

New Zealand Data Sheet

1. PRODUCT NAME

NAXEN® 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NAXEN 250 mg tablet contains 250 mg of Naproxen

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

NAXEN 250 mg tablets are yellow, biconvex, round tablet of 11 mm diameter with one face engraved NX250 and having a bisecting score.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

NAXEN is indicated in adults for the relief of symptoms associated with rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendonitis and bursitis, acute gout and primary dysmenorrhoea.

NAXEN is indicated in children for juvenile arthritis.

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 (*see Section 4.4*).

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 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.

Dose

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 two NAXEN 250 mg tablets 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. 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 stabilized 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 per day, maintaining 12 hour interval administration.

For tendonitis and bursitis

The recommended dose is 500 mg initially, followed by 250 mg at 6-8 hour intervals, if necessary.

For acute gout

The recommended dose is 750 mg initially, followed in 8 hours with 500 mg, and thereafter 250 mg at 8-hour intervals until the attack has passed.

For primary dysmenorrhoea

The recommended dose is 500 mg initially, followed by 250 mg at 6-8 hour intervals for up to 5 days, if necessary.

Special populations

Elderly population:

Caution is required and if naproxen is considered necessary, the lowest effective dose should be used and for the shortest possible duration (*see Section 4.4*).

Renal impairment:

A lower dose should be considered in patients with renal impairment (*see section 4.4*). 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.

Hepatic impairment

Naproxen should be administered to patients with impaired liver function only in case of necessity (*see Section 4.3*). A lower dose should be considered in such patients.

Paediatric population

For juvenile rheumatoid arthritis

Children over 5 years

The usual dose for children over 5 years is 10 mg/kg/day given as two divided doses at 12 hour intervals.

Children under 5 years

Therapy in children under 5 years of age is not recommended.

Method of Administration

Naxen tablets should be preferably taken with or after food.

4.3. Contraindications

Naxen is contraindicated in patients:

- who are hypersensitivity to the naproxen or to any of the excipients listed in section 6.1
- 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 (*see Section 4.2*)

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.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with NAXEN 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, and 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 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

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 Events

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 (*see section 4.5*).

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. 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 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 NAXEN 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 NAXEN concurrently. Therefore, benefits of prescribing NAXEN 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) 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 (*see Section 4.8*).

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 NAXEN.

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.), NAXEN 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.

Special populations:

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

Paediatric population

NAXEN is not recommended in children under 5 years of age as the safety and efficacy in this population has not been established (*see section 4.2*).

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-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 (*see section 5.2*); 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. NAXEN 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 or angiotensin receptor blockers

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

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/foetal development. Some data from epidemiological studies suggest an increased risk of miscarriage 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 and second trimester of pregnancy, NAXEN should not be given unless clearly necessary. If NAXEN is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible.

Breast-feeding

Naproxen can appear in the breast milk of lactating women (*see Section 5.2*). The use of naproxen/NSAIDs should be avoided in patients who are breast feeding unless the benefit outweighs the potential risk.

Labour and delivery

NAXEN 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 (*see section 4.8*). In women who have difficulty conceiving or are undergoing investigation of infertility withdrawal of NAXEN should be considered. Also *see section 5.3* for preclinical safety information.

4.7. Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness, drowsiness, vertigo, insomnia, fatigue, depression or visual disturbances, and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8. Undesirable effects

Summary of the safety profile

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%

Nervous system disorders: headache, dizziness, drowsiness

Ear and labyrinth disorders: tinnitus

Cardiac disorders: oedema

Respiratory, thoracic and mediastinal disorders: dyspnoea

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

Skin and subcutaneous tissue disorders: itching (pruritis), skin eruption, ecchymosis

Incidence between 1% and less than 3%

Nervous system disorders: light-headedness,

Eye disorders: visual disturbances

Ear and labyrinth disorders: Vertigo, hearing disturbances,

Cardiac disorders: palpitations

Gastrointestinal disorders: dyspepsia, diarrhoea, stomatitis

Skin and subcutaneous tissue disorders: sweating, purpura

Metabolism and nutrition disorders: 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.

Blood and lymphatic system disorders: eosinophilia, granulocytopenia, leukopenia, thrombocytopenia

Immune system disorders: anaphylactoid reactions (*see Section 4.4 – Anaphylactic Reactions*)

Metabolism and nutrition disorders: hyperkalaemia

Psychiatric disorders: Depression, dream abnormalities, insomnia

Nervous system disorders: inability to concentrate, aseptic meningitis

Ear and labyrinth disorders: hearing impairment

Cardiac disorders: congestive heart failure

Vascular disorders: vasculitis

Respiratory, thoracic and mediastinal disorders: eosinophilic pneumonitis

Gastrointestinal disorders: gastrointestinal bleeding, haematemesis, , melaena, peptic ulceration with bleeding and/or perforation, non-peptic gastrointestinal ulceration, vomiting, ulcerative stomatitis, colitis

Hepatobiliary disorders: abnormal liver function tests, jaundice, fatal hepatitis

Skin and subcutaneous tissue disorders: 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

Musculoskeletal and connective tissue disorders: myalgia, muscle weakness

Renal and urinary disorders: glomerular nephritis, haematuria, interstitial nephritis, nephrotic syndrome, renal disease, renal papillary necrosis, renal failure,

Reproductive system and breast disorders: menstrual disorders

General disorders and administration site conditions: Malaise, pyrexia (chills and fever), ,

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.

