PRONAXEN ORAL SUSPENSION 25 MG/ML

1. THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Propionic acid derivatives, ATC code: M01AE02.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre contains 25 mg of naproxen.

Excipients with known effect:
Sorbitol (E420) 400 mg/ml
Methyl parahydroxybenzoate (E218) 1 mg/ml
Propyl parahydroxybenzoate (E216) 0.2 mg/ml
Sodium 0.8 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension
White to off-white homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

- Rheumatoid arthritis, spondyloarthropathies (including ankylosing spondylitis)
- Osteoarthrosis
- Acute gout
- Acute musculoskeletal disorders with pain
- Dysmenorrhoea

Children

- Juvenile rheumatoid arthritis

4.2 Posology and method of administration

Posology

Adverse drug reactions may be reduced by using the lowest effective dose for the shortest duration possible to manage the symptoms (see section 4.4).

Adults

Usually, 250–500 mg (10–20 ml) twice a day based on the individual need.

If the predominant symptom in rheumatoid arthritis is morning stiffness, a single dose of 500–750 mg

(20–30 ml) in the evenings may be adequate.

In the treatment of acute gout, the recommended dose is 750 mg at once then 250 mg every 8 hours until the attack has passed.

In the treatment of acute musculoskeletal disorders and dysmenorrhoea the recommended dose is 500 mg initially followed by 250 mg at 6–8 hour intervals as needed, with a maximum daily dose after the first day of 1 250 mg.

Paediatric population (over 5 years):

For juvenile rheumatoid arthritis: in children aged over 5 years, the recommended daily dose is 10 mg/kg divided into two doses. Dosing as per the table below. Patients weighing over 50 kg may be administered the adult dosage.

weight	daily dose
20–24 kg	4 ml x 2
25–29 kg	5 ml x 2
30–34 kg	6 ml x 2
35–40 kg	7 ml x 2
40–44 kg	8 ml x 2
45–49 kg	9 ml x 2

Elderly patients

In those over 70, the concentration of free naproxen in plasma is higher than in younger persons, and the elimination of naproxen is slower. Elderly patients may be more susceptible than others to the adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs). For this reason, the lower single doses described above, i.e. 250 mg (10 ml) twice daily, are recommended for elderly patients.

Renal impairment

The lowest effective dose should be used in patients with mild renal insufficiency, and renal function should be monitored. If possible, the use of Pronaxen oral suspension should be avoided in patients with moderate (creatinine clearance 50 to 10 ml/min or serum creatinine 160 to 565 micromol/l) or severe renal insufficiency (creatinine clearance <10 ml/min or serum creatinine >565 micromol/l) (see section 4.4).

Hepatic impairment

Pronaxen oral suspension should be used with caution in patients with hepatic insufficiency (see section 4.4). If possible, the use of Pronaxen oral suspension should be avoided in patients with severe hepatic insufficiency or a cirrhotic hepatic condition.

Method of administration

For instructions on reconstitution of the medicinal product before administration of the medicine, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Asthma and allergy if the patient develops hypersensitivity symptoms in connection with the use of acetylsalicylic acid (ASA) or other NSAIDs
- Third trimester of pregnancy
- Severe cardiac insufficiency
- A history of gastrointestinal bleeding or perforation, related to the use of NSAIDs

- Acute gastric/duodenal ulcer or associated bleeding or history of recurrent episodes (at least two separate, confirmed episodes)
- Other conditions predisposing to gastrointestinal bleeding.

4.4 Special warnings and precautions for use

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

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms (see section 4.2, and the gastrointestinal and cardiovascular risks below). Patients treated with NSAIDs longterm should undergo regular medical supervision to monitor for adverse events.

Elderly patients:

The elderly has 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.

Effects on the heart, blood circulation and cerebral circulation:

Appropriate monitoring and advice are required for patients with hypertension and/or mild or moderate cardiac 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 other anti-inflammatory analgesics, particularly at a high dose and in long term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Although the current data suggests that the risk may be lower in connection with naproxen use (1,000 mg/day), it cannot be excluded entirely.

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 disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Serum potassium concentrations should be monitored especially in patients using ACE inhibitors, angiotensin receptor blockers, or potassium-sparing diuretics. Anti-inflammatory analgesics may reduce the efficacy of some antihypertensive drugs (see section 4.5).

