New Zealand Data Sheet

Sonaflam

Naproxen sodium, 275 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Sonaflam, 275 mg, film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient
Naproxen sodium
Film-coated tablets containing naproxen sodium 275 mg.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

275 mg: oval, blue, film-coated, biconvex tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sonaflam is indicated for the treatment of:

- acute musculoskeletal disorders (such as sprains and strains, direct trauma, lumbo-sacral
  pain, cervical spondylitis, fibrositis, bursitis and tendonitis);
- dysmenorrhoea, uterine pain following I.U.D. insertion;
- dental pain;
- migraine headaches, prophylaxis and acute treatment;
- rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gout;
- juvenile arthritis

4.2 Dose and method of administration

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

Although naproxen and naproxen-sodium-containing products all circulate in the plasma as naproxen, they have pharmacokinetic differences that may affect onset of action. Onset of pain relief can begin within 30 minutes in patients taking naproxen sodium and within 1 hour in patients taking naproxen.

The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and/or adverse events.

A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients. Sonaflam is not recommended in patients with baseline creatinine clearance less than 30 mL/minute because accumulation of naproxen metabolites has been seen in patients with severe renal failure or those on dialysis.

Standard dosage

Recommended formulations
Because the sodium salt of naproxen is more rapidly absorbed, naproxen sodium is recommended for the management of acute painful conditions when prompt onset of pain relief is desired.
Sonaflam may be given orally either in fasting state or with meals and/or antacids.

Adults

Acute musculoskeletal disorders
The recommended dosage is 550mg at once (two tablets), then 275 mg three or four times daily as needed; most patients will require only seven days treatment but some patients may require up to fourteen days treatment.

Dysmenorrhoea
The recommended dosage is 550 mg (two tablets) initially followed by 275 mg three or four times daily as needed.

Post-operative pain
The recommended regimen is 550 mg (two tablets) initially, followed by 275 mg three to four times daily as needed, with a maximum daily dose after the first day of 1375 mg (five tablets).

Acute treatment of migraine
The recommended dosage is 825 mg (three tablets) at the first symptom of an impending attack. An additional 275-550 mg (one to two tablets) can be taken throughout the day, if necessary, but not within 30 minutes of administration of the initial dose. The total dose of 1375 mg (five tablets) per day should not be exceeded.

Prophylaxis of common or classical migraine
The recommended starting dose is 275 mg twice daily. Adjustment of dosage (within the range of 275 mg – 550 mg twice daily), to establish the optimum dose, should be attempted within the first 2 weeks of therapy. If evidence of efficacy is not demonstrated after 3 weeks therapy, treatment should be discontinued.

Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis
Maintenance dose is usually 550 mg per day (two tablets) taken in two doses at 12-hour intervals i.e. 275 mg usually given with the morning meal and 275 mg about 12 hours later. Dosage adjustment within the range 550-1100 mg/day (two to four tablets) maintaining 12-hourly administration may be employed.
For the patient who requires 825 mg per day (three tablets) and whose night-time pain and/or morning stiffness are most troublesome, 550 mg (two tablets) should be taken before retiring and 275 mg upon awakening. For the patient whose day-time pain and reduced mobility are most troublesome, 550 mg (two tablets) should be taken upon awakening and 275 mg upon retiring.

Acute gout
The recommended dosage is 825 mg (three tablets) at once, then 275 mg every eight hours, as needed, until the attack has passed.

Special Dosage Instructions

Dose in Children
Safety and effectiveness in children below the age of 2 years have not been established.

Juvenile arthritis
Naproxen sodium has been reported to be effective in the treatment of juvenile arthritis in children over five years of age at a dosage of 10 mg/kg/day. As safety and efficacy studies in children are not yet complete, naproxen sodium is not recommended for use in other indications in children under sixteen years of age.

4.3 Contraindications

Naproxen sodium is contraindicated in patients who have had allergic reactions to prescription as well as to over-the-counter products containing naproxen or naproxen sodium. It is also contraindicated in patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic medicines induce the syndrome of asthma, rhinitis and nasal polyps. Both types of reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.

