

NOFLAM

1. Product Name

NOFLAM, 250 mg, 500 mg tablets.

2. Qualitative and Quantitative Composition

Each tablet contains 250 mg or 500 mg of naproxen.

Excipients with known effect: contains sugars as lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

NOFLAM 250 mg tablets: white flat bevel edged tablet, imprinted 'Naproxen 250' around the circumference on one side and a score line on the other side.

NOFLAM 500 mg tablets: white capsule shaped tablet, imprinted with 'NP' score line '500' on one side and blank on the other side.

Tablets can be halved along scoreline.

4. Clinical Particulars

4.1 *Therapeutic indications*

NOFLAM is indicated for its anti-inflammatory and analgesic action in the treatment of rheumatoid arthritis, osteoarthritis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, acute musculoskeletal disorders, post-operative pain and dysmenorrhoea.

4.2 *Dose and method of administration*

Dose

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

Although naproxen and naproxen sodium-containing products all circulate in the plasma as naproxen, they have pharmacokinetic differences that may affect onset of action. Onset of pain relief can begin within 30 minutes in patients taking naproxen sodium and within 1 hour in patients taking naproxen.

The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and/or adverse events.

A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients. Naproxen is not recommended in patients with baseline creatinine clearance less than 30 mL/minute because accumulation of naproxen metabolites has been seen in such patients.

During long-term administration the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. In patients who tolerate lower doses well, the dose may be increased to 1000mg per day when a higher level of anti-inflammatory/analgesic activity is required. When treating patients with naproxen 1000 mg/day, the physician should observe sufficient increased clinical benefit to offset the potential increased risk (see section 4.4).

The morning and evening doses do not have to be equal in size and administration of the medicine more frequently than twice daily does not generally make a difference in response.

Recommended formulations

Because the sodium salt of naproxen is more rapidly absorbed, naproxen sodium is recommended for the management of acute painful conditions when prompt onset of pain relief is desired.

Naproxen may be given orally either in fasting state or with meals and/or antacids.

Caution is required with dosage in the elderly and also in patients with renal impairment.

Adults

For rheumatoid arthritis, osteoarthritis and ankylosing spondylitis

Initial therapy

The usual dose is 500-1000 mg per day taken in two doses at 12 hour intervals. The tablets should be swallowed whole with liquid preferably after meals. Where 1000 mg per day is needed, the suggested regimen is one naproxen 500 mg tablet twice daily.

Maintenance treatment

The maintenance dose is usually 500 mg per day taken in two doses at 12 hour intervals, i.e. 250 mg on awakening and 250 mg before retiring. The tablets should be swallowed whole with liquid preferably after meals. Dosage adjustments within the range of 500-1000 mg per day, maintaining 12 hour interval administration, may be employed. The size of the morning and evening doses should be adjusted on the basis of predominant symptoms, i.e. night time pain or morning stiffness.

Alternatively, patients stabilised on a daily maintenance dose of 500 mg, 750 mg or 1000 mg may administer their daily requirements as a single dose as naproxen has been shown to be effective when administered as a single daily dose.

The total daily dose of naproxen should not exceed 1000 mg maintaining 12 hour interval administration.

For acute gout

750 mg should be given initially, followed in 8 hours with 500 mg, and thereafter 250 mg at 8 hour intervals until the attack has passed.

For dysmenorrhoea

500 mg should be given initially, followed by 250 mg at 6-8 hour intervals for up to 5 days, if necessary.

For adult usage in other indications (analgesic and acute muscular skeletal disorders)

500 mg should be given initially, followed by 250 mg at 6-8 hour intervals, if necessary.

Paediatric

For juvenile rheumatoid arthritis

The usual dose for children over 5 years is 10 mg/kg/day given as two divided doses at 12 hour intervals. Therapy in children under 5 years of age is not recommended.

