SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Naproxen 375mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: 375mg Naproxen.

Excipients with known effect:
Each tablet contains 111.00mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.
White, oval, biconvex, shallow concave, gastro-resistant tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Naproxen is indicated for the treatment of:

- Rheumatoid arthritis.
- Osteoarthritis (degenerative arthritis).
- Ankylosing spondylitis.
- Juvenile rheumatoid arthritis
- Acute gout.
- Acute musculoskeletal disorders
- 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
Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis
500mg to 1g taken in 2 doses at 12 hour intervals, or alternatively, as a single administration.
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 antirheumatic compound.
c) In osteoarthritis where pain is the predominant symptom.

Acute gout
Initially 750mg at once then 250mg every 8 hours until the attack has passed.

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 the elderly. The implication 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 and for the shortest duration possible as elderly patients are at increased risk of the serious consequences of adverse reactions. The patient should be monitored regularly for GI bleeding during NSAID therapy. For the effect of reduced elimination in elderly patients refer to section 4.4. Dosage should be reduced in the elderly where there is an impairment of renal function. (see section 4).

Paediatric population (over 5 years)
For juvenile rheumatoid arthritis
10mg/kg/day taken in 2 doses at 12 hour intervals.

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 or intolerance occurs.

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

4.3 Contraindications

Patients with active gastrointestinal bleeding or peptic ulceration, known hypersensitivity to naproxen, naproxen sodium or any other ingredient in the formulation. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.
Severe heart failure, hepatic failure and renal failure (see section 4.4).
During the last trimester of pregnancy (see section 4.6)
History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

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 and/ or debilitated patients
Elderly patients and/or debilitated patients are particularly susceptible to the adverse effects 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.

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.

Gastrointestinal bleeding, ulceration and perforation:
GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious 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)
- in the elderly
- when used with alcohol
- in smoking.

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 the 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 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, haematuria, proteinuria, renal papillary necrosis and occasionally nephrotic syndrome associated with naproxen.

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking esomeprazole and naproxen containing products and may occur at any point during naproxen therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Naproxen should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Renal failure linked to reduced prostaglandin production – cardiovascular, renal and hepatic impairment
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, angiotensin converting enzyme inhibitors, angiotensin-II receptor antagonists and the elderly. 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 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 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. The product should be used with caution in patients with a history of, or in those with impaired liver function.
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.

Respiratory disorders
Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

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 anticoagulation therapy (e.g. heparin or dicoumarol derivatives) may be at increased risk of bleeding if given naproxen-containing products concurrently (see section 4.5).

Impaired female fertility
The use of Naproxen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Naproxen should be considered.

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 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).

Severe cutaneous adverse reactions (SCARs)
Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), 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 the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reactions occurring in the majority of cases within the first month of treatment. Naproxen GR tablets

should be withdrawn immediately. If the patient has developed SJS, or TEN or DRESS with the use of Naproxen GR tablets, treatment with Naproxen GR tablets must not be restarted and should be permanently discontinued.

Combination with other NSAIDs
The combination of naproxen-containing products and other NSAIDs, including cyclooxygenase-2 selective inhibitors, should be avoided, because of the cumulative risks of inducing serious NSAID-related adverse events (see section 4.5).

Medication Overuse Headache (MOH)
After long term treatment with analgesics, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH - medication-overuse headache) should be suspected in patients who have frequent or daily headaches despite (or because of) regular use of analgesics. Patients with medication overuse headache should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

Important information about the ingredients of Naproxen 375mg Gastro-resistant Tablets

This medicinal product contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per gastro-resistant tablet, that is to say essentially ‘sodium-free’.

Potassium
This medicine contains potassium, less than 1 mmol (39 mg) per gastro-resistant tablet, i.e. essentially ‘potassium-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. Naproxen should be taken at least one hour before or four to six hours after colestyramine.
- 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 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 sulfonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.
- Caution is advised when Naproxen is co-administered with diuretics as there can be a decreased diuretic effect. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. 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. It is recommended that these levels are monitored whenever initiating, adjusting or discontinuing naproxen.
- Naproxen and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of anti-hypertensives. Concomitant use of NSAIDs with beta-blockers, 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 given 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 corticosteroids 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 haem arthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.
- 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. Sporadic abnormalities in laboratory tests (e.g. liver function test) have occurred in patients on naproxen therapy, but no definite trend was seen in any test indicating toxicity.
- Bisphosphonates: concomitant use of bisphosphonates and NSAIDs may increase the risk of gastric mucosal damage.

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 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 naproxen is contraindicated during the last trimester of pregnancy.

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.
See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or 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.

