SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Naproxen 250mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg Naproxen

3. PHARMACEUTICAL FORM

Tablet

Pale yellow flat tablet with a breakline on one face and plain on reverse

4. Clinical Particulars

4.1. Therapeutic Indications

Naproxen is indicated for the treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, and acute musculoskeletal disorders (such as sprains, strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis).

4.2. Posology and Method of Administration

Method of administration: Oral; the tablets should be taken preferably with or after food and swallowed with a drink of water.

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, osteoarthrosis and ankylosing spondylitis: The usual dose is 500mg to 1g per day taken in two doses at 12 hour intervals. Where 1g per day is needed, the suggested regime is 500mg twice daily.

In the following cases a loading dose of 750mg or 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 anti-rheumatic compound.
3. In osteoarthrosis where pain is the predominant symptom.

For the patient who requires 750mg per day, the size of the morning and evening doses can be adjusted on the basis of the predominant symptoms, i.e. night-time pain or morning stiffness.

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

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

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID (non-steroidal anti-inflammatory drug) is considered necessary, the lowest dose should be used and for the shortest possible duration. The patient should be monitored regularly for gastrointestinal bleeding during NSAID therapy.

Children: For the treatment of juvenile rheumatoid arthritis in children over five years of age, the usual dosage is 10mg per kg bodyweight per day taken in two doses at 12 hour intervals.

Renal/hepatic impairment:
A lower dose should be considered in patients with renal or hepatic impairment to avoid the possibility of excessive accumulation of naproxen metabolites. Naproxen is contra-indicated in patients with baseline creatinine clearance less than 30 ml/minute as accumulation of metabolites has been noted in patients with severe renal failure or those on dialysis (see section 4.3).

4.3. Contra-Indications

Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding.

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Hypersensitivity to naproxen or any of the tablet excipients or other naproxen sodium formulations.

Since the potential exists for cross-sensitivity reactions, naproxen should not be given to patients in whom aspirin, ibuprofen or other non-steroidal anti-inflammatory/analgesic drugs induce hypersensitivity reactions (eg. asthma, rhinitis, angioedema or urticaria).

Severe heart failure, hepatic failure and renal failure (see section 4.4).

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).

Respiratory disorders
Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

Elderly
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation, which may be fatal (see section 4.2).

The use of Naproxen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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 and the elderly. Renal function should be monitored in these patients (see also section 4.3).

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. Monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Naproxen is contraindicated in patients having a baseline creatinine clearance of less than 30 ml/minute (see section 4.3).

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

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 in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial

infraction 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 event (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal bleeding, ulceration and perforation
Gastrointestinal 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 gastrointestinal events.

The risk of gastrointestinal 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 the elderly. 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 gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment.

Care 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 gastrointestinal 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).

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).

Dermatological:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with 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 reaction 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.

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 fertility, withdrawal of Naproxen should be considered.

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

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

Hepatic effects:
As with other NSAIDs, 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 such as jaundice and hepatitis have been reported with naproxen. Fatalities have occurred. Cross-reactivity with other NSAIDs has been reported.]

Ocular effects:
In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilloedema have been reported in users of NSAIDs, although a causal relationship has not been established. Patients who develop visual disturbances during treatment with naproxen should undergo ophthalmological examination.

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. Interactions with other medicinal products and other forms of interaction

Due to the high plasma protein binding of naproxen, patients simultaneously receiving hydantoins, anticoagulants or a highly protein-bound sulphonamide should be observed for signs of overdosage of these drugs.

Colestyramine can delay the absorption of naproxen but does not affect its extent.

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risks of adverse effects (see section 4.4).

Anti-hypertensives: Naproxen and other NSAIDs may reduce the effect of antihypertensive agents.

Diuretics: There is an increased risk of nephrotoxicity when NSAIDs are used in conjunction with diuretics. The diuretic effect may also be reduced.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels when used in conjunction with cardiac glycosides.

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

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

Methotrexate: Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, since naproxen, among other non-steroidal anti-inflammatory drugs, decreases the elimination of methotrexate.

Ciclosporin: The concomitant use of ciclosporin may lead to an increased risk of nephrotoxicity.

Mifepristone: Naproxen should not be used for 8 to 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone

Corticosteroids: There is an increased risk of gastrointestinal ulceration or bleeding if corticosteroids are used concomitantly (see section 4.4).

Anti-coagulants: NSAIDs may enhance the effect of anti-coagulants such as warfarin (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

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

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: 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.

