Naproxen Effervescent Tablets BP 500 mg

Summary of Product Characteristics Updated 07-Jan-2025 | Aurobindo Pharma - Milpharm Ltd.

1. Name of the medicinal product

Naproxen Effervescent Tablets BP 500mg

2. Qualitative and quantitative composition

Each tablet contains 500mg Naproxen BP.

Excipient with known effect: Lactose.

For full list of excipients, see section 6.1.

3. Pharmaceutical form

Effervescent Tablets.

Naproxen Effervescent Tablets BP 500 mg are yellow coloured, capsule shaped uncoated Effervescent Tablets with score line between 'NPY' and '500' embossed on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications

***Adults*:**

Naproxen is used in the treatment of rheumatoid arthritis, osteoarthrosis (degenerative arthritis), ankylosing spondylitis, acute musculoskeletal disorders, dysmenorrhoea and acute gout.

***Children*:**

Juvenile rheumatoid arthritis.

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 anti-rheumatic compound.

c) In osteoarthrosis where pain is the predominant symptom.

Acute gout

In acute gout, an initial dose of 750 mg followed by 250 mg every 8 hours until the attack has passed.

Acute musculoskeletal disorders and dysmenorrhoea

500 mg may be given initially, followed by 250 mg every 6 to 8 hour intervals as needed, with a maximum daily dose after the first day of 1250mg.

Older people

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in older people. The implication of this finding for Naproxen dosing is unknown. The elderly are at increased risk of the serious consequences of adverse reactions. If NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy. For the effect of reduced elimination in the elderly refer to Section 4.4. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Paediatric population (over 5 years)

A dose of 10 mg per kg body weight daily, in two divided doses at 12-hour intervals has been used in children over 5 years of age with juvenile rheumatoid arthritis. Naproxen is not recommended for use in any other indication in children under 16 years of age.

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.

To be taken preferably with or after food.

4.3 Contraindications

1. Hypersensitivity to Naproxen sodium or to any of the excipients of naproxen Effervescent Tablets.

2. Since the potential exists for cross-sensitivity reactions, Naproxen is contraindicated in patients who have previously shown hypersensitivity reactions (e.g. nasal polyps, asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin or other non-steroidal anti-inflammatory/analgesic drugs. These reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.

3. Severe hepatic, renal and cardiac failure (See section 4.4 – special warnings and precautions for use).

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

5. Active or previous acute peptic ulcer or active gastrointestinal bleeding (two or more distinct episodes of proven ulceration or bleeding).

6. History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

7. Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (See section 4.5 Interactions).

4.4 Special warnings and precautions for use

In all patients:

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:

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 – Posology and administration). 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.

Respiratory disorders:

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

Renal failure linked to reduced prostaglandin production:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and the elderly. Renal function should also be monitored in these patients (See also section 4.3 – Contraindications)

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 significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Naproxen is contraindicated in patients having baseline creatinine clearance less than 30ml/minute. Certain patients, specifically those where 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 could also fall within this category. A reduction in the daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in the patients.

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

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.

Use in patients with impaired liver function:

Chronic alcoholic liver disease and probably 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.

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.

Use in patients with cardiovascular impairment:

Caution should be exercised in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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), 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).

Naproxen has been found to be well tolerated by patients exhibiting dyspepsia with other similar agents. None the less, episodes of gastro-intestinal bleeding have been reported in patients with naproxen therapy.

Patients with a history of GI toxicity, 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 gastrotoxicity, or bleeding, such as corticosteroids, or anticoagulants such as warfarin, selective serotonin reuptake inhibitors or anti-platelet agents such as aspirin (See section 4.5 – Interactions).

When GI bleeding or ulceration occurs in patients receiving naproxen, the treatment should be withdrawn

Naproxen should be given under close supervision to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (See section 4.8 – Undesirable effects).

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 – Undesirable effects).

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 (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, and smoking).

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

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

Anaphylactic (anaphylactoid) reactions

Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to aspirin, other non-steroidal anti-inflammatory

drugs or naproxen-containing products. They may also occur in individuals with a history of angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

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

Steroids

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

Ocular effects

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

Dermatological

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and Lyell syndrome/toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reactions occurring in the majority of cases within the first month of treatment. Naproxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association naproxen with treatment. If signs and symptoms suggestive of these reactions appear, naproxen should be withdrawn immediately. If the patient has developed SJS, or TEN or DRESS with the use of naproxen treatment with naproxen 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, is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Contains lactose

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interaction

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).

Anti-hypertensives:

Reduced anti-hypertensive effect.

Naproxen and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of antihypertensives. Concomitant use of NSAIDs with ACE inhibitors or angiotensin-II receptor antagonists may increase the risk of renal impairment, especially in patients with pre-existing poor renal function (See Section 4.4).

Diuretics:

Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class.

Caution is advised when Naproxen is co-administered with diuretics as there can be a decreased diuretic effect.

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

Probenecid:

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

Cardiac glycosides:

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels, when co-administered with cardiac glycosides.

Lithium:

Decreased elimination of lithium.

Inhibition of renal lithium clearance leading to increase in plasma lithium concentration has been reported.