Renal effects:

Patients with renal or hepatic failure, hypertension, or cardiac failure, and elderly patients should be monitored for renal function and haemodynamics during naproxen treatment. Naproxen should be avoided, if possible, in patients with moderate renal failure. Naproxen is contraindicated in patients with severe renal impairment (baseline creatinine clearance less than 30 ml/min) or severe hepatic impairment (see section 4.3).

Dehydration during the use of an anti-inflammatory analgesic (i.e. NSAID) increases the risk of acute renal failure, so the patient’s possible dehydration should be corrected before naproxen treatment is initiated. The naproxen treatment should be started with caution in patients with a history of considerable dehydration. Like other anti-inflammatory analgesics, long-term treatment with naproxen has caused renal papillary necrosis and other pathological renal alterations.

Renal toxicity has also been detected in patients in whom renal prostaglandins maintain the renal perfusion. In these patients, the use of anti-inflammatory analgesics may cause a dose-dependent reduction in the formation of prostaglandins, leading to reduced renal perfusion. This may progress into renal failure. The risk is highest in elderly patients, those using diuretics, ACE inhibitors or angiotensin-II receptor antagonists, and in patients with renal or hepatic impairment or cardiac failure. Discontinuation of treatment usually corrects the patient's status to the pretreatment level.

Gastrointestinal haemorrhages, ulcers and perforations:

Gastrointestinal 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. Naproxen reduces thrombocyte activation and aggregation but this effect is transient and lasts less than 48 hours after a single dose. This should be taken into account when treating postoperative patients with an increased risk of haemorrhage, patients on anticoagulant medication (see section 4.5), patients with haemophilia, or other patients with diseases impairing the functioning of the coagulation system or with thrombocytopenia. The risk of gastrointestinal haemorrhage increases even by this mechanism.

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 possible 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 acetylsalicylic acid, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI adverse reactions, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Pronaxen, the treatment should be withdrawn.
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

Cutaneous adverse effects:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnsons syndrome, and toxic epidermal necrolysis, have been reported (very rarely) 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 reaction occurring in the majority of cases within the first month of treatment. Pronaxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Anaphylactic (anaphylactoid) reactions:

Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to aspirin, other non-steroidal anti-inflammatory drugs or naproxen-containing products. They may also occur in individuals with a history of angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

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).

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.

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.

Anti-inflammatory analgesics may aggravate bronchospasm in patients with allergic disease (see section 4.3).

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.

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 Pronaxen dosing is unknown but it is prudent to use the lowest effective dose. Naproxen is contraindicated in patients with severe hepatic impairment (see section 4.3).

Pseudoporphyria (blistering cutaneous photosensitivity) has been reported in up to 10 % of paediatric rheumatic patients in connection with naproxen treatment exceeding four weeks. Patients should be monitored for this reversible phenomenon and the use of the preparation should be discontinued if symptoms occur.

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

Pronaxen oral suspension contains methyl parahydroxybenzoate (1.0 mg/ml) and propyl parahydroxybenzoate (0.2 mg/ml) as antimicrobial preservatives which may cause allergic reactions (possibly delayed).

Pronaxen oral suspension contains 400 mg/ml sorbitol. Daily doses as per instructions yield 1.6 g–20 g sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Sorbitol may have a mild laxative effect.

This medicinal product contains 0,8 mg/ml sodium, 24 mg sodium per 30 ml dose, which is equivalent to 1,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid slows down elimination of naproxen by competing for glucuronidation and biliary and tubular secretion. If these active substances are used concomitantly in the treatment of e.g. gout, a reduction in naproxen dosage and careful monitoring of the patient for possible adverse reactions are recommended.

Concomitant administration of antacid or cholestyramine can delay the absorption of naproxen but does not affect its extent.

Concomitant administration of food can delay the absorption of naproxen but does not affect its extent.

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

Due to the high plasma protein binding of naproxen, patients simultaneously receiving hydantoins, anticoagulants, other NSAIDs, aspirin or a highly proteinbound sulphonamide should be observed for signs of overdosage of these drugs. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide 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. 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.