Blood and lymphatic system disorders: agranulocytosis, aplastic anaemia, haemolytic anaemia

Immune System disorders: angioneurotic oedema

Metabolism and nutrition disorders: hyperglycaemia, hypoglycaemia hyperkalaemia

Nervous system disorders: cognitive dysfunction, convulsions, paraesthesia

Respiratory, thoracic and mediastinal disorders: sore throat

Skin and subcutaneous disorders: urticaria, photosensitivity

Post-Marketing

The following are adverse events which have been reported with NSAID use:

Infections and infestations: aseptic meningitis

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

Immune system disorders: anaphylactoid reactions

Metabolism 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

Gastrointestinal disorders: 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

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, 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

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 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 1 to 2 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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Mechanism of action

Naproxen is a phenylpropionic acid derivative having analgesic, anti-inflammatory and antipyretic activity. Such activity is thought to be mediated via inhibition of the enzyme complex prostaglandin synthetase with consequent reduction in the synthesis of prostaglandins from arachidonic acid.

Naproxen also inhibits platelet aggregation by inhibition of platelet thromboxane A₂. The onset of action of naproxen may be 2 or more hours after oral administration with therapeutic effects persisting for up to 7-8 hours.

Clinical efficacy and safety

It is comparable to aspirin and indomethacin in controlling disease activity with less frequent and milder side effects. Clinical improvement induced by naproxen is not dependent on age, sex, severity or duration of disease.

In ⁵¹Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg naproxen has been demonstrated to cause significantly less gastric bleeding and erosion than 3250 mg of aspirin.

5.2. Pharmacokinetic properties

Absorption

Naproxen is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are attained 2-4 hours after ingestion. Mean peak plasma concentrations of about 37 and 78 mcg/mL are achieved after doses of 250 mg and 500 mg.

Absorption tends to occur more rapidly in fasted than non-fasted subjects; however, the peak plasma concentration and area under the plasma concentration-time curve do not differ significantly. The absorption of naproxen is not adversely affected by food. Onset of pain relief can begin within 1 hour in patients taking naproxen.

Distribution

Naproxen is highly bound to plasma protein, accounting for about 99.6% at a total plasma level of 23-40 mcg/mL. Naproxen crosses the placental barrier within 20-30 minutes of oral administration to pregnant women. It also appears in breast milk at approximately 1% of the concentration in maternal plasma. The apparent volume of distribution in man is low, one measurement giving a value of 0.09 L/kg in man.

Biotransformation

After a single dose, 70% is eliminated as naproxen either unchanged (10%) or conjugated with glucuronic acid (60%). Approximately 28% of the dose undergoes 6-demethylation. 5% of the original dose, therefore, appears in the urine as the inactive metabolite 6-O-desmethylnaproxen and 22% as conjugates of this metabolite.

Elimination

Nearly all of a dose of naproxen is excreted in the urine, only 0.1-3% appears in the faeces. The renal clearance is 2-3 times the glomerular filtration rate indicating active tubular secretion is involved. Furthermore, naproxen enters breast milk achieving concentrations of approximately 1% of those in plasma.

The plasma half-life of naproxen after oral administration ranges from 12-15 hours and is not affected by dose or by continuous administration.

Other special population(s)

Renal impairment

In patients with mild to moderate renal impairment (C_{cr} 15-60 mL/min), there is little change in the pharmacokinetics of naproxen, but changes are more marked when the creatinine clearance is between 1-10 mL/min. There is a reduction in total AUC and urinary recovery. The excretion of total, free and conjugated 6-O-desmethyl naproxen is increased while that of conjugated naproxen is decreased. In patients treated with maintenance dialysis for terminal renal failure, the metabolite 6-O-desmethyl naproxen is dialysed but naproxen is not

Paediatric population

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

5.3. Preclinical safety data

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 cerevisiae* (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. List of excipients

NAXEN 250 mg tablets contain the following excipients:

Lactose monohydrate, magnesium stearate, maize starch, povidone, quinoline yellow, sodium starch glycolate, sunset yellow FCF

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months from date of manufacture

6.4. Special precautions for storage

Store at or below 30°C.

6.5. Nature and contents of container

NAXEN 250 mg tablets: HDPE bottle

Pack sizes: 100 and 500 tablets

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd

P O Box 45 027

Auckland 0651

New Zealand

Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

15 December 1983

10. DATE OF REVISION OF THE TEXT

04 September 2017

Summary table of changes

Section Changed	Summary of new information
All	Data Sheet updated to align with SmPC format
All	Data Sheet updated in line with the innovator's data sheet
4.6	Additional pregnancy warning regarding increased risk of miscarriages