4.3 Contraindications

NOFLAM is contraindicated in patients:

- who are hypersensitive to naproxen or naproxen sodium or in whom acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory/analgesic agents induce allergic manifestations, e.g. asthma, nasal polyps, rhinitis and urticaria. Severe anaphylactic-like reactions to naproxen have been reported in such patients.
- with either active, or a history of peptic or gastrointestinal ulceration, chronic dyspepsia or active gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- with active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding) unrelated to previous NSAIDs therapy.
- under 2 years of age since safety in this age group has not been established.
- with severe heart failure.
- undergoing treatment of perioperative pain in setting of coronary artery surgery (CABG).
- with severe hepatic impairment.
- During the third trimester of pregnancy.

4.4 Special warnings and precautions for use

Cardiovascular thrombotic events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see section 4.2).

Physicians and patients should remain alert for such CV events even in the absence of previous CV symptoms. Patients should be informed about signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Clinical trial and epidemiological data suggest that the use of coxibs and some NSAIDs (particularly at high doses and with either short or long-term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke).

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension, and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore, caution is advised in patients with fluid retention or heart failure.

Gastrointestinal events

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal, gastrointestinal effects such as ulcers, irritation, bleeding and perforation, which may increase with dose or duration of use, but can occur at any time without warning symptoms. Upper gastrointestinal ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 - 6 months and in about 2 - 4% patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short-term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. elderly, debilitated patients, those with a history of serious gastrointestinal events, smoking and alcoholism.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis; Crohn's disease) as their condition may be exacerbated. Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment. When gastrointestinal bleeding or ulceration occurs in patients receiving NSAIDs, treatment should be withdrawn immediately. Physicians should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

Studies to date have not identified any subset of patients not at risk of developing peptic ulcer and bleeding. However, the elderly have an increased frequency of adverse effects to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal. Debilitated patients do not seem to tolerate ulceration or bleeding as well as others. Most of the fatal gastrointestinal events associated with NSAIDs occurred with the elderly and/or debilitated patients.

In patients with active peptic ulcer or inflammatory disease of the gastrointestinal tract and active rheumatoid arthritis, an attempt might be made to treat the arthritis with a non-ulcerogenic drug.

Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding (see section 4.5). The concurrent use of aspirin and NSAIDs also increase the risk of serious gastrointestinal adverse events.

Patients with risk factors should commence treatment on the lowest dose available.

Use in renal impairment

There have been reported cases of impaired renal function, renal failure, acute interstitial nephritis, haematuria, proteinuria, renal papillary necrosis and occasionally nephritic syndrome associated with naproxen.

Naproxen should not be given to patients with creatinine clearance less than 30 mL/minute because accumulation of naproxen metabolites has been seen in such patients.

As with other NSAIDs, naproxen should be used with caution in patients with impaired renal function or a history of kidney disease because naproxen is an inhibitor of prostaglandin synthesis. Caution should be observed in patients with conditions leading to a reduction in blood volume and/or renal blood flow as prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of naproxen or other NSAIDs may cause a dose-dependent reduction in renal prostaglandin formation and may precipitate overt renal decompensation or failure. Patients at greatest risk are those with impaired renal function, hypovolaemia, heart failure, liver dysfunction, salt depletion, those taking diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers and the elderly. Discontinuation of naproxen is usually followed by recovery to the pre-treatment state; however serious adverse events may persist. Naproxen should be used with great caution in such patients and the monitoring of serum creatinine and/or creatinine clearance is advised and patients should be adequately hydrated. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

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

Haematological

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined (see section 4.4).

Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen is administered. Patients at high risk of bleeding and those on anticoagulation therapy (e.g. heparin or dicoumarol derivatives) may be at increased risk of bleeding if given naproxen concurrently. Therefore, the benefits of prescribing naproxen should be weighed against these risks.

Patients with initial haemoglobin values of 10 grams or less, and who are to receive long-term therapy should have haemoglobin values determined frequently.

Patients on other drugs such as hydantoins, sulfonamides, sulfonylureas or methotrexate should be observed for increased effect or toxicity (see section 4.5).

Severe skin reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

DRESS has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection.

Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue NSAID and evaluate the patient immediately.

Anaphylactic 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 NSAIDs or naproxen containing product. 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.