Concomitant use of bisphosphonates and NSAIDs may increase the risk of gastric mucosal damage.

Combination use with diuretics, ACE inhibitors and angiotensin II antagonists:

NSAIDs may reduce the antihypertensive effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the coadministration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. 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. Diuretics may increase renal toxicity of anti-inflammatory analgesics.

Furthermore, the effect of other antihypertensive drugs (betablockers) may reduce. This should be taken into account at the onset of antihypertensive medication.

Naproxen should not be used concomitantly with other anti-inflammatory analgesics as this may increase adverse effects.

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.

Acetylsalicylic acid displaces naproxen from protein binding sites in plasma, which accelerates elimination of naproxen.

Corticosteroids: Increased risk of a gastrointestinal ulcer or haemorrhage (see section 4.4). If these drugs are used concomitantly, the patient’s status should be monitored carefully.

Anticoagulants: Anti-inflammatory analgesics may enhance the effect of anticoagulants, such as warfarin (see section 4.4).

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

Significant interactions between naproxen and oral hypoglycaemic drugs or antiepileptics are unlikely. Naproxen has been shown to displace valproic acid from protein binding sites in plasma, but the clinical significance of this phenomenon is likely to be minor.

Serum digoxin concentrations should be monitored in patients with renal failure and on digitalis treatment, and the digoxin dose should be adjusted, if needed, if naproxen is added to or removed from the medication.

Naproxen slows down elimination of lithium. Serum lithium concentrations should be monitored and the lithium dosage adjusted, if needed, if naproxen is added to or removed from the patient's medication.

Naproxen may slow down elimination of methotrexate, ciclosporin and aminoglycoside antibiotics (directly dependent on glomerular filtration) and increase their toxicity. Interaction is, however, unlikely in connection with a low-dose (at doses used in the treatment of rheumatic diseases) methotrexate treatment.

Naproxen may change plasma protein binding of tacrolimus and expose to renal toxicity. Caution is advised in combination use, and if possible, the drug doses should be adjusted based on serum concentration determinations.

Naproxen may change the metabolism of zidovudine. The clinical significance of this phenomenon is not known.

Naproxen may interfere with urinary tests for 17-ketogenic steroids and 5-hydroxy-indoleacetic acid (diagnostics in adrenal gland diseases). This is avoided by discontinuing naproxen 72 hours before sampling.

4.6 Fertility, pregnancy and lactation

The inhibition of prostaglandin synthesis may have adverse effects on pregnancy and/or foetal development. Epidemiological studies indicate that the use of a prostaglandin synthesis inhibitor in early pregnancy increases the risk of miscarriage, foetal heart malformations and gastroschisis. The absolute risk of cardiovascular malformations increased from less than 1 % to about 1.5 %. The risk is believed to increase with higher doses of the medicine and with prolonged use. In animal studies, the use of a prostaglandin synthesis inhibitor has been shown to result in increased egg loss (both before and after implantation) and increased foetal mortality. On the basis of animal studies, the incidence of various (e.g. cardiovascular) malformations have also been reported to increase when a prostaglandin synthesis inhibitor has been administered during organogenesis.

Use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment 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 naproxen should not be used during the first and second trimester of pregnancy unless it is absolutely necessary. If a woman uses naproxen while trying to become pregnant or while in the first/second trimester of pregnancy, the lowest possible dose should be used for the shortest possible time. 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.

The use of a prostaglandin synthesis inhibitor during the third trimester of pregnancy predisposes the foetus to:

- cardiac and respiratory toxicity (premature arterial duct constriction/closure and increased pulmonary artery pressure)

- renal dysfunction, which may result in renal failure and a decreased quantity of amniotic fluid. (see above)

The use of a prostaglandin synthesis inhibitor in the late stages of pregnancy exposes the mother and the neonate to:
- inhibition of platelet aggregation and possibly a prolongation in bleeding time, potentially even at low doses
- weakening of uterine contractions, which may result in delayed or prolonged labour.

For this reason, naproxen is contraindicated during the last trimester of pregnancy.

Naproxen is excreted into human breast milk in very small quantities. If necessary, it may be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Naproxen has usually no influence on the ability to drive or use machines. Occasional adverse effects include tiredness, impaired ability to concentrate, dizziness, or visual disturbances (see section 4.8). If these symptoms occur, driving a car or using machines should be avoided.