Methotrexate:

Decreased elimination of methotrexate.

Caution is advised when methotrexate is administered concurrently because of possible enhancement of its toxicity since naproxen has been reported to reduce the tubular secretion of methotrexate in the animal model.

Ciclosporin:

As with all NSAIDs caution is advised when ciclosporin is co-administered because of the 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:

As with all NSAIDs, caution should be taken when co-administering with cortico-steroids because of the increased risk of GI bleeding or gastrointestinal ulceration (See section 4.4 – Special warnings and precautions for use).

Anti-coagulants:

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 – Special warnings and precautions for use). Due to the plasma protein binding of naproxen, patients simultaneously receiving anticoagulants should be observed for signs of overdosage of these drugs.

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.

Tacrolimus:

Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Sulphonamides and hydantoins:

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

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 (for diabetes), like glimepiride or Glipizide, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

Anti-platelet agents and Selective serotonins reuptake inhibitors

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.

Zidovudine and Ibuprofen

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

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.

Antacid or Colestyramine:

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

Laboratory tests

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.

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 (with 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.

Breast feeding:

Naproxen has been found in the milk of lactating women The use of naproxen should be avoided in patients who are breastfeeding.

Fertility:

The use of Naproxen, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of naproxen should be considered.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Metabolic and nutrition disorders: hyperkalaemia.

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

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

Eye Disorders: Visual disturbances, corneal opacity, papillitis and papilloedema.

Ear and Labyrinth disorders: Tinnitus, hearing disturbances including impairment and vertigo.

Cardiac Disorders: Oedema, palpations, 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.

Renal and urinary disorders: Nephropathy and nephrotoxicity in various forms, including but not limited to glomerular nephritis, interstitial nephritis, nephrotic syndrome, haematuria, raised serum creatinine, renal papillary necrosis and renal failure.

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

Blood and lymphatic system disorders: Granulocytopenia, thrombocytopenia, neutropenia, agranulocytosis, eosinophilia, leucopenia, aplastic anaemia and haemolytic anaemia.

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

If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

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

Musculoskeletal and connective tissue disorders: Myalgia and muscle weakness.

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 afters authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard **or search for MHRA Yellow Card in the Google Play or Apple App Store**

4.9 Overdose

a) Symptoms

Symptoms include headache, nausea, vomiting, indigestion, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, heartburn, 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.

b) Management

Patients should be treated symptomatically as required. Should a patient ingest a large amount of naproxen, the stomach may be emptied and usual supportive measures employed (it is not known what dose of drug would be life threatening).

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding. However, haemodialysis may still be appropriate in a patient with renal failure who has taken naproxen.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids.

ATC code: M01AE02

Naproxen is a non-steroidal anti-inflammatory analgesic compound with antipyretic properties as has been demonstrated in classical animal test systems. Naproxen exhibits its anti-inflammatory effect even in adrenalectomised animals, indicating that its action is not mediated through the pituitary-adrenal axis.

Naproxen inhibits prostaglandin synthetase (as do other NSAIDs). As with other NSAIDs, however, the exact mechanism of its anti-inflammatory action is not known.

5.2 Pharmacokinetic properties

Naproxen is completely absorbed from the gastro-intestinal tract, and peak plasma levels are reached in 2 to 4 hours. Naproxen is present in the blood mainly as unchanged drug, extensively bound to plasma proteins. The plasma half-life is between 12 and 15 hours, enabling a steady state to be achieved within 3 days of initiation of therapy on a twice daily dose regimen. The degree of absorption is not significantly affected by either foods or most antacids. Excretion is almost entirely via the urine, mainly as conjugated naproxen, with some unchanged drug. Metabolism in children is similar to that in adults. Chronic alcoholic liver disease reduces the total plasma concentration of naproxen but the concentration of unbound naproxen increases. In the elderly, the unbound plasma concentration of naproxen is increased although total plasma concentration is unchanged.

5.3 Preclinical safety data

Carcinogenicity

Naproxen was administered with food to Sprague-Dawley rats for 24 months at doses of 8, 16 and 24mg/kg/day. Naproxen was not carcinogenic in rats.

Mutagenicity

Mutagenicity was not seen in *Salmonella typhimurium* (5 cell lines*), 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

Lactose, starch (maize), polyvinyl pyrrolidone, magnesium stearate, sodium starch glycollate and quinoline yellow (E104).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place below 25°C. Protect from light. Keep container tightly closed.

6.5 Nature and contents of container

Tamper evident container comprised of polyethylene and polypropylene.

Pack sizes: 28, 30, 56, 60, 84, 100, 250, 500 and 1000 Effervescent Tablets.

Blister pack: 60 GSM PVDC coated 250 microns, white opaque PVC film and 25 microns aluminium foil.

Pack sizes: 28, 30, 56, 60, 84 and 100 Effervescent Tablets.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. Marketing authorisation holder

Milpharm Limited

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8. Marketing authorisation number(s)

PL 16363/0658

9. Date of first authorisation/renewal of the authorisation

15/10/1996 / 27/06/2011

10. Date of revision of the text

02/01/2025

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