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

Use in hepatic impairment

As with other NSAIDs, elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. The ALT test is probably the most sensitive indicator of liver dysfunction. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled clinical trials in less than 1% of patients. Physicians and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity. A patient with symptoms and/or signs suggesting hepatic dysfunction (e.g. nausea, fatigue, lethargy,

pruritis, jaundice, abdominal tenderness in the right upper quadrant and 'flu-like' symptoms), or in whom an abnormal hepatic test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with naproxen.

Hepatic abnormalities may be the result of hypersensitivity or direct toxicity.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen as with other NSAIDs. Cross reactivity has been reported. Although such reactions are rare, if abnormal hepatic tests persist or worsen, if clinical signs and symptoms consistent with hepatic disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), naproxen should be discontinued.

Chronic alcoholic hepatic disease and potentially other forms of cirrhosis reduce the total plasma concentration of naproxen; however the plasma concentration of unbound naproxen is increased. The implication of this finding for naproxen dosing is unknown.

In patients with impaired hepatic function, the lowest effective dose is recommended.

Infection

The antipyretic, anti-inflammatory and analgesic effects of naproxen may mask the usual signs or symptoms of infection.

Ocular effects

Adverse ophthalmological effects have been observed with NSAIDs. 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 should have an ophthalmological examination.

Fluid retention and oedema

Peripheral oedema has been observed in some patients taking naproxen or other NSAIDs. Although sodium retention has not been reported in metabolic studies, it is possible that patients with compromised cardiac function may be at greater risk when taking naproxen. For this reason, naproxen should be used with caution in patients with fluid retention, hypertension or heart failure.

Paediatric use

Naproxen is not recommended in children under 5 years of age as the safety and efficacy in this population has not been established.

Use in the elderly

The lowest effective dose is recommended in elderly patients.

Studies indicate that although the total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly.

Effects on laboratory tests

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

Naproxen may result in artefactual interference with some tests for 17-ketogenic steroid and may interfere with some urinary assays for 5-hydroxy-indoleacetic acid (5HIAA). 17-hydroxycorticosteroid measurements (Porter/Silber test) do not appear to be altered.

Naproxen therapy should be temporarily discontinued for at least 72 hours before testing adrenal function.

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of sucralfate or cholestyramine can delay the absorption of naproxen, but does not affect its extent. Antacids have a variable effect on absorption.

Other NSAIDs

Combination of naproxen and other NSAIDs, including cyclooxygenase-2 (COX-2) selective inhibitors, is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Protein binding

Naproxen is highly bound to plasma albumin; thus naproxen has a theoretical potential for interaction with other albumin-bound medicines, for example, warfarin or bishydroxycoumarin may be displaced and induce excessively prolonged prothrombin times. Similarly, patients receiving hydantoins, sulfonamides or sulfonylureas should be observed for increased effect or toxicity (see section 4.4).

Warfarin

The concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal, haemorrhage. The exact mechanism of the interaction between NSAIDs and warfarin is unknown, but may involve enhanced bleeding from NSAID-induced gastrointestinal ulceration, or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs. Naproxen should be used in combination with warfarin only if absolutely necessary, and patients taking this combination of drugs should be closely monitored.

Anticoagulants/ antiplatelets

Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen is administered. Patients on full anticoagulation therapy (e.g., heparin or dicoumarol derivatives) may be at increased risk of bleeding if given naproxen concurrently. Thus, the benefits should be weighed against these risks.

There is an increased risk of gastrointestinal bleeding when anti-platelet agents are combined with NSAIDs.

Selective serotonin reuptake inhibitors (SSRIs)

There is an increased risk of gastrointestinal bleeding when SSRIs are combined with NSAIDs.

Steroids

If steroid dosage is reduced or eliminated during naproxen 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 underlying disease.

Probenecid

Probenecid significantly prolongs the half-life of naproxen (from 14 to 37 hrs). This is associated with a decrease in conjugated metabolites and an increase in 6-O-desmethyl naproxen.

Methotrexate

Concomitant administration of naproxen and methotrexate should be administered with caution, because naproxen has been reported among other NSAIDs to reduce the tubular secretion of methotrexate in animal models, and have been reported to reduce the clearance of methotrexate; and thus possibly increasing the toxicity of methotrexate.