4.8 Undesirable effects

Adverse effects caused by naproxen mostly occur in the gastrointestinal tract and as central nervous system adverse effects, and they are usually dose-dependent.

The frequency categories for adverse effects are defined as follows:
Very common (≥1/10),
Common (≥1/100 to <1/10),
Uncommon (≥1/1,000 to <1/100),
Rare (≥1/10,000 to <1/1,000),
Very rare (<1/10,000)
Not known (cannot be estimated from the available data).

	Very common	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders					eosinophilia, thrombo-cytopaenia, leucopenia, pancytopaenia, haemolytic anaemia, aplastic anaemia, agranulocytosis, neutropenia
Immune system disorders				hypersensitivity reactions, anaphylaxis, angioedema	
Metabolism and nutrition disorders			hyperkalaemia		
Psychiatric disorders			mood changes, depression, impaired ability to concentrate,		hallucinations, confusion

			cognitive disorder, insomnia, sleep disorders		
Nervous system disorders		headache, light-headedness, dizziness			aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), exacerbation of Parkinson's disease, convulsions, paraesthesia, retrobulbar, optic neuritis
Eye disorders		visual disturbances			corneal opacity, papillitis and papilloedema
Ear and labyrinth disorders		tinnitus, hearing disorders		impaired hearing	
Cardiac disorders*)		exacerbation of cardiac failure (oedema, dyspnoea)	palpitations		
Vascular disorders*)					vasculitis
Respiratory, thoracic and mediastinal disorders				exacerbation of asthma	eosinophilic pneumonitis, dyspnoea, bronchospasm
Gastrointestinal disorders**)	upper abdominal pain, heartburn, nausea, constipation	stomatitis, diarrhoea, vomiting, dyspepsia	gastrointestinal ulcers, haemorrhages and/or perforations, haematemesis, melaena, obstruction		sialadenitis, pancreatitis
Hepatobiliary disorders			elevated liver enzyme levels, jaundice	toxic hepatitis	
Skin and subcutaneous tissue disorders***)		pruritus, skin rashes, urticaria, increased		hair loss, photosensitivity, pseudoporphyria	exacerbation of *lichen planus*, exacerbation of *erythema*

		sweating, purpura, ecchymosis			*nodosum*, exacerbation of *lupus erythematosus disseminatus* (SLE), toxic epidermal necrolysis, *erythema multiforme*, Stevens–Johnson syndrome, fixed drug eruption, pustular reaction, epidermolysis bullosa-like reactions
Musculoskeletal and connective tissue disorders				myalgia, muscle weakness	
Renal and urinary disorders					haematuria, renal failure, glomerulo-nephritis, interstitial nephritis, nephrotic syndrome, papillary necrosis, raised serum creatinine
Reproductive system and breast disorders			menstrual disorders		female infertility
General disorders and administration site conditions		tiredness			drowsiness, thirst, pyrexia, fatigue, malaise

*) Cardiac and vascular disorders:
Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of some anti-inflammatory analgesics, particularly at a high dose and in long term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke, see section 4.4).

**) Gastrointestinal disorders:
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) have been reported following administration. Less frequently, gastritis has been observed.

***) Skin and subcutaneous tissue disorders:
Bullous skin reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis have been reported very rarely.

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.

4.9 Overdose

Symptoms
Symptoms of overdosage 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. In adults, overdoses from 5 to 25 g have been described without any specific adverse effects, yet in some individuals overdoses as low as 6–12 g have caused a serious intoxication (metabolic acidosis, renal failure, convulsions, apnoea, central nervous system suppression).

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. Activated charcoal should be administered to the patient within one hour to inhibit absorption and to interrupt the enterohepatic circulation. Alternatively in adults gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

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. Haemodialysis can accelerate elimination of the main metabolite of naproxen, 6-O-demethylnaproxen.