Naproxen sodium is contraindicated in patients with active or a history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Naproxen sodium is also contraindicated in patients with active, or a history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

As with other NSAIDs, naproxen sodium is contraindicated in patients with severe heart failure.

Naproxen sodium is relatively contraindicated in liver dysfunction.

Naproxen sodium is contraindicated in children under 2 years of age since safety in this age group has not been established.

4.4 Special warnings and precautions for use

General
The use of naproxen sodium with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see Dosage and Administration; Gastrointestinal effects and Cardiovascular and cerebrovascular effects below).

Cardiovascular and cerebrovascular effects
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 or cardiovascular risk factors may also be at greater risk.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen sodium after careful consideration. Similar

consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking). To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Dosage and Administration).

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.

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.

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). Although data suggest that the use of naproxen (1000 mg per day) may be associated with a lower risk; some risk cannot be excluded.

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.

Gastrointestinal effects

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal, gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper gastrointestinal ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events e.g. elderly, debilitated patients, those with a history of serious gastrointestinal events, smoking and alcoholism.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis; Crohn's disease) as their condition may be exacerbated. Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding) particularly in the initial stages of treatment. When gastrointestinal bleeding or ulceration occurs in patients receiving NSAIDs, treatment should be withdrawn immediately. Physicians should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

Studies to date have not identified any subset of patients not at risk of developing peptic ulcer and bleeding. However, the elderly have an increased frequency of adverse 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.

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.

Patients with risk factors should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant low dose aspirin or other medicines likely to increase gastrointestinal toxicity.

Precautions related to elderly patients
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. In elderly patients, the clearance is reduced. Use of the lower end of the dosage range is recommended (see Dosage and Administration).

Skin reactions
NSAIDs may very rarely cause cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their physician at the first appearance of a skin rash or any other sign of hypersensitivity.

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, other non-steroidal anti-inflammatory medicines 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.

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

As with other NSAIDs, naproxen sodium 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 renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of naproxen sodium 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 of this reaction are those with impaired renal function, hypovolaemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and the elderly. Discontinuation of naproxen sodium is usually followed by recovery to the pretreatment state. Naproxen sodium should be used with great caution in such patients and the monitoring of serum creatinine and/or creatinine clearance is advised. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

Naproxen sodium is not recommended in patients with baseline creatinine clearance less than 30 mL/min because accumulation of naproxen metabolites has been seen in such patients.
Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

Hepatic effects
As with other non-steroidal anti-inflammatory medicines, elevations of one or more liver function tests may occur. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. Severe hepatic reactions, including jaundice and hepatitis (some cases of hepatitis have been fatal) have been reported with this medicine as with other non-steroidal anti-inflammatory medicines. Cross reactivity has been reported.

Haematological
Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.
Patients who have coagulation disorders or are receiving therapy that interferes with haemostasis should be carefully observed if naproxen sodium is administered. Patients at high risk of bleeding and those on full anticoagulation therapy (e.g. dicoumarol derivatives) may be at increased risk of bleeding if given naproxen sodium concurrently.

Antipyretic effects
The antipyretic and anti-inflammatory activities of naproxen sodium may reduce fever and inflammation, thus diminishing their utility as diagnostic signs.

Steroids
If steroid dosage is reduced or eliminated during 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 arthritis.

Ocular effects
Studies have not shown changes in the eye attributable to naproxen sodium administration. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilloedema, have been reported in users of NSAIDs including naproxen sodium, although a cause-and-effect relationship cannot be established;

accordingly, patients who develop visual disturbances during treatment with naproxen sodium should have an ophthalmological examination.

Sodium
A 275 mg tablet of Sonaflam contains 25 mg (about 1 mEq) of sodium, so the total amount of sodium ingested with the maximum recommended daily dose is 125 mg, about 16% of the 800 mg of sodium permitted on a severely sodium-restricted diet.

