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# Australian Product Information – NAPROSYN<sup>®</sup> and NAPROSYN<sup>®</sup> 500 (naproxen)

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## 1. NAME OF THE MEDICINE

Naproxen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NAPROSYN is available as a tablet containing 250 mg of naproxen.

NAPROSYN 500 is available as a tablet containing 500 mg of naproxen.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

## 3. PHARMACEUTICAL FORM

NAPROSYN is available as round yellow tablets debossed NPR LE 250 on one side and a break-bar on the other.

NAPROSYN 500 is available as oblong yellow tablets debossed NPR LE 500 on one side and break-bar on the other.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

NAPROSYN 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 ration in each individual patient, the lowest effective dose for the shortest possible duration should be used.

#### Chronic Conditions

##### ***Osteoarthritis / Rheumatoid arthritis / Ankylosing spondylitis / Chronic pain states in which there is an inflammatory component***

The dosage range of NAPROSYN is 375 mg to 1000 mg daily in two divided doses. The starting dose should not be less than 500 mg daily and may be varied stepwise within the range of 375 mg 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 NAPROSYN tablets 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 of NAPROSYN tablets 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 treatment of acute migraine headache, the recommended dose of NAPROSYN tablets is 750 mg at the first symptom of an impending headache. An additional dose of 250 mg to 500 mg can be given throughout the day if necessary, at least an hour after initial dose. The total daily dose should not exceed 1250 mg.

## Children

### *Juvenile Rheumatoid Arthritis*

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

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

## Pregnancy

See Section 4.6 FERTILITY, PREGNANCY AND LACTATION.

## 4.3 CONTRAINDICATIONS

NAPROSYN is contraindicated in patients:

- who are hypersensitive to naproxen or naproxen sodium or in whom acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory/analgesic agents induce allergic manifestations, e.g. asthma, nasal polyps, rhinitis and urticaria. Severe anaphylactic-like reactions to naproxen have been reported in such patients
- with either active, or a history of peptic or gastrointestinal ulceration, chronic dyspepsia or active gastrointestinal bleeding or perforation, related to previous NSAID therapy
- with active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding) unrelated to previous NSAIDs therapy
- under 2 years of age since safety in this age group has not been established
- with severe heart failure
- undergoing treatment of perioperative pain in setting of coronary artery surgery (CABG)
- with severe hepatic impairment
- in the 3<sup>rd</sup> trimester of pregnancy

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### Cardiovascular Thrombotic Events

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

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

### Heart Failure

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

## Gastrointestinal

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal, gastrointestinal effects such as ulcers, irritation, bleeding and perforation, which may increase with dose or duration of use, but can occur at any time without warning symptoms. Upper gastrointestinal ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 - 6 months and in about 2 - 4% 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 symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment. When gastrointestinal bleeding or ulceration occurs in patients receiving NSAIDs, treatment should be withdrawn immediately. Physicians should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

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

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

Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). The concurrent use of aspirin and NSAIDs also increase the risk of serious gastrointestinal adverse effects.

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 NAPROSYN 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 NAPROSYN concurrently. Therefore, benefits of prescribing NAPROSYN 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 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), 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 physician at the first appearance of a skin rash or other sign of hypersensitivity.

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

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

### **Anaphylactic Reactions**

Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to aspirin 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 NAPROSYN, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with NAPROSYN should have an ophthalmological examination.

### **Fluid Retention and Oedema**

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

### **Use in hepatic impairment**

As with other NSAIDs, elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. The ALT test is probably the most sensitive indicator of liver dysfunction. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled clinical trials in less than 1% of patients. Physicians and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity. A patient with symptoms and/or signs suggesting hepatic dysfunction (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms), or in whom an abnormal hepatic test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with NAPROSYN.

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.), NAPROSYN 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 reports of impaired renal function, renal failure, acute interstitial nephritis, haematuria, proteinuria, renal papillary necrosis, and occasionally nephritic syndrome associated with NAPROSYN.

NAPROSYN 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 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 NAPROSYN or other NSAIDs may cause a dose-dependant 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 NAPROSYN is usually followed by recovery to the pre-treatment state; however, serious adverse events may persist. NAPROSYN 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.

### **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**

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

### **Effects on laboratory tests**

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

NAPROSYN 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 risk 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 hydantoin, 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, 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 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 NAPROSYN therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of underlying disease.

### **Probenecid**

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

### **Methotrexate**

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

### **Beta-Blockers**

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

### **Diuretics**

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

### **Lithium**

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

### **Sodium Bicarbonate**

Sodium bicarbonate may enhance the rate of naproxen absorption.