Beta-blockers

Naproxen and other NSAIDs can reduce the anti-hypertensive effect of beta-blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), and angiotensin receptor blockers (ARBs).

Diuretics

As with other NSAIDs, naproxen may inhibit the natriuretic effect of furosemide.

Lithium

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

Sodium bicarbonate

Sodium bicarbonate may enhance the rate of naproxen absorption.

Zidovudine

In vitro studies have shown that naproxen may interfere with the metabolism of zidovudine, resulting in higher zidovudine plasma levels. Therefore, to avoid the potential side effects associated with increased zidovudine plasma levels, dose reduction should be considered.

ACE-inhibitors

Concomitant use of NSAIDs with ACE inhibitors or angiotensin receptor blockers may increase the risk of renal dysfunction, especially in patients with pre-existing poor renal function (see section 4.4).

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time (triple whammy) increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the initiation of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

Naproxen is contraindicated in third trimester of pregnancy.

NSAIDs inhibit prostaglandin synthesis and, when given during the second or third trimester of pregnancy, may cause premature closure of the foetal ductus arteriosus (see Premature closure of foetal ductus arteriosus), foetal renal dysfunction leading to oligohydramnios and neonatal renal impairment (see Oligohydramnios and neonatal renal impairment), prolong labour and delay birth. Oligohydramnios is generally seen after days to weeks of treatment, although it has been reported as soon as 48 hours after NSAID initiation. Oligohydramnios is usually, but not always, reversible after treatment discontinuation. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with Naproxen if oligohydramnios occurs.

NSAID use during the 3rd trimester may cause premature closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and may delay labour and birth. NSAID use in the 3rd trimester of pregnancy is therefore contraindicated.

Naproxen should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the fetus.

Data from epidemiological studies suggest an increased risk of miscarriage and congenital malformation associated with NSAID use in early pregnancy.

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.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetal development. Some data from epidemiological studies suggest an increased risk of miscarriage and congenital malformation after use of a prostaglandin synthesis inhibitor (such as NSAIDs) in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss. During the first two trimester of pregnancy, naproxen should not be given unless the expected benefits to the mother outweigh the risks to the fetus. If there is a compelling need for naproxen use by a woman attempting to conceive, or during the first and second trimester of pregnancy, limit use to the lowest effective dose and shortest duration possible.

Premature closure of foetal ductus arteriosus

Naproxen may cause premature closure of the foetal ductus arteriosus. Avoid use of naproxen in pregnant women starting at about 30 weeks of gestation (third trimester) and later. Naproxen increases the risk of premature closure of the foetal ductus arteriosus at approximately this gestational age.

Oligohydramnios and neonatal renal impairment

Use of NSAIDs from 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. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If, after careful consideration of alternative treatment options for pain management, naproxen treatment is necessary from about 20 weeks, limit naproxen use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if naproxen treatment extends beyond 48 hours. Discontinue treatment with naproxen if oligohydramnios occurs and follow up according to clinical practice.

Use in lactation

Naproxen has been found in the milk of lactating mothers at a concentration of approximately 1% of that found in plasma. As the effect of naproxen in the newborn is not known, the use of naproxen in lactating mothers is not recommended.

Fertility

No data available.

4.7 *Effects on ability to drive and use machines*

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of naproxen. If patients experience these or similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

4.8 *Undesirable effects*

Adverse effects reported in controlled clinical trials in patients treated for rheumatoid arthritis and osteoarthritis are listed below. In general, these effects were reported 2 to 10 times more frequently than they were in studies of 962 patients treated for mild to moderate pain.

Incidence between 3% and 9%

Gastrointestinal: The most frequently reported adverse events were related to the gastrointestinal tract. These were: constipation, heartburn, abdominal pain, nausea.

Central nervous system: headache, dizziness, drowsiness.

Dermatologic: itching (pruritis), skin eruption, ecchymoses.

Special senses: tinnitus.

Cardiovascular: oedema, dyspnoea.

Incidence between 1% and less than 3%

Gastrointestinal: dyspepsia, diarrhoea, stomatitis.

Central nervous system: light-headedness, vertigo.

