SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Naproxen 500 mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg naproxen.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets.

White colour, circular shaped biconvex enteric coated tablets debossed with "500" on one side and plain on the other side.

Dimension: 16.50 mm x 7.70 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Naproxen Gastro-resistant Tablets are indicated in adults for the treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, 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

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
Therapy should be started at the lowest recommended dose, especially in older people.

Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis
The usual dose is 500mg to 1g daily taken in 2 doses at 12-hour intervals. Where 1g per day is needed either one 500mg tablet twice daily or two 500mg tablets in a single administration (morning or evening) is recommended. 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 anti-rheumatic compound.
c) In osteoarthrosis where pain is the predominant symptom.

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

Elderly
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 Naproxen dosing is unknown. As with other drugs used in older people it is prudent to use the lowest effective dose and for the shortest possible duration as older people 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 older people see section 4.4.

Paediatric Population
Naproxen Gastro-resistant Tablets should not be used in children aged under 16 years.

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.

Method of Administration
For oral administration.
To be taken preferably with or after food.
Naproxen Gastro-resistant Tablets should be swallowed whole and not broken or crushed.

4.3 Contraindications

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

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Since the potential exists for cross-sensitivity reactions, Naproxen Gastro-resistant Tablets 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.

Naproxen is contraindicated 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). Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

Older people and/or debilitated patients are particularly susceptible to the adverse events 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.

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

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.

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

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.

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 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 section 4.5).

Patients with a history of GI toxicity, particularly when older, 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 corticosteroid, 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.

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 (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, such as in 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 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.

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 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.

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 angio-oedema, 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 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.

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 (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).

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 the use of NSAIDs (see 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. Naproxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Combination with other NSAIDs
The combination of naproxen-containing products and other NSAIDs, including cyclooxygenase-2 selective inhibitors, is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Severe cutaneous adverse reactions (SCARs)
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 Naproxen Gastro-resistant Tablets treatment. If signs and symptoms suggestive of these reactions appear, Naproxen Gastro-resistant Tablets should be withdrawn immediately. If the patient has developed SJS, or TEN or DRESS with the use of Naproxen Gastro-resistant Tablets, treatment with Naproxen Gastro-resistant Tablets must not be restarted and should be permanently discontinued.

Information on sodium content
This medicine contains less than 1 mmol sodium (23 mg) per Tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of 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.

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 sulfonamide should be observed for signs of overdosage of these drugs. Patients simultaneously receiving Naproxen Gastro-resistant Tablets 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 sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

Caution is advised when Naproxen Gastro-resistant Tablets is co-administered with diuretics as there can be a decreased diuretic effect. 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 anti-hypertensive effect of anti-hypertensives. Concomitant use of NSAIDs with 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 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 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.

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking 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 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 haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

It is suggested that Naproxen Gastro-resistant Tablets 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 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 and gastroschisis 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 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 pregnancy. See point 4.3 and 5.3).

Breast-feeding

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

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Gastrointestinal disorders: The most commonly observed adverse events are gastrointestinal in nature. Heartburn, nausea, vomiting, constipation, diarrhoea, flatulence, dyspepsia, abdominal discomfort and epigastric distress. More serious reactions which may occur are gastro-intestinal bleeding, which is sometimes fatal, particularly in older people (see section 4.4), inflammation, ulceration, perforation, and obstruction of the upper and lower gastrointestinal tract, melaena, haematemesis, stomatitis, exacerbation of ulcerative colitis and Crohn's disease (see section 4.4), oesophagitis, gastritis and pancreatitis.

Blood and lymphatic system disorders: Neutropenia, thrombocytopenia, granulocytopenia including agranulocytosis, eosinophilia, leucopenia, aplastic anaemia 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.

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

Nervous system disorders*:* Convulsions, dizziness, headache, lightheadedness, drowsiness, paraesthesia, 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, cardiac failure and congestive heart failure have been reported.

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) (see section 4.4).
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 fixed drug eruption, itching (pruritus), urticaria, ecchymoses, purpura, sweating. Alopecia, erythema multiforme, Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis, very rarely toxic epidermal necrolysis, photosensitivity reactions (including cases in which skin resembles porphyria cutanea tarda “pseudoporphyria”) or epidermolysis bullosa-like reactions which may occur rarely.

Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4) (Frequency: Not known)

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, 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 Yellow Card Scheme at 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, drowsiness, dizziness, tinnitus, fainting. 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 hypothrombinaemia may have been due to selective inhibition of the synthesis of vitamin-K dependent clotting factors.

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.

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 antirheumatic products, nonsteroids,
ATC code: M01AE02

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

Naproxen 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.

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), *Saccharomyces 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 indomethacin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Croscarmellose sodium
Povidone

Magnesium stearate
Methacrylic acid ethylacrylate copolymer (1:1) dispersion 30%
Sodium hydroxide
Triethyl citrate
Talc

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

White opaque PVC/Aluminium foil blisters in a carton, 4 blisters containing 14 tablets each.
The pack size is 56 tablets

6.6 Special precautions for disposal

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

Medreich PLC
Warwick House
Plane Tree Crescent

Feltham TW13 7HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 21880/0252

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/12/2019 / 02/05/2025

10 DATE OF REVISION OF THE TEXT

02/05/2025