Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naprosyn EC 500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg of Naproxen

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Gastro resistant, film-coated tablet.

Capsule shaped, white, film-coated tablets marked with “NPR EC 500” in black on one side, plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Naprosyn EC is indicated 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 administration

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

Adults:
Naprosyn EC tablets should be swallowed whole and not broken or crushed.

***Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis*:**
The usual dose is 500 mg to 1 g daily taken in two doses at 12 hour intervals. Where 1g per day is needed one 500mg tablet twice daily or two 500mg tablets in a single administration (morning or evening) is recommended.

Acute Gout:
The recommended dose is 750 mg initially, then 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 hourly intervals as needed, with a maximum daily dose after the first day of 1250 mg.

Use in the 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 Naprosyn EC Tablets dosing is unknown. As with other drugs used in the elderly it is prudent to use the lowest effective dose as elderly patients are more prone to adverse events. For the effect of reduced-elimination in the elderly refer *to section 4.4*. Use in patients with impaired renal function

Children:
Naprosyn EC is effective in the treatment of juvenile rheumatoid arthritis in children over 5 years of age at a dose of 10 mg/kg/day taken in 2 doses at 12 hour intervals. Naprosyn EC is not recommended for use in any other indication in children under 16 years of age. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen.

4.3 Contraindications

Active peptic ulceration or intestinal inflammation. Hypersensitivity to naproxen and naproxen sodium formulations. Since the potential exists for cross-sensitivity reactions, Naprosyn EC should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce asthma, rhinitis or urticaria.

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Severe heart failure.

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 patients are particularly susceptible to the adverse events of NSAIDs. Prolonged use of the NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

The use of Naprosyn 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 Naprosyn should be considered.

The use of Naprosyn with concomitant NSAIDs including cyclooxygenase-2 selectiveinhibitors should be avoided.

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 antipyretic and anti-inflammatory activities of Naprosyn EC 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 Naprosyn EC therapy, but no definite trend indicating toxicity was seen in any test.

Naprosyn EC 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 Naprosyn EC. 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 Naprosyn EC.

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 the use of xocibs 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 suggests 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 aerterial disease, and/ore cerebrovascular disease should not 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).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Gastro-intestinal effects
Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime 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 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 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 Naprosyn, 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 their condition may be exacerbated *(see section 4.8 – undesirable effects).*

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. Naprosyn EC is not recommended in patients having a baseline creatinine clearance of less than 20 ml/minute.

Certain patients, specifically those whose renal blood flow is compromised, because of extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestion heart failure, and pre-existing renal disease, should have renal function assessed before and during Naprosyn EC 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 naprosyn EC 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 risk of bleeding if given naproxen containing products concurrently.

Skin
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported rarely in association with the use of NSAIDs *(see 4.8).* Patients appear to be at highest risk of 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. Naprosyn should be discontinued at the first appearance of skin rash, mucoal lesions, or any other sign of hypersensitivity.

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 steroids 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 papilitis, 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding *(see section 4.4)*

Anti coagulants: NSAIDs may enhance the effects 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)*

Concomitant administration of an antacid or cholestyramine 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.

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 overdose of these drugs. **It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.**

No interactions have been observed in clinical studies with naproxen and anticoagulants or sulphonylureas, but caution is nevertheless advised since interaction has been seen with other NSAIDs 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.

Naprosyn and other NSAIDs can reduce the antihypertensive effect of popranolol and other beta-blockers and may increase the risk of renal impairment associated with the use of ACE-inhibitors.

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

Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, since Naprosyn , in common with 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 if 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-administration with cortico-steroids because of the increased risk of bleeding.

The concomitant administration of two or more NSAIDs should be avoided.

Patients taking quinolones may have an increased risk of developing convulsions.

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

4.6 Pregnancy and lactation

Teratology studies in rats and rabbits at dose levels equivalent on a human multiple basis to those which have produced foetal abnormality with certain other NSAIDs e.g. aspirin, have not produced evidence of foetal damage with Naprosyn. As with other drugs of this type Naprosyn delays parturition in animals (the relevance of this finding to human patients is unknown) and also affects the human foetal cardiovascular system (closure of the ductus arteriosus).

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

Naprosyn has been found in the milk of lactating mothers. The use of Naprosyn EC should therefore be avoided in patients who are breast-feeding.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

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

Clinical trial and epidemiological data suggests 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).*

Gastro-intestinal: 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.

Dermatological: Skin rashes, urticaria, angio-oedema. Alopecia, erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis, and photosensitivity reactions, including photosensitive dermatitis and the rare cases in which the skin resembles porphyria cutanea tarda ('pseudoporphyria') or epidermolysis bullosa, may occur rarely.

Renal: Including but not limited to glomerular nephritis, interstitial nephritis, nephrotic syndrome, haematuria, renal papillary necrosis and 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: Tinnitus, hearing impairment, vertigo, mild peripheral oedema. Anaphylactic reaction, to naproxen and naproxen sodium formulations have been reported in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs. Jaundice, fatal hepatitis, visual disturbances, eosinophilic pneumonitis, vasculitis, hyperkalaemia, aseptic meningitis, and ulcerative stomatitis have been reported rarely.

4.9 Overdose

Significant overdose of the drug may be characterised by drowsiness, heartburn, indigestion, nausea or vomiting. A few patients have experienced seizures, but it is not clear whether these were naproxen related or not. It is not known what dose of the drug would be life-threatening.

Should a patient ingest a large amount of Naprosyn accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. Animal studies indicate 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 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

Naproxen has been shown to have anti-inflammatory, analgesic and antipyreti properties when tested in classical animal test systems. It exhibits its anti-inflammatory effects even in adrenalestomised animals, indicating that its action is not mediated through the pituitary-adrenal axis. It inhibits prostaglandin synthetase, as do other non-steroidal anti-inflammatory agents. As with other agents, however, the exact mechanism of its anti-inflammatory actions is not known.

5.2 Pharmacokinetic properties

Naproxen is completely absorbed from the gastro-intestinal tract, and peak plasma levels are reached in 2-4 hours. Naproxen is present in the blood mainly as unchanged drugs, extensively bound to plasma proteins. The plasma half-life is 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 absorption is not significantly affected by either foods or most antacids. Excretion is almost entirely via the urine, mainly as conjugated naproxen, with some unchanged drug.

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, the unbound plasma

concentration of naproxen is increased although total plasma concentration is unchanged.

When naproxen is administered in the enteric-coated form, the peak plasma levels are delayed compared to those seen with standard tablets. However, the mean areas under the plasma concentration-time curves, and hence bioavability, are equivalent. The tablets, therefore, perform, as one would anticipate for a drug, which does not distinegrate until it reaches the small intestine, where dissolution is rapid and complete.

5.3 Preclinical safety data

No evidence of carcinogenicity was found in rats. Reproduction studies performed in rats, rabbits and mice at doses up to 6 times the human dose revealed no evidence of impairment fertility or harm to the foetus. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K-90
Croscarmellose sodium (type A)
Magnesium stearate (E5720)
Purified water
Opacode S-1-8106
Methacrylic acid copolymer (type C)
Purified talc(E553(b))
Sodium hydroxide
Triethyl citrate
Simethicone emulsion

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C. Store in original package.

6.5 Nature and contents of container

Blister packs of 56 tablets contained in an outer cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Limited
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/031/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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