### **Zidovudine**

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

### **ACE-Inhibitors**

Concomitant use of NSAIDs with ACE inhibitors or angiotensin receptor blockers may increase the risk of renal dysfunction, especially in patients with pre-existing poor renal function (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

### **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 NAPROSYN, 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

PREGNANCY CATEGORY: C

Naproxen is contraindicated in 3<sup>rd</sup> trimester of pregnancy.

Naproxen should not be used during the first two trimesters of pregnancy, 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.

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

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 of NSAIDs in the second or third trimester may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, 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.

NSAIDs inhibit prostaglandin synthesis and, when given during the 3<sup>rd</sup> trimester of pregnancy, may cause premature closure of the foetal ductus arteriosus (see Premature Closure of Foetal Ductus Arteriosus), foetal renal dysfunction leading to oligohydramnios and neonatal renal impairment (see Oligohydramnios and Neonatal Renal Impairment), inhibition of platelet aggregation, prolong labour and delay labour and birth. NSAID use in the 3<sup>rd</sup> trimester of pregnancy is therefore contraindicated.

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

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy.

### **Premature Closure of Foetal Ductus Arteriosus**

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

### **Oligohydramnios and Neonatal Renal Impairment**

Use of NSAIDs from about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

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

## Use in lactation

Naproxen has been found in the milk of lactating mothers at a concentration approximately 1% of that found in plasma. As the effect of naproxen in the newborn is not known, the use of NAPROSYN 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 NAPROSYN. 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 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 in post-marketing reports. The probability of a causal relationship exists between naproxen and these adverse effects.

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

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

*Haematologic:* eosinophilia, granulocytopenia, leukopenia, thrombocytopenia

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

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

*Special Senses:* hearing impairment

*Cardiovascular:* vasculitis, congestive heart failure



*General:* menstrual disorders, pyrexia (chills and fever), eosinophilic pneumonitis, anaphylactoid reactions (see Section 4.4 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, 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 Experience**

The following adverse effects have been reported with NSAIDS and NAPROSYN:

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

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

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

*Musculoskeletal and Connective Tissue Disorders:* myalgia, muscle weakness

*Renal and Urinary Disorders:* haematuria, interstitial nephritis, nephritic syndrome, renal disease, renal failure, renal papillary necrosis

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

*Reproductive System:* female infertility

*General Disorders:* oedema, thirst

*Investigations:* abnormal liver function tests, raised serum creatinine

### **Reporting 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 <https://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 sodium 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 4 hours of ingestion or following a large overdose. Forced diuresis, alkalinization of urine, haemodialysis or haemoperfusion may not be useful due to high protein binding.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

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

#### **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 2 - 4 hours, depending on food intake.

#### **Distribution**

Naproxen has a relatively small volume of distribution ( $0.09 \pm 0.03$  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 approximately 1% of that found in plasma.

### **Metabolism**

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

### **Excretion**

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

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

### **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**

Povidone

Croscarmellose sodium

Iron oxide yellow

Magnesium stearate

### **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). The expiry date can be found on the packaging.

### **6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Store below 30°C. Protect from light.

### **6.5 NATURE AND CONTENTS OF CONTAINER**

The tablets are available in PVC/aluminium blister packs of 50s.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

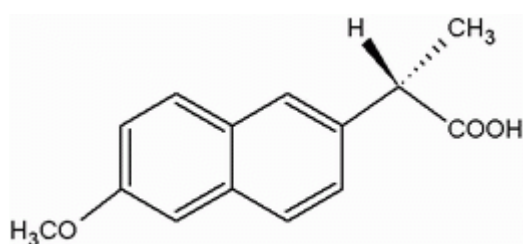
## 6.7 PHYSICOCHEMICAL PROPERTIES

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

Naproxen is a propionic acid derivative related to the arylacetic acid class of drugs. It is unrelated to salicylates and the corticosteroid hormones.

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

### Chemical structure



### CAS number

22204-53-1

## 7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription only medicine

## 8. SPONSOR

Atnahs Pharma Australia Pty Ltd

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Sydney, NSW, 2000, Australia

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## 9. DATE OF FIRST APPROVAL

24 September 1998

## 10. DATE OF REVISION

22 June 2023

### Summary table of changes

Section changed	Summary of new information
4.3	Update to Contraindications - Addition of 3rd trimester pregnancy as a contraindication
4.6	Update to Fertility, Pregnancy and Lactation - include additional information and clarity about the contraindication of NAPROXEN during pregnancy, and the risk of oligohydramnios and neonatal renal impairment with NSAID use