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

	Frequency not known (cannot be estimated from the

System Organ Class	available data)
Blood and lymphatic system disorders	haemolytic anaemia, aplastic anaemia, granulo-cyctopenia, thrombo-cytopenia, agranulocytosis, neutropenia
Immune system disorders	allergic and hyper-sensitivity reactions, anaphylaxis
Endocrine disorders	
Metabolism and nutrition disorders	hyperkalaemia
Psychiatric disorders	depression, cognitive dysfunction, insomnia, loss of concentration, abnormal dreams, hallucinations
Nervous system disorders	confusion, dizziness, drowsiness, headache, convulsions, aseptic meningitis*, vertigo, paraesthesia, malaise
Eye disorders	visual disturbances, optic neuritis, papilloedema
Ear and labyrinth disorders	tinnitus, hearing impairment
Cardiac disorders	palpitations
Vascular disorders	vasculitis, arterial thrombotic events e.g. myocardial infarction or stroke(see 4.4)
Respiratory, thoracic and mediastinal disorders	aggravated asthma, eosinophilic pneumontitis, bronchospasm, dyspnoea, pulmonary oedema
Gastro-intestinal disorders	pancreatitis, thirst
Hepatobiliary	hepatitis (sometimes fatal), jaundice, abnormal liver function,
Skin and subcutaneous tissue disorders	rash, pruritis, purpura, urticaria, photosensitivity, alopecia, pseudo-porphyria, erythema multiforme, Stevens Johnsons syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4), epidermolysis bullosa, angio-oedema, epidermal necrosis, exfoliative and bullous dermatoses, lichen planus, fixed drug eruption
Musculo-skeletal and connective tissue disorders	myalgia, muscle weakness
Renal and urinary disorders	glomerular nephritis, haematuria, tubulointerstitial nephritis (with possible progression to renal failure), nephritic syndrome, renal papillary necrosis, renal failure, nephropathy, increase in serum creatinine
Reproductive system and breast disorders	impaired female fertility (see 4.4)
General disorders and administration site complications	fatigue, mild peripheral oedema, pyrexia

*especially in patients with existing auto-immune disorders, such as system lupus erythematosus, mixed connective tissue disease, with symptoms such as stiff neck headache, nausea, vomiting, fever and disorientation.

Clinical trial and epidemiological data suggests that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke (see section 4.4).

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 website: 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, occasionally convulsions/ seizures. 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.

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.

Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids. Propionic acid derivatives.

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

Naproxen reduces the synthesis of prostaglandins primarily by inhibiting the enzyme cyclo-oxygenase. Naproxen has been shown to have anti-inflammatory activity in a number of experimental models. Naproxen inhibits prostaglandin E_2 synthesis *in vitro* by human rheumatoid synovial microsomes. It also inhibits prostaglandin E_2

production by phytohaemagglutin-stimulated peripheral blood mononuclear cells. At 10^{-4} M ($23mg.1^{-1}$) naproxen inhibits neutral protease activity derived from human polymorphonuclear leucocytes. Naproxen also inhibits *in vitro* the activity of cathepsin-β and other hydrolytic enzymes derived from lysosomes. Naproxen is a potent in inhibitor of leucocyte migration and produces effects comparable to those of colchicine.

5.2 Pharmacokinetic properties

Absorption
Naproxen is completely absorbed from the gastro-intestinal tract. The degree of absorption is not significantly affected by either foods or most antacids.

Distribution
Peak plasma levels are reached in 2 to 4 hours. Plasma concentrations of naproxen increase proportionally with dose up to about 500mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. Naproxen is present in the blood mainly as unchanged drug, at therapeutic concentrations naproxen is more than 99% bound to plasma proteins and has a plasma half-life 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.

Elimination
Approximately 95% of a dose is excreted in urine as naproxen and 6-O-desmethylnaproxen and their conjugates. Less than 3% of a dose has been recovered in the faeces. Naproxen crosses the placenta and is excreted in breast milk.

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 patients, the unbound plasma concentration of naproxen is increased although total plasma concentration is unchanged.

5.3 Preclinical safety data

Genotoxicity
Mutagenicity was not seen in *Salmonella typhimurium* (5 cell lines*), Sachharomyces cerevisisae* (1 cell line) and mouse lymphoma tests.

Reproductive and developmental toxicity
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.

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

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 indometacin.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methacrylic acid-ethylacrylate copolymer (1:1)
Lactose
Magnesium stearate
Maize starch
Crospovidone
Propylene glycol
Sodium hydroxide
Triethyl citrate
Titanium dioxide (E171)
Potassium sorbate (E202)
Sodium citrate (E331)
Xanthan gum (E415)
Hydroxypropyl cellulose (E463)
Purified talc (E553)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf-life
36 months from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.

Shelf-life after first opening
Not applicable.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container

PVC/PVdC/Aluminium blister. Pack sizes of 28, 30, 56, 60, 84, 90, 100, 112 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/0438

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/03/2009

10 DATE OF REVISION OF THE TEXT

20/08/2024