NAPROXEN SUSPENSION

(NAPROXEN)

1 NAME OF THE MEDICINE

Naproxen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Naproxen is a propionic acid derivative related to the arylacetic acid class of drugs. It is unrelated to salicylates and the corticosteroid hormones. It is an odourless, white to off white crystalline substance. It is lipid soluble, practically insoluble in water at low pH and freely soluble in water at high pH.

Naproxen Suspension is a suspension containing 25 mg/mL of naproxen.

Excipients with known effect: sugars (as sucrose), sorbitol, sodium and hydroxybenzoates.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Naproxen Suspension is available as an orange aqueous suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Naproxen Suspension is indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis; for the symptomatic treatment of primary dysmenorrhoea; for the relief of acute and/or chronic pain states in which there is an inflammatory component and as an analgesic in acute migraine attack.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Patients on long term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

Chronic conditions
Osteoarthritis/ rheumatoid arthritis/ ankylosing spondylitis/ chronic pain states in which there is an inflammatory component

The starting dose of Naproxen Suspension should not be less than 500 mg daily and may be varied stepwise within the range 375 to 1000 mg daily maintaining twice-daily administration for long term maintenance, depending on the needs of the patient.

Acute conditions
Acute pain states in which there is an inflammatory component

The recommended dose of Naproxen Suspension is 500 mg initially followed by 250 mg every six to eight hours as required. The total daily dose should not exceed 1250 mg.

Dysmenorrhoea

In the symptomatic treatment of primary dysmenorrhoea, the recommended dose is 500 mg initially at the first sign of dysmenorrhoea or menstrual bleeding (whichever occurs first), followed by 250 mg every six to eight hours as required. The total daily dose should not exceed 1250 mg.

Migraine

For the treatment of acute migraine headache, the recommended dose of Naproxen Suspension is 750 mg at the first symptom of an impending headache. An additional dose of 250 to 500 mg can be given throughout the day if necessary, at least an hour after the initial dose. The total daily dose should not exceed 1250 mg.

Pregnancy

See Section 4.3 Contraindications and Section 4.6 Fertility, Pregnancy and Lactation.

Children

Juvenile rheumatoid arthritis

The recommended daily dose for children 5 years and above is 10 mg/kg in two equally divided doses (i.e. 5 mg/kg twice a day).

4.3 CONTRAINDICATIONS

Naproxen Suspension 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
- third trimester of pregnancy (see Section 4.6 Fertility, Pregnancy and Lactation)
- under 2 years of age since safety in this age group has not been established
- with severe heart failure
- treatment of perioperative pain in the setting of coronary bypass surgery (CABG).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiovascular thrombotic events

Observational studies have indicated that nonselective 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 known 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 Dose and Method of Administration). Healthcare

professionals and patients should remain alert for such cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

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

Clinical trial and epidemiological data suggest that the use of coxibs and some NSAIDs (particularly at high doses and 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 the 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

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. 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% of 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 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 Interactions with Other Medicines and Other Forms of Interactions). The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

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

Haematological

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are being determined. (See Section 4.4 Special Warnings and Precautions for Use, Effects on laboratory tests).

Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if Naproxen Suspension 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 Suspension concurrently. Therefore, the benefits of prescribing Naproxen Suspension should be weighed against these risks.

Patients with initial haemoglobin values of 10 g 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 Interactions with Other Medicines and Other Forms of Interactions).

Severe skin reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) 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 physician at the first appearance of a skin rash or any other sign of hypersensitivity.

Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)

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 the 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; or other NSAIDs or naproxen-containing products. They may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

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

Infection

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

Ocular events

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 Suspension, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with Naproxen Suspension should have an ophthalmological examination.

Sodium

Each mL of Naproxen Suspension liquid contains 8 mg of sodium. This should be considered in patients whose overall intake of sodium must be restricted.

Fluid retention and oedema

Peripheral oedema has been observed in some patients taking Naproxen Suspension 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 Suspension. For this reason, Naproxen Suspension should be used with caution in patients with fluid retention, hypertension or heart failure.

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. A patient with symptoms and/or signs suggesting hepatic dysfunction, 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 Suspension.

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 Suspension 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.

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 Suspension.

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

As with other NSAIDs, Naproxen Suspension 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 Suspension 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 and the elderly. Discontinuation of Naproxen Suspension is usually followed by recovery to the pre-treatment state; however, serious adverse events may persist. Naproxen Suspension should be used with great caution in such patients and the monitoring of serum creatinine and/or creatinine clearance is advised. A reduction of 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.

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.

Paediatric use

The recommended dosage form of naproxen in children (5 years and over) is Naproxen Suspension 25 mg/mL.

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

Effect on laboratory tests

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

Naproxen Suspension 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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-containing products 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 drugs, 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 Special Warnings and Precautions for Use, Haematological).

Warfarin

The concurrent use of NSAIDs and warfarin has been associated with severe and 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 Suspension should be used in combination with warfarin only if absolutely necessary, and patients taking this combination of drugs should be closely monitored.

Anticoagulants/ antiplatelet agents

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 antiplatelet 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 Suspension 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 6-0-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.

Diuretics

As with other NSAIDS, naproxen may inhibit the natriuretic effect of frusemide.