Sodium/fluid retention in cardiovascular conditions and peripheral oedema
Although sodium retention has not been reported in metabolic studies with naproxen sodium, patients with compromised cardiac function may be at greater risk when taking naproxen sodium, 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.

Peripheral oedema has been observed in some patients taking naproxen sodium or other NSAIDs.

4.5 Interaction with other medicines and other forms of interaction

Combination with other NSAIDs
The combination of naproxen sodium and other NSAIDs is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Concomitant administration of antacid or cholestyramine can delay the absorption of naproxen, but does not affect its extent. Concomitant administration of food can delay the absorption of naproxen, but does not affect its extent.

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound medicines such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs and aspirin. Patients simultaneously receiving naproxen sodium and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Although no significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants, NSAIDs may enhance the effects of anti-coagulants such as warfarin. Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

Caution is advised when probenecid is administered concurrently, since increases in naproxen plasma concentrations and increased half-life of naproxen have been reported with this combination.

Caution is advised when methotrexate is administered concurrently, since naproxen and other prostaglandin synthesis-inhibiting medicines have been reported to reduce the clearance of methotrexate, and thus possibly enhance its toxicity.

Naproxen sodium can reduce the anti-hypertensive effect of beta blockers.

As with other non-steroidal anti-inflammatory medicines, naproxen may inhibit the natriuretic effect of frusemide.

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

It is suggested that naproxen therapy should be temporarily discontinued 48 hours before adrenal function tests are performed, because naproxen may artefactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen sodium therapy may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

There is an increased risk of gastrointestinal bleeding (see Warnings and Precautions) when anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

4.6 Fertility, pregnancy and lactation

Fertility
The use of naproxen sodium, as with any medicine known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of naproxen sodium should be considered.

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo/fetal 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, Sonaflam should not be given unless clearly necessary. If Sonaflam 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.

As with other medicines of this type, naproxen produces delay in parturition in animals and also affects the human foetal cardiovascular system (closure of ductus arteriosus). Therefore, naproxen sodium should not be used during pregnancy unless clearly needed.

Labour and delivery
Naproxen sodium 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.

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

4.7 Effects on ability to drive and use machines

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of naproxen sodium. If patients experience these or similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

4.8 Undesirable effects

The following adverse events have been reported with NSAIDs and with naproxen:

Gastrointestinal: Peptic ulcers, perforation or gastrointestinal bleeding sometimes fatal, particularly in the elderly (see Warnings and Precautions), 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 (see Warnings and Precautions), pancreatitis, gastritis

Infections: aseptic meningitis

Blood and lymphatic system disorders: agranulocytosis, aplastic anaemia, eosinophilia, haemolytic anaemia, leucopaenia, thrombocytopaenia

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 has been reported in association with NSAID treatment, congestive heart failure

Vascular disorders: hypertension, vasculitis

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example, myocardial infarction or stroke). Although data suggests that the use of naproxen (1000 mg per day) may be associated with a lower risk, some risk cannot be excluded.

Respiratory, thoracic and mediastinal disorders: dyspnoea, pulmonary oedema, asthma, eosinophilic pneumonitis

Hepatobiliary disorders: hepatitis (some cases of hepatitis have been fatal), jaundice

Skin and subcutaneous tissue disorders: ecchymoses, itching (pruritus), purpura, skin eruptions, sweating, alopecia, epidermal necrolysis, very rarely toxic epidermal

necrolysis, erythema multiforme, bullous reactions including Stevens-Johnson syndrome, 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 adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms and signs
Significant naproxen overdosage may be characterised by dizziness, drowsiness, epigastric pain, abdominal discomfort, indigestion, nausea, transient alterations in liver function, hypoprothrombinaemia, renal dysfunction, metabolic acidosis, apnoea, disorientation or vomiting. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, but it is not clear whether or not these were naproxen related.

Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may occur after the ingestion of NSAIDs, but are rare.

Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Treatment
Patients should be managed by symptomatic and supportive care following NSAIDs overdose. There are no specific antidotes. Prevention of further absorption (e.g. activated charcoal) may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinisation of urine, haemodialysis, or haemoperfusion may not be useful due to high protein binding.

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: Propionic acid derivatives **ATC code**: MO1AE02

Naproxen sodium is a non-steroidal anti-inflammatory (NSAID) with analgesic, anti-inflammatory and antipyretic properties. The onset of pain relief is more rapid with naproxen sodium than with naproxen, therefore naproxen sodium is recommended for the management of acute painful conditions.

Naproxen is a propionic acid derivative related to the arylacetic acid class of medicines. The chemical name of naproxen is (+)-6-methoxy-alpha-methyl-2-naphthaleneacetic acid. It is an odourless, white to off-white crystalline substance. It is lipid soluble, practically insoluble in water at low pH and freely soluble in water at high pH. Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

Mechanism of action
Naproxen has been shown to have striking anti-inflammatory properties when tested in human clinical studies and classical animal test systems. In addition, it has marked analgesic and antipyretic actions. It exhibits its anti-inflammatory effects even in adrenalectomised animals, indicating that its action is not mediated through the pituitary axis. It inhibits synthesis of prostaglandins as with other similar agents; however, the exact mechanism of its anti-inflammatory action is not known.

5.2 Pharmacokinetic properties

Absorption
Naproxen and naproxen sodium are rapidly and completely absorbed from the gastrointestinal tract after oral administration. Naproxen sodium is more rapidly absorbed than naproxen. Concomitant administration of food can delay the absorption of naproxen and naproxen sodium, but does not affect its extent.

Naproxen sodium tablets: After oral administration of naproxen sodium tablets, 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. The difference in rates between the two products is due to the increased aqueous solubility of the sodium salt of naproxen.

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

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

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

Metabolism
Naproxen is extensively metabolised in the liver to 6-0-desmethyl naproxen.

Elimination
Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%), or their conjugates (66 - 92%). The rate of excretion of metabolites and conjugates has been found to coincide closely with the rate of naproxen disappearance from the plasma.

Small amounts, 3% or less, are excreted in the faeces.

The clearance of naproxen is approximately 0.13 mL/min/kg. The elimination half-life of naproxen is approximately 14 hours and is independent of the chemical form or the formulation.

Pharmacokinetics in special populations

Renal impairment
Given that naproxen and its metabolites are primarily excreted by the kidney, the potential exists for accumulation in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. In patients who are severely renally impaired (creatinine clearance <10 mL/min), there is higher clearance of naproxen than estimated from the degree of renal impairment alone.

Children
The pharmacokinetic profile of naproxen in children aged 5 - 16 years is similar to that in adults 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), Saccharomyces cerevisisae (1 cell line), and mouse lymphoma tests.

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

Teratogenicity
Naproxen was not teratogenic when administered orally at doses of 20mg/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
Core: Silicon dioxide, maize starch, povidone, purified talc, magnesium stearate, crospovidone.
Coating: Opadry blue

6.2 Incompatibilities
None known.

6.3 Shelf life
36 months. This medicine must not be used after the expiry date shown on the pack.

6.4 Special precautions for storage
Store at or below 25°C.

6.5 Nature and contents of container
Sonaflam 275 mg film-coated tablets are available in blister packs of 12, 24 and 120. (Not all pack sizes may be available)

7. MEDICINE SCHEDULE
120 tablet pack: Prescription Medicine
12 and 24 tablet pack: Pharmacy Medicine

8. SPONSOR
Multichem NZ Ltd
8 Apollo Drive
Rosedale
North Shore City 0632
Auckland
Telephone: (09) 488 0330

9. DATE OF FIRST APPROVAL
03 May 2007

10. DATE OF REVISION OF THE TEXT
18 July 2017

SUMMARY TABLE OF CHANGES

DATE	CHANGE
18 July 2017	Update to SPC-style format; Update to MARC recommendations re: spontaneous abortion with NSAIDs