Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naprosyn EC 500mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg Naproxen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets.
Capsule-shaped, white film-coated tablet marked 'NPR EC 500' in black ink on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Naprosyn EC is indicated in adults and adolescents (16 years and above) for the treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, acute gout, acute musculo-skeletal disorders (such as sprains and strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis) and dysmenorrhoea.

4.2 Posology and method of administration

Posology
For oral administration
Naprosyn EC tablets should be swallowed whole and not broken or crushed.

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

Acute musculo-skeletal 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.

Older people:
Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in older people. The implication of this finding for Naprosyn EC dosing is unknown. As with other drugs used in older people it is prudent to use the lowest effective dose as older patients are more prone to adverse events. For the effect of reduced elimination in older people see section 4.4: *Use in patients with impaired renal function*.

Children:
Naprosyn EC is not recommended for use in children under 16 years of age.

Renal/hepatic impairment:
A lower dose should be considered in patients with renal or hepatic impairment. Naprosyn is not recommended in patients with a 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.

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

4.3 Contraindications

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

Hypersensitivity to naproxen, naproxen sodium or any of the excipients. 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, nasal polyps or urticaria. These reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.

Severe renal, hepatic or heart failure.

Naprosyn EC is contraindicated during the last trimester of pregnancy (see Section 4.6).

4.4 Special warnings and precautions for use

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

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.

Gastrointestinal ulceration, bleeding 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 older people. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients and also for patients requiring concomitant low dose aspirin or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

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). Patients with a history of GI toxicity, particularly in older people, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. When GI bleeding or ulceration occurs in patients receiving Naprosyn, the treatment should be withdrawn. Episodes of gastro-intestinal bleeding have been reported in patients with naproxen therapy. Naprosyn EC should be given under close supervision to patients with a history of gastro-intestinal disease.

Studies to date have not identified any subset of patients not at risk of developing peptic ulcer and bleeding. However, older people and debilitated patients tolerate gastro-intestinal ulceration or bleeding less well than others. Most of the serious gastro-intestinal events associated with non-steroidal anti-inflammatory drugs occurred in this patient population.

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-uptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

Precautions related to older people

Older people have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal. In older people the clearance is reduced. Use of the lower end of the dosage range is recommended (see section 4.2).

Prolonged use of NSAIDs in older people is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

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).

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens- Johnson syndrome(SJS) and Lyell syndrome/toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported very rarely in association with the use of NSAIDs (see section 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, mucosal lesions or any other sign of hypersensitivity.
If the patient has developed SJS, or TEN or DRESS with the use of Naprosyn, treatment with Naprosyn must not be restarted and should be permanently discontinued.

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.

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

Renal Effects

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

Renal failure linked to reduced prostaglandin production

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

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. Naprosyn EC is not recommended in patients having a baseline creatinine clearance of less than 30 ml/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 Naprosyn EC therapy. Some older people in whom impaired renal function may be expected, as well as patients using diuretics, may also fall within this category. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

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

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.

Hepatic effects

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.

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

Antipyretic effects:

The antipyretic and anti-inflammatory activities of Naprosyn EC may reduce fever and inflammation, thereby diminishing their utility as diagnostic signs.

Steroids:

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

Ocular effects:

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

Sodium/fluid retention in cardiovascular conditions and peripheraloedema

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 Naprosyn EC.

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.

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 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 arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with

risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Precautions related to 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 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

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

Due to the high plasma protein binding of naproxen, patients simultaneously receiving hydantoins, anticoagulants, other NSAIDs, aspirin or a highly protein-bound sulfonamide should be observed for signs of overdosage of these drugs. Patients simultaneously receiving Naprosyn EC and a hydantoin, sulfonamide or sulfonylurea should be observed for adjustment of dose if required.

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 sulfonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class. NSAIDs may enhance the effects of anti-coagulants such as warfarin.

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.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

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

Naproxen and other non-steroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers and may increase the risk of renal impairment associated with the use of ACE-inhibitors.

Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or older people with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking naproxen concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in older people. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

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

Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, since naproxen, 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 ciclosporin is co-administered because of the increased risk of nephrotoxicity.

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

As with all NSAIDs, caution should be taken when co-administering with cortico-steroids because of the increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

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 naproxen may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxyindoleacetic acid.

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 an increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Fertility, 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. 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, Naprosyn EC should not be given unless clearly necessary. If Naprosyn EC 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 Naprosyn EC for several days from gestational week 20 onward. Naprosyn EC 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 Naprosyn EC, is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Labour and delivery

Naproxen containing products are not recommended in labour and delivery because, through their prostaglandin synthesis inhibitory effect, naproxen may adversely affect foetal circulation and inhibit uterine contractions thus increasing the risk of uterine haemorrhage.