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

4.6. Pregnancy and Lactation

Pregnancy:
Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contra-indicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

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

4.7. Effects on Ability to Drive and Use Machine

Dizziness, drowsiness, fatigue, visual disturbances or headaches are possible undesirable effects after taking NSAIDs. If affected, patients 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 gastrointestinal bleeding,

sometimes fatal particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain or discomfort, melaena, haematemesis, ulcerative stomatitis, oesophagitis ulcerative, large intestinal ulcer, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently gastritis has been observed. Pancreatitis has been reported very rarely.

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) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea (c) assorted skin disorders including rashes of various types: pruritis, urticaria, , angio-oedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Metabolic and nutrition disorders: hyperkalaemia

Cardiovascular and cerebrovascular:
Oedema, palpitations, cardiac failure and congestive heart failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of 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).

Blood and lymphatic system disorders: Thrombocytopenia, neutropenia, granulocytopenia, agranulocytosis, eosinophilia, aplastic anaemia and haemolytic anaemia.

Nervous system and psychiatric disorders: Headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing autoimmune 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), inability to concentrate, cognitive dysfunction, dizziness and drowsiness.

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

Eye disorders: Visual disturbances, corneal opacity, papillitis and papilloedema.

Ear and labyrinth disorders: Tinnitus, vertigo, hearing impaired

Vascular disorders: Hypertension, vasculitis

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

Hepatobiliary disorders: Abnormal liver function tests, fatal hepatitis and jaundice

Skin and subcutaneous tissue disorders: Bullous reactions including Stevens Johnson syndrome and toxic epidermal necrolysis (very rare). (see also immune system disorders). Fixed drug eruption, lichen planus, alopecia, photosensitivity, (including cases of pseudoporphyria, where skin lesions resemble those seen in porphyria cutanea tarda).

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

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, malaise and fatigue

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 at: www.mhra.gov.uk/yellowcard.

4.9. Overdose

No evidence of toxicity or late sequelae have been reported 5 to 15 months after ingestion, for three to seven days, of doses of up to 3g per day. One patient ingested a single dose of 25g of naproxen and experienced mild nausea and indigestion. It is not known what dose of the drug would be life-threatening.

a) Symptoms
Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness,

tinnitus, fainting, occasionally convulsions. In cases of significant poisoning, acute renal failure and liver damage are possible.

b) Therapeutic measures
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 its protein binding. However, haemodialysis may still be appropriated in a patient with renal failure who has taken naproxen.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Naproxen has analgesic, anti-inflammatory and antipyretic properties. It is an inhibitor of prostaglandin synthetase. Naproxen is used in rheumatic disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis, in mild to moderate pain such as dysmenorrhoea, migraine, and some musculoskeletal disorders, and in acute gout.

5.2. Pharmacokinetic Properties

Naproxen is fully absorbed when administered orally. The rapidity, but not the extent, of absorption is influenced by the presence of food in the stomach. Peak concentrations in plasma occur within 2 to 4 hours and may be achieved more rapidly after administration of naproxen sodium. Absorption may be accelerated by the concurrent administration of sodium bicarbonate or reduced by magnesium oxide or aluminium hydroxide.

Naproxen and its metabolites are almost entirely excreted in the urine. About 30% of the drug undergoes 6-methylation and most glucuronides or other conjugates. Naproxen is almost completely (90 %) bound to plasma protein following normal therapeutic doses. Naproxen crosses the placenta and appears in the milk of lactating women at appropriately 1 % of the maternal plasma concentration.

5.3. Preclinical Safety Data

No data of relevance additional to that already included in other sections of the SPC.

6. Pharmaceutical Particulars

6.1. List of Excipients

Sodium laurilsulfate, lactose monohydrate, quinoline yellow (E104), sunset yellow (E110), maize starch, crospovidone, magnesium stearate.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

Blister Packs - 4 years
Polypropylene tubes and Tracer packs – 3 years

6.4. Special precautions for storage

Do not store above 25°C
Store in the original container to protect from light

6.5 Nature and Contents of Container

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: 56 and 250 tablets

3. Blister packs consisting of clear PVC and hard temper aluminium foil contained in a carton

   Pack sizes: 28

6.6 Instruction for Use/Handling

Not applicable

7 Marketing Authorisation Holder

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Metro Centre
Tolpits Lane
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United Kingdom
Trading as: Co-pharma

8 Marketing Authorisation Number

PL 13606/0150

9 Date of First Authorisation/Renewal of Authorisation

19th June 2006

10 Date of (Partial) Revision of the Text

19.05.2016