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

As with other NSAIDs, naproxen may increase the risk of renal impairment associated with the use of angiotensin I-converting enzyme (ACE) inhibitors.

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

Effects on fertility

The use of Naproxen Suspension, 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.

Use in pregnancy

Naproxen Suspension is Pregnancy Category C - *Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.*

Contraindicated in the third trimester of pregnancy (see Section 4.3 Contraindications)

NSAIDs inhibit prostaglandin synthesis. Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy. When given during the latter part of pregnancy, NSAIDs may cause closure of the fetal ductus arteriosus, fetal renal dysfunction leading to oligohydramnios and neonatal renal impairment (see Oligohydramnios and Neonatal Renal Impairment), prolong

labour and delay birth. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided. Continuous treatment with NSAIDs during the last month of pregnancy should only be given when clearly needed.

Oligohydramnios and Neonatal Renal Impairment

Use of NSAIDs from about 20 weeks gestation or later in pregnancy may cause fetal 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, NSAID treatment is necessary from about 20 weeks, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue NSAID treatment if oligohydramnios occurs and follow up according to clinical practice.

Naproxen Suspension should only be administered during pregnancy if the benefit justifies the potential risk.

Use in lactation

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

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 Suspension. If patients experience these or similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects reported in controlled clinical trials in 960 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 (pruritus), 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 reactions were reported less frequently than 1% during controlled clinical trials and in postmarketing 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, nonpeptic gastrointestinal ulceration, vomiting, ulcerative stomatitis, colitis, fatal hepatitis.

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

Haematological: eosinophilia, granulocytopenia, leucopenia, thrombocytopenia.

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

Dermatological: 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 epidemolysis bullosa.

Special Senses: hearing impairment.

Cardiovascular: vasculitis, congestive heart failure.

General: menstrual disorder, pyrexia (chills and fever), eosinophilic pneumonitis, anaphylactoid reactions (see Section 4.4 Special Warnings and Precautions for Use, Anaphylactic reactions).

CAUSAL RELATIONSHIP UNKNOWN

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

Haematological: agranulocytosis, aplastic anaemia, haemolytic anaemia.

Central and Peripheral Nervous System: cognitive dysfunction, convulsions, paraesthesia.

Dermatological: urticaria, photosensitivity.

Mouth and Throat: sore throat.

General: angioneurotic oedema, hyperglycaemia, hypoglycaemia, hyperkalaemia.

Reproductive: female infertility.

Post-marketing experience

The following adverse effects have been reported with NSAIDs and Naproxen Suspension.

Gastrointestinal: peptic ulcers, perforation, gastrointestinal bleeding, 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.

Infection: 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), erythema nodosum, fixed drug eruption, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), lichen planus, pustular reaction, skin rashes, systemic lupus erythomatosus (SLE), urticaria, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa or 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.

Reproductive System: female infertility.

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

General Disorders: oedema, thirst.

Investigations: abnormal liver function tests, raised serum creatinine.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 unclear if these were causally related to naproxen. It is not known what dose of Naproxen Suspension 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 ingestion of NSAIDs and may occur following an overdose.

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 four 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 information on the management of overdosage, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Naproxen Suspension is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties.

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 effect 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.

Clinical trials

No data available.

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 Naprosyn tablets, peak plasma levels are attained in two to four 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 and crosses the placenta. It has been found in the milk of lactating mothers at a concentration of approximately 1% of that found in plasma.

Metabolism

Naproxen is metabolised in the liver to 6-0-desmethyl naproxen (approximately 28% of an intravenous dose).

Excretion

Approximately 95% of the naproxen is excreted in the urine, primarily as naproxen (10%), 6-0-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.

Pharmacokinetics in 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 Special Warnings and Precautions for Use, Use in renal impairment).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each 50 mL of Naproxen Suspension also contains sucrose 12.75 g, sorbitol 6.43 g, sodium chloride 1 g, aluminium magnesium silicate 1 g, fumaric acid 0.25 g, methyl hydroxybenzoate 0.05 g, imitation orange flavour, imitation pineapple flavour, the colour sunset yellow FCF and purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[1]. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Naproxen Suspension containing naproxen 25 mg in 1 mL is available as an orange aqueous suspension in bottles of 474 mL.

Phebra product code - SOL048

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

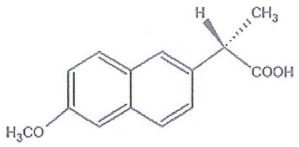
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The chemical name of naproxen is (+)-6-methoxy-α-methyl-2- naphthaleneacetic acid. Its molecular formula is $C_{14}H_{14}O_3$ and molecular weight is 230.3.

[1] AUST R 196596

Chemical structure



CAS number

2224531

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Phebra[2] Pty Ltd, 19 Orion Road, Lane Cove West NSW 2066, Australia.
Telephone: 1800 720 020

9 DATE OF FIRST APPROVAL

1 Jun 2012

10 DATE OF REVISION

11 Aug 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2, 4.3, 4.4, 4.6 and 4.8	Updated the safety wordings concerning the risk of oligohydramnios and fetal renal impairment with NSAID use during pregnancy, and drug reaction with Eosinophilia with Systemic Symptoms (DRESS)
6.1	Update the quantities and units for the list of excipients

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