SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Naproxen 250mg Gastro-resistant Tablets

Period Pain Reliever 250mg Gastro-resistant Tablets

Boots Period Pain Reliever 250mg Gastro-Resistant Tablets

Almus Period Pain Reliever 250mg Gastro-Resistant Tablets

Ultravana™ Period Pain Relief 250 mg Gastro-resistant tablets

Numark Period Pain Reliever 250mg Gastro-Resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: 250mg Naproxen

Excipient(s) with known effect
Each gastro-resistant tablet contains 74.00mg of lactose.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablets.
White, round, biconvex enteric-coated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the treatment of primary dysmenorrhoea in women aged 15 to 50 years.

4.2 Posology and method of administration

Posology

Adolescents (post puberty) and adult females between the ages of 15 and 50:

On the first day 2 tablets (500 mg) should be taken initially and then one tablet (250 mg) after 6 to 8 hours if needed.

On the second and third day, if needed, one tablet (250mg) should be taken every 6 to 8 hours. Not more than 3 tablets to be taken per day. The maximum duration of continuous treatment in any one cycle (period) is 3 days.

Method of administration

For oral use, to be taken preferably with or after food swallowed whole with water. Not to be broken or crushed.

4.3 Contraindications

Naproxen is contraindicated for patients with known hypersensitivity to naproxen, naproxen sodium formulations or any of the excipients listed in section 6.1.

Naproxen is contraindicated in patients with a history of, or active, peptic ulceration and active gastrointestinal bleeding (two or more distinct episodes of proven ulceration or bleeding).

Naproxen is contraindicated in patients with a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Naproxen should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, nasal polyps, angioedema or urticaria, as the potential exists for cross-sensitivity reactions. These reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.

Naproxen should not be given to patients with severe heart failure, hepatic or renal failure (see section 4.4).

During the last trimester of pregnancy (see section 4.6 – Pregnancy and lactation).

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 warnings on GI and cardiovascular risks below). Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

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

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 nonsteroidal 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.

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

Elderly
The elderly and/or debilitated patients have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Prolonged use of NSAIDs in these patients is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Respiratory disorders
Caution is required if administered to patients suffering from, or with a history of, bronchial asthma or allergic disease, since administration of naproxen or other NSAIDs may elicit bronchospasm.

Cardiovascular, Hepatic Impairment and 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 and the elderly. Renal function should be monitored in these patients (see also section 4.3)

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, hypertension 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 (1000 mg 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).

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.

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.

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.

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.

Gastrointestinal effects

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see 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 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.

Serious gastro-intestinal adverse reactions may occur at any time in patients on therapy with non-steroidal anti-inflammatory drugs. The duration of therapy does not seem to change the risk of occurrence. Studies to date have not identified any subset of patients not at risk of developing peptic ulcer and bleeding. However, elderly 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.

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).

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 angioedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

Anaphylactoid reactions, like anaphylaxis may have a fatal outcome.

Steroids
Patients taking steroids should not take naproxen except under the supervision of their doctor. 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.

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. If signs and symptoms suggestive of these reactions appear, naproxen should be withdrawn immediately. If the patient has developed SJS, TEN, or DRESS with the use of naproxen, treatment with naproxen must not be restarted and should be permanently discontinued.

Impaired female fertility
The use of naproxen, as with any drug known to inhibit cyclooxygenase/ prostaglandin synthesis, 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 fertility, withdrawal of naproxen should be considered.

This product should not be taken, except on the advice of a doctor, by women who first experience period pain more than a year after starting menstruation.

Excipients
Lactose
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 film-coated tablet, that is to say essentially 'sodium-free'.

The label will include:
Read the enclosed leaflet before taking this product.

Do not take if you:
- have or have ever had a stomach ulcer, perforation or bleeding
- are allergic to naproxen or any other ingredients of the product, aspirin, ibuprofen or other related painkillers
- are taking other NSAID painkillers, or aspirin

Speak to a pharmacist or your doctor before taking this product if you:
- have asthma, liver, heart, kidney or bowel problems
- there is a chance you may be pregnant or are breast-feeding

If symptoms persist or worsen, consult your doctor.

4.5 Interaction with other medicinal products and other forms of interaction

Naproxen should not be taken with other medication except on the advice of a doctor, pharmacist or nurse.
Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

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 Special Warnings and Special Precautions for use).
Concomitant administration of antacid, colestyramine or food may delay the absorption of naproxen but does not affect its extent.

Anti-hypertensives: reduced anti-hypertensive effect.

Naproxen and other non-steroidal anti-inflammatory drugs may increase the risk of renal impairment associated with the use of ACE-inhibitors.

