</sup>) naproxen inhibits neutral protease activity derived from human polymorphonuclear leucocytes. Naproxen also inhibits *in vitro* the activity of cathepsin-β and other hydrolytic enzymes derived from lysosomes. Naproxen is a potent inhibitor of leucocyte migration and produces effects comparable to those of colchicine.

### 5.2 Pharmacokinetic properties

#### Absorption

Naproxen is completely absorbed from the gastro-intestinal tract. The degree of absorption is not significantly affected by either foods or most antacids.

#### Distribution

Peak plasma levels are reached in 2 to 4 hours. Plasma concentrations of Naproxen increase proportionally with dose up to about 500mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. Naproxen is present in the blood mainly as unchanged drug, at therapeutic concentrations naproxen is more than 99% bound to plasma proteins and has a plasma half-life 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.

#### Elimination

Approximately 95% of a dose is excreted in urine as naproxen and 6-O-desmethylnaproxen and their conjugates. Less than 3% of a dose has been recovered in the faeces. Naproxen crosses the placenta and is excreted in breast milk.



### Metabolism

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 elderly patients, 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 doses 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  
Sodium lauryl sulphate  
Quinoline yellow (E104)  
Sunset yellow (E110)  
Maize starch  
Crospovidone  
Magnesium stearate

### **6.2 Incompatibilities**

None known.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Store in a cool dry place.

Protect from light. Do not store above 25°C

**6.5 Nature and contents of container****PL 17907/0339**

1. Polypropylene tubes fitted with low-density polyethylene caps.
2. Tracer Packs: Child resistant containers consisting of polypropylene tubes fitted with high density polyethylene caps.

Pack sizes: 28, 56 and 250 tablets.

3. PVC/Aluminium blisters

Pack sizes: 28, 56, 84 and 112 tablets.

**PL 17907/0340**

1. Polypropylene tubes fitted with low-density polyethylene caps.
2. Tracer Packs: Child resistant containers consisting of polypropylene tubes fitted with high density polyethylene caps.

Pack sizes: 28, 56, 100 and 500 tablets.

3. PVC/Aluminium

Pack sizes : 28,56,84 and 112 tablets.

**6.6 Special precautions for disposal**

None stated.

**7. MARKETING AUTHORISATION HOLDER**

Bristol Laboratories Limited  
Unit 3, Canalside, Northbridge Road  
Berkhamsted  
Herts  
HP4 1EG  
UK

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

PL 17907/0339

PL 17907/0340

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

Date Of First Authorisation: 22 April 2002

Renewal Of the Authorisation: 25 November 2008

**10.DATE OF REVISION OF THE TEXT**

07/03/2025