Administration of a H2 blocker or proton-pump inhibitor should be considered to prevent gastrointestinal complications. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Naproxen is a racemic anti-inflammatory analgesic with a non-steroidal structure, belonging to the group of propionic acid derivatives. The pharmacological activity is considered to lie with the S enantiomer, which is the sole enantiomer in the clinically used naproxen, and it is based on inhibition of cyclooxygenase enzymes and prostaglandin synthesis. Naproxen reduces fever through inhibition of central prostaglandin synthesis and alleviates inflammation and pain by inhibiting peripheral prostaglandin synthesis, which in turn reduces release of mediators which intensify pain and inflammation. The effects of naproxen on the protective mechanisms of gastric mucosa and on renal

circulation and platelet function are also explained by the inhibition of prostaglandin synthesis.

5.2 Pharmacokinetic properties

Following oral administration, naproxen is absorbed completely (95–100 %). Concomitant food intake delays absorption but does not impair bioavailability. Following a single dose of 250 mg (25 mg/ml, 10 ml) to healthy adults, the peak plasma concentration is achieved in 1 to 1.5 hours, and the peak concentration is about 50 microg/ml. The therapeutic plasma concentration is considered to be 30–90 microg/ml. Naproxen is strongly bound to plasma proteins (>99 %), mainly to albumin but also to globulins, and the volume of distribution is approx. 0,15 l/kg. The total naproxen concentration in synovial fluid is 65–70 % from that in plasma, whereas the concentrations of unbound naproxen are the same. The pharmacokinetics of naproxen are linear with single doses of up to 500 mg. At higher doses, plasma protein binding is saturated, the plasma concentrations of free naproxen increase and elimination is accelerated. The elimination half-life in plasma is 12 to 15 hours, and in synovial fluid, up to 30 hours. Naproxen is metabolised in the liver (CYP450 isoenzymes 1A2, 2C8 and 2C9) into pharmacologically inactive 6-O-demethylnaproxen. Naproxen and 6-O-demethylnaproxen are excreted mainly in the urine as sulphate and glucuronide conjugates. Enterohepatic circulation apparently exists but its degree is not known. Only 1–2 % of the total dose is excreted in the faeces. Pharmacokinetics of naproxen in children do not differ from those in adults, whereas in elderly patients, the plasma concentrations of unbound naproxen are higher and elimination is slower. Naproxen does not accumulate significantly in renal insufficiency. Naproxen is not dialysable. If creatinine clearance is less than 10 ml/min, 6-O-demethylnaproxen is accumulated but it can be eliminated in haemodialysis. In hepatic failure, elimination of naproxen slows down, and if plasma albumin concentrations decrease, plasma concentrations of unbound naproxen increase.

5.3 Preclinical safety data

In laboratory animals, acute naproxen toxicity has manifested at rather high dose levels: LD_{50} in mice >1,000 mg/kg orally, in rats >472 mg/kg orally, in hamsters >1,400 mg/kg orally, in guinea pigs >665 mg/kg orally and in dogs >1,000 mg/kg orally. Causes of death have included gastrointestinal ulcers and haemorrhages and occasionally stimulation or suppression of the central nervous system accompanied by tremor and convulsions. Subchronic and chronic toxicity have manifested, in addition to gastrointestinal irritation, as renal alterations. At clinically relevant dose levels, naproxen has not been shown to be a mutagenic, carcinogenic, or teratogenic compound in animal tests. Naproxen has not been found to have any effect on the fertility of laboratory animals. In rats, inhibition of labour has been seen in about 10% of animals at daily doses of 10–20 mg/kg. Gastrointestinal ulcers as well as cardiac and pulmonary alterations related to the premature closure of ductus arteriosus have been observed in the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Citric acid, anhydrous
Sodium citrate
Glycerol 85 %
Xanthan gum
Microcrystalline cellulose
Sodium carboxymethyl cellulose
Polysorbate 80
Sucralose (E955)
Purified water
Chocolate flavour

Chocolate flavour:
Ethyl vanillin
Vanillin
Isoamyl phenylacetate
Heliotropin
2,3,5-trimethyl pyrazine
Maltol
Cinnamic aldehyde
Propylene glycol (E1520)
Triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle: 36 Months.
After first opening: use within 6 Months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

HDPE bottle, child resistant PP cap.
Pack sizes: 100 ml, 200 ml

6.6 Special precautions for disposal and other handling

Shake before use.

Product registrant:
Orion Pharma (SG) Pte. Ltd.

Manufactured by:
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