Diuretics: can decrease 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.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: Decreased renal elimination of lithium leading to increases in plasma lithium concentrations.

Methotrexate: Possible enhancement of methotrexate toxicity due to decreased elimination of methotrexate.

Ciclosporin: Increased risk of nephrotoxicity.

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

Corticosteroids: Increased risk of GI ulceration or bleeding. See section 4.4 Special Warnings and Special Precautions for use.

Anti-coagulants and sulphonylureas: NSAIDs may enhance the effects of anticoagulants, such as warfarin and heparin. See section 4.4 Special Warnings and Special Precautions for use.
Naproxen is highly bound to plasma proteins and if anti-coagulants, hydantoins, other NSAIDs, aspirin or highly protein-bound sulphonamides are given simultaneously, overdosage of these drugs may result.
Patients simultaneously receiving Naproxen and a hydantoin, sulphonamide or sulphonylurea 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.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Co-administration of probenecid inhibits the renal tubule secretion of naproxen, so raising its plasma concentration and prolonging its half-life.

It is suggested that naproxen is withdrawn 48 hours before adrenal function tests as it may interfere with some tests for 17-ketogenic steroids. Naproxen may interfere with some assays of urinary 5-hydroxy-indoleacetic acid.

Tacrolimus: Possible increase risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: 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.

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.

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 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 its prostaglandin synthesis inhibitory effect, naproxen may adversely affect foetal circulation and inhibit contractions, with an increased bleeding tendency in both mother and child (See section 4.3 – Contraindications). The onset of labour may be delayed and the duration increased

Breast-feeding
Naproxen/NSAIDs can appear in the breast milk of lactating women. The use of naproxen/NSAIDs should be avoided in patients who are breast feeding.

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, 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.

Blood and lymphatic system disorders: Neutropenia, thrombocytopenia, agranulocytosis, 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, angioedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Metabolism and nutrition disorders: Hyperkalaemia.

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

Nervous system disorders: Convulsions, dizziness, retrobulbar, optic neuritis, headaches, light-headedness, drowsiness, paraesthesia, inability to concentrate and cognitive dysfunction have been reported. Reports of aseptic meningitis (especially in patients with existing autoimmune 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, hypertension, 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.

Gastrointestinal disorders: The most commonly observed adverse events are gastrointestinal in nature. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, heartburn and epigastric distress. More serious reactions which may occur are gastro-intestinal ulceration, which is sometimes fatal, particularly in the elderly (see section 4.4), peptic ulceration, perforation, non-peptic gastro-intestinal ulceration, melaena, haematemesis, stomatitis, ulcerative stomatitis exacerbation of ulcerative colitis and Crohn's disease (see section 4.4) and oesophagitis have been reported following administration. Less frequently, gastritis has been observed. Pancreatitis has been reported very rarely.

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

Skin and subcutaneous tissue disorders: Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare). Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4). Skin rashes including fixed drug eruption, itching (pruritus), urticaria, ecchymoses, purpura, sweating. Alopecia, erythema multiforme, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis, photosensitivity reactions (including cases in which skin resembles porphyria cutanea tarda "pseudoporphyria") or epidermolysis bullosa-like reactions which may occur rarely.

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: Nephrotoxicity in various forms, including glomerular nephritis, tubulointerstitial nephritis (with possible progression to renal failure), 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 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. 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 functions 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, propionic acid derivatives, ATC code: M01AE02

Naproxen is a propionic acid derivative. Naproxen has been shown to have anti-inflammatory, analgesic and anti-pyretic 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

Animal studies suggest that prompt administration of activated charcoal would reduce the absorption of naproxen.
Following oral administration, naproxen is fully absorbed from the gastro-intestinal tract. Depending on food in-take, peak plasma concentrations are reached 2 to 4 hours after ingestion. Naproxen is present in the blood mainly as unchanged drug, extensively bound to plasma proteins. More than 99% is 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 in urine accounts for approximately 95% of the dose. Naproxen crosses the placental barrier 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 the elderly, the unbound plasma concentration of naproxen is increased although total plasma concentration is unchanged.
When naproxen is administered in the enteric-coated form, the peak plasma levels are delayed when compared with the standard tablets. However, the mean areas under the plasma concentration time curves, and hence bioavailability, are equivalent. The tablets do not disintegrate until they reach the small intestine, where dissolution is rapid and complete. This delay in absorption makes Naproxen EC of value for patients in whom gastric dissolution is undesirable.

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), *Sachharomyces 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 indometacin.

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 3,6,8,9 tablets.
(Not all pack sizes will be marketed).

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
Middlesex
HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0619

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