
NEW ZEALAND DATA SHEET

1 NAPROSYN SR (Sustained release tablets)

Naprosyn® SR 750 mg sustained release (SR) tablets.

Naprosyn® SR 1000 mg sustained release (SR) tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sustained release tablet contains 750 mg or 1000 mg of naproxen.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sustained release tablets

750 mg: Peach, capsule shaped tablet, with marking NPR SR-750 on one side.

1000 mg: Peach, oblong tablet, with marking NPR SR-1000 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Naprosyn SR is indicated for its anti-inflammatory and analgesic action in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and other musculoskeletal disorders.

4.2 Dosage and Administration

Dose

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used (see Section 4.4).

The total required daily dose of naproxen can be achieved by administering the appropriate single daily dose i.e. Naprosyn SR 750 mg or Naprosyn SR 1000 mg.

The total daily dose of naproxen should not exceed 1000 mg.

NAPROSYN SR TABLETS ARE NOT INTENDED FOR PATIENTS REQUIRING SHORT-TERM TREATMENT FOR ACUTE INDICATIONS.

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 1000 mg 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).

A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (see Section 4.4).

Cardiovascular

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

Paediatric

The safety and efficacy of naproxen in children under 5 years of age has not been established. Refer to section 4.3 and 4.4.

Pregnancy

See Section 4.6.

Method of Administration

Naprosyn SR tablets should be taken whole and not chewed or broken.

4.3 Contraindications

Naprosyn SR 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. Both types of reactions have the potential of being fatal.
- with either active, or a history of, peptic or gastrointestinal ulceration, or chronic dyspepsia or active gastrointestinal bleeding or perforation, related to previous NSAIDs 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: 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
- in the 3rd trimester of pregnancy

4.4 Special Warnings and Precautions for Use

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

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Section 4.2).

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.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking). 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 to suggest that 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 use of coxibs and some NSAIDs (particularly at high doses or long-term treatment) may be associated with an increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Adverse cardiovascular events can occur with short term use.

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

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.

Gastrointestinal

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal gastrointestinal effects such as ulcers, irritation and 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. the elderly, 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 ulcerations occur 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 reactions 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 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, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin. The concurrent use of aspirin and NSAIDs also increase the risk of serious gastrointestinal adverse effects.

Renal Impairment

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

Naprosyn SR 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, Naprosyn SR 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. Naprosyn SR 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 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.

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 – Effects on Laboratory Tests).

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, benefits of prescribing Naprosyn SR 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).

Skin reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS) and toxic epidermal necrolysis (TEN) 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 in patients both with, and without, a history of hypersensitivity or exposure to aspirin, 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.

Hepatic Impairment

As with other NSAIDs borderline 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 reactions 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 and anti-inflammatory activities of naproxen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs of 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 patients with compromised cardiac function may be at greater risk when taking naproxen, and caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Effects on Laboratory Tests

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

Naproxen may artefactually interfere 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 48 hours before testing adrenal function.

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.

Elderly Patients

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.

Naproxen is not recommended in elderly patients with hepatic or renal impairment.

4.5 Interactions with Other Medicinal Products 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-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 - Haematological).

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. Naprosyn SR should be used in combination with warfarin only if absolutely necessary, and patients taking this combination of drugs should be closely monitored.

Anticoagulants/ Anti-platelet 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 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

Concomitant administration of naproxen and probenecid should be done with caution, as 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 done with caution, because naproxen has been reported among other NSAIDs to reduce the tubular secretion of methotrexate in animal models, 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 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

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 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

PREGNANCY CATEGORY: C

Naprosyn SR is contraindicated in 3rd trimester of pregnancy.

Naproxen should not be used during the first two trimesters of pregnancy, or in women trying to conceive, unless the expected benefits to the mother outweigh the risks to the foetus. If there is a compelling need for NSAID treatment during the first or second trimester, limit use to the lowest effective dose and shortest duration possible. NSAIDs inhibit prostaglandin synthesis and data from epidemiological studies suggest an increased risk of miscarriage and congenital malformation associated with NSAID use in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

Use in the second or third trimester may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment (see Oligohydramnios/neonatal renal impairment). 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 foetal ductus arteriosus (see Premature closure of the foetal ductus arteriosus), foetal renal impairment, inhibition of platelet aggregation, and may delay labour and birth. NSAID use in the 3rd trimester of pregnancy is therefore contraindicated.

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/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.

Breast Feeding

The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in plasma. Because of the possible adverse effects of prostaglandin-inhibiting medicines on neonates, use in nursing mothers is not recommended.

Labour and delivery

Naproxen is not recommended in labour and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect foetal circulation and inhibit uterine contractions, thus increasing the risk of uterine haemorrhage.