Breast feeding

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

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. See Section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Some patients may experience drowsiness, dizziness, vertigo, insomnia, or depression with the use of Naprosyn. If patients experience these or similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

4.8 Undesirable effects

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

Gastro-intestinal: The most commonly observed adverse events are gastrointestinal in nature. Inflammation, bleeding (sometimes fatal, particularly in older people), ulceration, perforation and obstruction of the upper and lower gastrointestinal tract (see section 4.4). Heartburn, nausea, oesophagitis, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, stomatitis, exacerbation of ulcerative colitis and Crohn's disease (see section 4.4), pancreatitis and gastritis have been reported following administration.

Blood and lymphatic system disorders: thrombocytopenia, granulocytopenia including agranulocytosis, aplastic anaemia, eosinophilia, leucopoenia and haemolytic anaemia

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

Metabolic and nutrition disorders: hyperkalaemia

Psychiatricdisorders: depression, dream abnormalities, insomnia
Nervous system disorders: convulsions, dizziness, drowsiness, headache, lightheadedness, retrobulbar optic neuritis, inability to concentrate and cognitive dysfunction have been reported. Aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

Eye disorders: visual disturbances, corneal opacity, papillitis and papilloedema

Ear and labyrinth disorders: tinnitus, hearing disturbances including impairment and vertigo

Cardiac disorders: oedema, palpitations, congestive heart failure, hypertension and cardiac failure have been reported in association with NSAID treatment.

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).

Vascular disorders: hypertension, vasculitis

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

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

Skin and subcutaneous tissue disorders: skin rashes including itching (pruritus), urticaria, ecchymoses, purpura, sweating, angio-oedema. Alopecia, erythema multiforme, bullous reactions including Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis, very rarely toxic epidermal necrolysis, photosensitivity reactions (including cases in which the skin resembles porphyria cutanea tarda, "pseudoporphyria") or epidermolysis bullosa may occur rarely.
Frequency: Not known – fixed drug eruption
Frequency: Not known - Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

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: 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 anda dministration site conditions: thirst, pyrexia, mild peripheral oedema, fatigue and malaise.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Symptoms and signs

Significant overdosage of the drug may be characterised by drowsiness, dizziness, heartburn, epigastric pain, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnoea, disorientation or vomiting. A few patients have experienced seizures, but it is not known whether these were naproxen-related or not. It is not known what dose of the drug would be life-threatening.

Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may occur after the ingestion of NSAIDs but are rare.

Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Treatment

Patients should be managed by symptomatic and supportive care following NSAID overdose. There are no specific antidotes. Prevention of further absorption (e.g. activated charcoal) may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinisation of urine, haemodialysis or haemoperfusion may not be useful due to high protein binding.

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.

However, haemodialysis may still be appropiate in a patient with renal failure who has taken naproxen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids. ATC code: M01AE02

Naproxen has been shown to have anti-inflammatory, analgesic and antipyretic properties when tested in classical animal test systems. It exhibits its anti-inflammatory effect even in adrenalectomised 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 action is not known.

5.2 Pharmacokinetic properties

Naproxen is completely absorbed from the gastro-intestinal tract, and peak plasma levels are reached in 2 to 4 hours. Naproxen is present in the blood mainly as unchanged drug, 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 older people, 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 bioavailability, are equivalent. The tablets, therefore, perform as one would anticipate for a drug which does not disintegrate until it reaches the small intestine, where dissolution is rapid and complete.

5.3 Preclinical safety data

Carcinogenicity

Naproxen was administered with food to Sprague-Dawley rats for 24 months at doses of 8, 16 and 24 mg/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 30 mg/kg/day to males and 20 mg/kg/day to females.

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

Perinatal/Postnatal Reproduction
Oral administration of naproxen to pregnant rats of doses of 2, 10 and 20 mg/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

Tablet Core
Povidone K-90
Croscarmellose sodium (Type A)
Magnesium stearate

Tablet Coating
Methacrylic acid – ethyl acrylate copolymer (1:1)
Purified talc (E553b)
Sodium hydroxide (E524)
Triethyl citrate (E1505)

Printing Ink
Iron oxide, black (E172)
Shellac (E904)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Naprosyn EC 500 Tablets in PVC blisters of 56 tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Copenhagen Towers,
Ørestads Boulevard 108, 5.tv
DK-2300 København S,
Denmark

8 MARKETING AUTHORISATION NUMBER

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