Dermatologic: sweating, purpura.

Special senses: hearing disturbances, visual disturbances.

Cardiovascular: palpitations.

General: thirst.

Incidence less than 1%

Probable causal relationship

The following adverse effects were reported less frequently than 1% during controlled clinical trials and in post marketing reports. The probability of a causal relationship exists between naproxen and these adverse effects.

Gastrointestinal: abnormal liver function tests, gastrointestinal bleeding, haematemesis, jaundice, melaena, peptic ulceration with bleeding and/or perforation, non-peptic gastrointestinal ulceration, vomiting, ulcerative stomatitis, colitis, fatal hepatitis.

Renal: glomerular nephritis, haematuria, interstitial nephritis, renal papillary necrosis, nephrotic syndrome, renal disease, hyperkalaemia, renal failure.

Haematologic: eosinophilia, granulocytopenia, leukopenia, thrombocytopenia.

Central nervous system: depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis.

Dermatologic: porphyria cutanea tarda, epidermolysis bullosa, alopecia, skin rashes, epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome (SJS), photosensitivity reactions including rare cases in which the skin resembles porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa.

Special senses: hearing impairment.

Cardiovascular: vasculitis, congestive heart failure.

General: menstrual disorders, pyrexia (chills and fever), eosinophilic pneumonitis, anaphylactoid reactions (see section 4.4).

Causal relationship unknown

Other reactions have been reported in circumstances in which a causal relationship could not be established. Although rarely reported, the physician should be alerted to these.

Haematologic: agranulocytosis, aplastic anaemia, haemolytic anaemia.

Central and peripheral nervous system: cognitive dysfunction, convulsions, paraesthesia.

Dermatologic: urticaria, photosensitivity.

Mouth and throat: sore throat.

General: angioneurotic oedema, hyperglycaemia, hypoglycaemia, hyperkalaemia.

Reproductive: female infertility.

Post-marketing

The following are the adverse events that have been reported with NSAIDs and with naproxen:

Gastrointestinal: inflammation, peptic ulcers, ulceration, perforation and obstruction of the upper and lower gastrointestinal tract, gastrointestinal bleeding (sometimes fatal particularly in the elderly), heartburn, nausea, oesophagitis, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, non-peptic gastrointestinal ulceration, melaena, haematemesis, stomatitis, ulcerative stomatitis, exacerbation of ulcerative colitis and Crohn's disease, pancreatitis, gastritis.

Infections: aseptic meningitis.

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

Immune system disorders: anaphylactoid reactions.

Metabolic and nutrition disorders: hyperkalaemia.

Psychiatric disorders: depression, dream abnormalities, insomnia.

Nervous system disorders: dizziness, drowsiness, headache, light-headedness, retrobulbar optic neuritis, convulsions, cognitive dysfunction, inability to concentrate.

Eye disorders: visual disturbances, corneal opacity, papillitis, papilloedema.

Ear and labyrinth disorders: hearing impairment, hearing disturbances, tinnitus, vertigo.

Cardiac disorders: palpitations, cardiac failure, congestive heart failure.

Vascular disorders: hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders: dyspnoea, pulmonary oedema, asthma, eosinophilic pneumonitis.

Hepatobiliary disorders: hepatitis, jaundice.

Skin and subcutaneous tissue disorders: ecchymoses, itching (pruritus), purpura, skin eruptions, sweating, alopecia, epidermal necrolysis, very rarely toxic epidermal necrolysis (TEN), erythema multiforme, bullous reactions, (including SJS, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)), erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, skin rashes, systemic lupus erythematosus (SLE), urticaria, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria), or epidermolysis bullosa, and angioneurotic oedema.

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, muscle weakness.

Renal and urinary disorders: haematuria, interstitial nephritis, nephritic syndrome, renal disease, renal failure, renal papillary necrosis.

Pregnancy, puerperium and perinatal conditions: oligohydramnios, neonatal renal impairment

Reproductive system: female infertility.

General disorders: oedema, thirst.

