Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naproxen 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Naproxen 250 mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Pale peach round tablet embossed with 'S73' and a breakline on one side and 'STERWIN' on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of rheumatoid arthritis, osteoarthritis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, acute musculoskeletal disorders (such as sprains and strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis) and dysmenorrhoea.

4.2 Posology and method of adminstration

Adults:
For rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, the usual dose is 500mg to 1000mg per day taken in two doses at 12 hour intervals or alternatively as a single administration of two tablets, morning or evening.

In the following cases a loading dose of 750mg or 1000mg per day for the acute phase is recommended:
(a) In patients reporting severe night-time pain and/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.

For the patient who requires 750mg or 1000mg per day, the size of the morning and evening doses can be adjusted on the basis of the predominant symptoms, i.e. night pain or morning stiffness.

For the treatment of acute musculoskeletal disorders and dysmenorrhoea, the recommended dose is 500mg initially followed by 250mg at 6-8 hour intervals as needed, with a maximum daily dose after the first day of 1250mg.

In acute gout, the recommended dosage is 750mg initially then 250mg every eight hours until the attack has passed.

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

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

The safety of the drug in children under the age of 5 years has not been demonstrated and its use cannot therefore be

recommended in this group.

Elderly
Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. The implications 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. For the effect of reduced elimination in the elderly refer to the section - 'Use in patients with impaired renal function'.

Naproxen tablets are for oral administration only.

4.3 Contraindications

Use in patients with peptic ulcer disease, active peptic ulceration or intestinal inflammatory disease.

Hypersensitivity to naproxen or naproxen sodium formulations. Since the potential exists for cross-sensitivity reactions, naproxen must not be given to patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis or urticaria, as severe anaphylactic-like reactions have been reported in such patients.

4.4 Special warnings and precautions for use

Episodes of gastro-intestinal bleeding have been reported in patients with naproxen therapy. Naproxen should be given under close supervision to patients with a history of gastro-intestinal disease. Serious gastro-intestinal adverse reactions, including haemorrhage and perforation, can occur at any time in patients on therapy with non-steroidal anti-inflammatory drugs. The risk of their occurrence appears to increase linearly with the duration of use and is probably associated with the use of higher doses of these drugs. Studies to date have not identified any subset of patients not at risk of developing peptic ulcer or bleeding.

However, elderly and debilitated patients tolerate gastro-intestinal ulceration or bleeding less well than others; most serious gastro-intestinal events associated with non-steroidal anti-inflammatory drugs occurred in this patient population.

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.

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.

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.

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 in these patients. Naproxen is not recommended in patients having baseline creatinine clearance less than 20ml/minute. 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.

Haematological
Patients who have coagulation disorders, or who are receiving drug therapy that interferes with haemostasis, should be carefully observed if they are taking naproxen. Patients on full anticoagulant therapy (e.g. heparin or warfarin) may be at increased risk of bleeding if given naproxen concurrently. Therefore, the benefits should be weighed against the risks.

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.

Combination with other NSAIDs
The combination of naproxen-containing products and other NSAIDs is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

4.5 Interaction with other medicinal products and other forms of interaction

Naproxen is highly bound to plasma protein so that caution should be exercised in use in patients concomitantly receiving other drugs strongly protein bound such as anticoagulants, sulphonamides, hydantoins. Such patients should be observed for signs of overdose of these drugs. No interactions have been observed in clinical studies with naproxen and anti-coagulants or sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

The natriuretic effect of frusemide has been reported to be inhibited by some drugs of this class. 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 anti-hypertensive effect of propranolol and other beta-blockers and may increase the risk of renal impairment associated with the use of ACE-inhibitors.

Probenecid given concurrently increases naproxen plasma levels and extends its plasma half-life considerably. Caution is advised where methotrexate is administered 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 cyclosporin 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 cortico-steroids because of the increased risk of bleeding.

Patients taking quinolones may have an increased risk of developing convulsions**.**
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 Pregnancy and lactation

Naproxen should not be used in pregnancy unless considered essential by the physician. There is no evidence of teratogenic effects in animal studies. The drug appears in milk during lactation. Therefore the use of Naproxen should be avoided in patients who are breast feeding.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Gastrointestinal:
The more frequent reactions are nausea, vomiting, abdominal discomfort and epigastric distress. More serious reactions which may occur occasionally are gastrointestinal bleeding and peptic ulceration (sometimes with haemorrhage and perforation), non-peptic gastro-intestinal ulceration and colitis.

Dermatological/hypersensitivity:
Skin rashes, urticaria, angio-oedema. Eosinophilic pneumonitis, alopecia, erythema multiforme, Stevens Johnson syndrome, epidermal necrolysis and photosensitive dermatitis may occur rarely. Anaphylactic reactions to naproxen and naproxen sodium formulations have been reported in patients with, or without, a history of previous hypersensitivity reactions to NSAIDS.

Renal:
Including but not limited to glomerular nephritis, interstitial nephritis, nephrotic syndrome, haematuria, renal papillary necrosis, renal failure.

CNS:
Convulsions, headache, insomnia, inability to concentrate and cognitive dysfunction have been reported.

Haematological:
Thrombocytopenia, granulocytopenia, including agranulocytosis, aplastic anaemia and haemolytic anaemia may occur rarely.

Other:
Tinnitis, hearing impairment, vertigo, mild peripheral oedema. Jaundice, fatal hepatitis, visual disturbances, vasculitis, aseptic meningitis, hyperkalemia and ulcerative stomatitis have been reported rarely.

4.9 Overdose

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea or vomiting. A few patients have experienced seizures, but it not clear whether these were naproxen related or not. No evidence of toxicity or late sequelae have been reported 5-15 months after ingestion, for three to seven days, of doses up to 3g/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. Should a patient ingest a large amount of naproxen accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. Animal studies indicated that the prompt administration of activated charcoal in adequate amounts would tend to reduce markedly the absorption of the drug.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its 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; ATC code: M01A E02

Naproxen has been shown to have striking anti-inflammatory analgesic and antipyretic properties. It inhibits prostaglandin synthetase, as do other non-steroidal anti-inflammatory agents.

5.2 Pharmacokinetic properties

Naproxen is readily absorbed from the gastro-intestinal tract. It is extensively bound to plasma proteins and has a half-life of about 14 hours. About half of a dose is excreted in the urine in 24 hours and about 94% in 5 days, largely as the glucuronide.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soluble starch
Maize starch
Povidone
Purified talc
Magnesium stearate
Croscarmellose sodium
Dalfcol orange KLS1/26/1 containing:
Quinoline yellow (E104)
Carmoisine (E122)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Naproxen 250 mg tablets are packed in PVC blisters comprising of 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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