Australian Product Information – ANAPROX® 550 (naproxen sodium)

1. NAME OF THE MEDICINE

Naproxen sodium

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ANAPROX 550 is available as a film-coated tablet containing 550 mg of naproxen sodium.

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

List of excipients with known effect: each film-coated tablet contains 50 mg of sodium.

3. PHARMACEUTICAL FORM

Film-coated tablet.

ANAPROX 550 is supplied as an oblong, dark blue film-coated tablet engraved "NPS 550" on one side, with a break-line on both faces.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ANAPROX 550 is indicated as an analgesic in acute migraine attacks, for the treatment of gout, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and for the relief of acute and/or chronic pain states in which there is an inflammatory component.

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.

Acute Migraine Headache

The recommended dose is 825 mg at the first symptom of an impending headache. An additional 275 mg to 550 mg dose can be given at least an hour after the initial dose, if necessary. The total daily dose should not exceed 1375 mg.

Acute Pain States with an Inflammatory Component

The recommended dose is 550 mg initially followed by 275 mg every six to eight hours as required. The total daily dose should not exceed 1375 mg.

Rheumatoid Arthritis, Osteoarthritis, Ankylosing Spondylitis and Chronic Pain States with an Inflammatory Component

The dosage range of naproxen sodium is 550 mg to 1100 mg daily in two divided doses. The starting dose should not be less than 550 mg daily. The dose may be increased gradually up to 1100 mg daily, depending on the needs of the patient.

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

ANAPROX 550 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 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
- less than 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 3rd 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 ANAPROX 550 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 ANAPROX 550 concurrently. Therefore, benefits of prescribing ANAPROX 550 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 ANAPROX 550, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with ANAPROX 550 should have an ophthalmological examination.

Sodium

A 550 mg tablet of ANAPROX 550 contains approximately 50 mg of sodium. This should be considered in patients whose overall intake of sodium must be markedly restricted.

Fluid Retention and Oedema

Peripheral oedema has been observed in some patients taking ANAPROX 550 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 ANAPROX 550.

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 sodium 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.), ANAPROX 550 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 ANAPROX 550.

ANAPROX 550 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, ANAPROX 550 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 ANAPROX 550 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 ANAPROX 550 is usually followed by recovery to the pre-treatment state; however, serious adverse events may persist. ANAPROX 550 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

ANAPROX 550 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 sodium decreases platelet aggregation and prolongs bleeding time. This effect should be considered when bleeding times are determined.

ANAPROX 550 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 sodium 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 sodium is highly bound to plasma albumin; thus naproxen sodium has a theoretical potential for interaction with other albumin-bound drugs, for example, warfarin or bishydroxycoumarin, may be displaced and induce excessively prolonged prothrombin times. Similarly, patients receiving hydantoins, sulfonamides or sulfonylureas should be observed for increased effect or toxicity (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Haematological).

Warfarin

The concurrent use of NSAIDs and warfarin has been associated with severe, 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. ANAPROX 550 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 sodium is administered. Patients on full anticoagulation therapy (e.g., heparin or dicoumarol derivatives) may be at increased risk of bleeding if given naproxen sodium 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 ANAPROX 550 therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of underlying disease.

Probenecid

Probenecid significantly prolongs the half-life of naproxen (from 14 to 37 hrs). This is associated with a decrease in conjugated metabolites and an increase in 6-0-desmethyl naproxen.

Methotrexate

Concomitant administration of naproxen sodium 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 sodium 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 sodium 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 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 ANAPROX 550, 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 3rd 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.

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 3rd 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 3rd trimester of pregnancy is therefore contraindicated.

ANAPROX 550 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, ANAPROX 550 treatment is necessary from about 20 weeks, limit ANAPROX 550 use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ANAPROX 550 treatment extends beyond 48 hours. Discontinue treatment with ANAPROX 550 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 ANAPROX 550 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 ANAPROX 550. 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. A causal relationship probably exists between naproxen sodium 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 Sys*tem: cognitive dysfunction, convulsions, paraesthesia

Dermatologic: urticaria, photosensitivity

Mouth and Throat: sore throat

General: angioneurotic oedema, hyperglycaemia, hypoglycaemia

Reproductive: female infertility

Post-Marketing Experience

The following adverse effects have been reported with ANAPROX 550:

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 effects

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

ANAPROX 550 dissociates into the naproxen anion and sodium in vivo at physiological pH.

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

After oral administration of ANAPROX 550, because of rapid and complete absorption, clinically significant plasma levels and pain relief are obtained in patients within 30 minutes of administration. Peak plasma levels are attained in 1 - 2 hours, depending on food intake.

Distribution

Naproxen has a relatively small volume of distribution (0.09 + 0.03 L/kg), which corresponds to about 10% of the body weight in humans. At therapeutic levels naproxen is greater than 99% albumin-bound.

The plasma concentration of naproxen increases proportionally with doses up to 500 mg twice daily. Larger doses result in a less than proportional increase due to accelerated renal clearance of disproportionately increased amounts of non-protein bound drug. However, whether this effect increases or decreases the toxicity of naproxen has not been established.

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

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

Metabolism

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

Elimination

Approximately 95% of the naproxen is excreted in the urine, primarily as naproxen (10%), 6-0-desmethyl naproxen (5%) or their conjugates. The rate of excretion of metabolites and conjugates has been found to coincide closely with the rate of naproxen clearance from the plasma. Small amounts, 5% or less, are excreted in the faeces.

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

Pharmacokinetics in Special Populations

Children

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

Renal Impairment

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose

Magnesium stearate

Purified water

Povidone

Purified talc

Opadry Blue YS-1R-4216 ARTG PI No. 3174

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

ANAPROX 550 is available in PVC/aluminium blister packs of 50 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

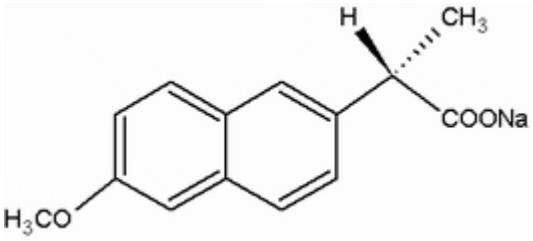
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Naproxen sodium 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 sodium is (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid, sodium salt. It has a molecular formula of $C_{14}H_{13}NaO_3$ and a molecular weight of 252.2. Naproxen sodium is an odourless, white to off-white crystalline substance. It is soluble in water.

Chemical structure



CAS number

26159-34-2

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

Ph: 1800 899 005

9. DATE OF FIRST APPROVAL

3 November 1998

10. DATE OF REVISION

02 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