Investigations: abnormal liver function tests, raised serum creatinine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms

Significant overdose of the medicine may be characterised by dizziness, drowsiness, epigastric pain, abdominal discomfort, indigestion, transient alterations in liver function, hypoprothrombinaemia, renal dysfunction, metabolic acidosis, apnoea, disorientation, nausea or vomiting. A few patients have experienced seizures, but it is not clear if these were causally related to naproxen. It is not known what dose of naproxen would be life threatening.

Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may occur after the ingestion of NSAIDs, and may occur following an overdose.

Anaphylactoid reactions have been reported with therapeutic ingestions of NSAIDs, and may occur following an overdose.

Treatment

Patients should be managed by symptomatic and supportive care following NSAIDs overdose. There are no specific antidotes. Prevention of further absorption (e.g. activated charcoal) may be indicated in symptomatic patients seen within 4 hours of ingestion or following a large overdose. Forced diuresis, alkalinisation of urine, haemodialysis, or haemoperfusion may not be useful due to high protein binding.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, ATC code: M01AE

Mechanism of action

Naproxen has been shown to have anti-inflammatory properties when tested in human clinical studies. In addition, it has analgesic and antipyretic actions. It exhibits its anti-inflammatory effects even in adrenalectomised animals, indicating that its action is not mediated through the pituitary axis. It inhibits prostaglandin synthetase, as do other NSAIDs, however, the exact mechanism of its anti-inflammatory action is not known.

5.2 Pharmacokinetic properties

Absorption

In humans naproxen is completely absorbed from the gastrointestinal tract after oral administration. Concomitant administration of food can delay the absorption of naproxen, but does not affect its extent.

After administration of naproxen tablets, peak plasma levels are attained in 2 to 4 hours depending on food intake.

Distribution

Naproxen has a relatively small volume of distribution (0.09 ± 0.03 L/kg), which corresponds to about 10% of the body weight in humans. At therapeutic levels naproxen is greater than 99% albumin-bound. The plasma concentration of naproxen increases proportionally with doses up to 500 mg twice daily. Larger doses result in a less than proportional increase due to accelerated renal clearance of disproportionately increased amounts of non-protein bound drug. However, whether this effect increases or decreases the toxicity of naproxen has not been established.

Steady-state plasma levels of naproxen are reached after 4 to 5 doses.

Naproxen enters synovial fluid, crosses the placenta. It has been found in the milk of lactating mothers at a concentration approximately 1% of that found in plasma.

Biotransformation

Naproxen is metabolised in the liver to 6-O-desmethyl naproxen (approximately 28% of an IV dose).

Elimination

Approximately 95% of the naproxen is excreted in the urine, primarily as naproxen (10%), 6-O-desmethyl naproxen (5%), or their conjugates. The rate of excretion of metabolites and conjugates has been found to coincide closely with the rate of naproxen clearance from the plasma. Small amounts, 5% or less, are excreted in the faeces.

The elimination half-life of naproxen is approximately 14 hours.

Special populations

Children

The pharmacokinetic profile of naproxen in children aged 5 - 16 years is similar to that in adults.

Renal impairment

Given that naproxen and its metabolites are primarily excreted by the kidney, the potential exists for accumulation in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment (creatinine clearance <20 mL/min), in whom there is higher clearance of naproxen than estimated from the degree of renal impairment alone (see section 4.4).

5.3 Preclinical safety data

No data available.

6. Pharmaceutical Particulars

6.1 List of excipients

Naproxen tablet also contains:

- Lactose monohydrate

- Maize starch
- Povidone
- Sodium starch glycollate
- Purified talc
- Magnesium stearate
- Polysorbate 80

Naproxen tablets contains sugars as lactose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C. Protect from light.

6.5 Nature and contents of container

HDPE bottle with PP cap, with or without plastissue filler.

250 mg: pack size of 100 or 500 tablets.

500 mg: pack size of 100 or 250 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

15 December 1983

10. Date of Revision of the Text

7 July 2022

Section Changed	Summary of New Information
2	Addition of "Excipients with known effect"
4.3	Addition of "third trimester of pregnancy" as a contraindication
4.6	Additional warning information for use of Naproxen during pregnancy
6.1	Declaration of allergen statement