Fertility

The use of naproxen, as with any medicine 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 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 960 patients treated for rheumatoid arthritis and osteoarthritis are listed below. In general, these adverse 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 effects 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 through post-marketing reports. A causal relationship probably 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, nephrotic syndrome, renal disease, renal papillary necrosis, renal failure, hyperkalaemia

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 – Anaphylactic Reactions)

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 adverse events which have been reported with NSAIDs and Naprosyn SR use:

Gastrointestinal: inflammation, ulceration, perforation and obstruction of the upper or lower intestinal tract, bleeding (sometimes fatal, particularly in the elderly - see Section 4.4); heartburn, nausea, Oesophagitis, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, stomatitis, exacerbation of ulcerative colitis and Crohn's disease (see Section 4.4), 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 (some cases of hepatitis have been fatal), jaundice

Skin and subcutaneous tissue disorders: ecchymoses, itching (pruritus), purpura, skin eruptions, sweating, alopecia, epidermal necrolysis, very rarely toxic epidermal necrolysis, erythema multiforme, bullous reactions, including Stevens-Johnson syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, skin rashes, systemic lupus erythematosus, 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, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis

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

Reproductive system and breast disorders: female infertility

General disorders and administration site conditions: oedema, thirst, pyrexia (chills and fever), malaise

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 unclear 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 ingestion 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 patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinisation of urine, haemodialysis, or haemoperfusion may not be useful due to high protein binding. Due to the sustained-release characteristic of Naprosyn SR tablets, it should be expected that naproxen will continue to be absorbed for up to 16 hours after ingestion.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES AND EFFECTS

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives, ATC code: M01AE02

Naprosyn SR (naproxen) is a non-steroidal anti-inflammatory (NSAID) with analgesic, anti-inflammatory and antipyretic properties.

Naproxen is a propionic acid derivative related to the arylacetic acid class of medicines. The chemical name of naproxen is (+)-6-methoxy- α -methyl-2-naphthaleneacetic acid. 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.

Mechanism of action

Naproxen has been shown to have anti-inflammatory properties when tested in human clinical studies and classical animal test systems. In addition, it has marked 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 synthesis of prostaglandins as with other similar agents, however, the exact mechanism of its anti-inflammatory action is not known.

5.2 Pharmacokinetic Properties

Absorption

Naprosyn SR tablets have a matrix formulation which remains intact during its transit through the gastrointestinal tract. When the tablet comes in contact with gastrointestinal fluids it forms a gelatinous layer which controls the rate of release of naproxen.

Food does not alter the bioavailability of Naprosyn SR tablets. Food decreases the rate of transit of Naprosyn SR tablets from the stomach to the intestines in both young and old adult patients. These results are unlikely to be of clinical significance.

Distribution

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day, there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses. However, the concentration of unbound naproxen continues to increase proportionally to dose.

Steady-state plasma levels of naproxen are reached after 3 - 4 days.

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

Metabolism

Naproxen is extensively metabolised in the liver to 6-O-desmethyl naproxen.

Elimination

Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-O-desmethyl naproxen (less than 1%), or their conjugates (66 - 92%). 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, 3% or less, are excreted in the faeces.

The clearance of naproxen is approximately 0.13 mL/min/kg. The elimination half-life of naproxen is approximately 14 hours.

Pharmacokinetics in special clinical situations

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. In patients who are severely renally impaired (creatinine clearance <10 mL/min), there is higher clearance of naproxen than estimated from the degree of renal impairment alone.

Children

The pharmacokinetic profile of naproxen in children aged 5 - 16 years is similar to that in adults. Pharmacokinetic studies of naproxen were not performed in children less than 5 years of age.

5.3 Preclinical Safety

Carcinogenicity

Naproxen was administered with food to Sprague-Dawley rats for 24 months at doses of 8, 16 and 24 mg/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.

Impairment of Fertility

Naproxen did not affect the fertility of rats when administered orally at doses of 30 mg/kg/day to males and 20 mg/kg/day to females.

Teratogenicity

Naproxen was not teratogenic when administered orally at doses of 20 mg/kg/day during organogenesis to rats and rabbits.

Perinatal/postnatal reproduction

Oral administration of naproxen to pregnant rats at doses of 2, 10 and 20 mg/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 indomethacin.

6 PHARMACEUTICAL PARTICULARS

6.1 Excipients

Hydroxypropyl methyl cellulose, magnesium stearate, sunset yellow FCF, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

36 months

This medicine must not be used after the expiry date shown on the pack.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Naprosyn SR 750mg tablets	blisters containing 28 tablets
Naprosyn SR 1000mg tablets	blisters containing 28 tablets

Naprosyn SR 750mg tablets	bottle containing 90 tablets
Naprosyn SR 1000mg tablets	bottle containing 90 tablets

Not all pack sizes and presentations may be available.

6.6 Special precautions for disposal

No special requirements

7 MEDICINE CLASSIFICATION

Prescription medicine

8 SPONSOR

Clinect NZ Pty Limited
C/- Ebos Group Limited
108 Wrights Road
Christchurch 8024
NEW ZEALAND

Telephone: 0800 138 803

9 DATE OF FIRST APPROVAL

750 mg: 06 October 1985
1000 mg: 06 October 1985

10 DATE OF REVISION OF THE TEXT

30 June 2022

Summary Table of Changes

Section Changed	Summary of New Information
4.3	Update to Contraindications - Addition of 3 rd trimester pregnancy as a contraindication
4.6	Update to Fertility, Pregnancy and Lactation - include additional information and clarity about the contraindication of NAPROSYN SR during pregnancy, and the risk of oligohydramnios and neonatal renal impairment with NSAID use
ALL	Editorial changes