PACK INSERT FOR SINGAPORE

Synflex®

ATNAHS

Naproxen sodium

Non-steroidal anti-inflammatory agent

Composition
Active ingredient: naproxen sodium.

Synflex tablets: film-coated tablets containing naproxen sodium 275 mg.

Excipients:
Microcrystalline cellulose, povidone K29/32, talc, magnesium stearate, purified water, opadry (YS-1-4215/16).

Synflex 275 mg film-coated tablets are oval, light blue with markings NPS 275 on one side.

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

Naproxen is a propionic acid derivative related to the arylacetic acid class of drugs. 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.

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.

Pharmacokinetics
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.

After oral administration of Synflex 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 1/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 feces.

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

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

Indications
Synflex (naproxen sodium) is indicated in the relief of mild to moderate pain including post partum pain, pain following IUD insertion, post-operative pain and pain due to orthopedic surgery, for the treatment of primary dysmenorrhea and for the relief (prophylaxis) of migraine headache. It is also indicated for the treatment of the signs and symptoms of mild to moderately severe, acute or chronic, musculoskeletal and soft tissue inflammation and acute gout.

Dosage and administration
General
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. Synflex is not recommended in patients with baseline creatinine clearance less than 20 ml/minute because accumulation of naproxen metabolites has been seen in such patients.

Recommended formulations
Because the sodium salt of naproxen is more rapidly absorbed, Synflex is recommended for the management of acute painful conditions when prompt onset of pain relief is desired.

Synflex may be given orally either in fasting state or with meals and/or antacids.

Dose in adults
Analgesia / Dysmenorrhea / Acute musculoskeletal conditions/ Acute pain states in which there is an inflammatory component:

Because the sodium salt of naproxen is more rapidly absorbed, Synflex is recommended for the management of acute painful conditions when prompt onset of pain relief is desired.

The recommended starting dose is Synflex 550 mg followed by Synflex 275 mg every 6-8 hours as required. The total daily dose should not exceed 1375mg.

Acute gout: The recommended starting dose is 825 mg of Synflex followed by 275 mg every 8 hours as needed.

Migraine: For treatment of acute migraine headache, the dose is Synflex 825 mg at the first symptom of an impending attack. An additional dose of Synflex 275 mg to 550 mg can be taken throughout the day, if necessary, but not before half an hour after the initial dose. The total daily dose should not exceed 1375mg.

For prophylaxis of migraine headache, the dose of Synflex is 550 mg twice daily. If no improvement is seen within 4-6 weeks, the drug should be discontinued.

Dose in children
Synflex is not recommended for use in children under 16 years of age.

Contraindications
All naproxen products are 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 nonsteroidal anti-inflammatory/ analgesic drugs 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. All products containing naproxen or naproxen sodium are CONTRAINDICATED in patients with active peptic ulceration or active gastrointestinal bleeding.

Products containing naproxen or naproxen sodium are contraindicated in children under 2 years of age since safety in this age group has not been established.

Warnings
Risk of GI ulceration, bleeding and perforation with NSAIDs
Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without symptoms, in patients treated with NSAID therapy. Although minor GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Precautions
Gastrointestinal ulceration, bleeding and perforation
Gastrointestinal mucosal injury may occur. Serious gastrointestinal toxicity, such as gastrointestinal irritation, bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAIDs including naproxen therapy. Studies to date have not identified any subset of patients not at risk of developing peptic ulcer and bleeding. Postmarketing experience with naproxen and with other NSAIDs suggests that there may be a greater risk of gastrointestinal ulceration, bleeding and perforation in elderly and debilitated patients, who seem to tolerate ulceration or bleeding less well than others. Most of the fatal gastrointestinal events associated with non-steroidal anti-inflammatory drugs occurred in this patient population.

In patients with a history of gastrointestinal disease, Synflex should be given under close supervision. Open studies in patients with rheumatoid arthritis who had upper gastrointestinal dysfunction and/or were intolerant of other commonly used NSAIDs indicated that naproxen is generally well tolerated. As with other nonsteroidal anti-inflammatory drugs, the incidence and severity of gastrointestinal complications may increase with increasing dose and duration of treatment with Synflex.

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

As with other NSAIDs, naproxen-containing products 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 where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of naproxen-containing products 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, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor blockers and the elderly. Discontinuation of naproxen-containing products is usually followed by recovery to the pretreatment state. Naproxen-containing products 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 in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

Naproxen-containing products are not recommended in patients with baseline creatinine clearance less than 20 ml/min because accumulation of naproxen metabolites has been seen in such patients.

Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

Hematological
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 drug therapy that interferes with hemostasis should be carefully observed if naproxen-containing products are 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-containing products concurrently.

Anaphylactic (anaphylactoid) 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 drugs or naproxen-containing products. They may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

Bronchospasm may be precipitated in patients suffering from, or with a history of, asthma or allergic disease or aspirin sensitivity.

Hepatic effects
As with other non-steroidal anti-inflammatory drugs, 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 drug as with other non-steroidal anti-inflammatory drugs. Cross reactivity has been reported.

Antipyretic effects
The antipyretic and anti-inflammatory activities of naproxen 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 administration. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilledema, have been reported in users of NSAIDs including naproxen, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with naproxen-containing products should have an ophthalmological examination.

Driving and operating machinery
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.

Sodium
A 275 mg tablet of Synflex contains approximately 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.

Edema
Peripheral edema has been observed in some patients. Although sodium retention has not been reported in metabolic studies, it is possible that patients with questionable or compromised cardiac function may be at greater risk when taking naproxen.

Cardiovascular and cerebrovascular effects
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 and long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg/d) may be associated with a lower risk, some risk cannot be excluded.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Precautions related to elderly patients
Elderly patients may be at a greater risk of experiencing undesirable effects than younger patients. In elderly patients the clearance is reduced. Use of the lower end of the dosage range is recommended (see Dosage and administration).

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

Pregnancy, nursing mothers
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/Neonatal Renal Impairment
Use of NSAIDs, including naproxen at 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 treatment is necessary between about 20 weeks and 30 weeks gestation, limit naproxen use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if naproxen treatment extends beyond 48 hours. Discontinue naproxen if oligohydramnios occurs and follow up according to clinical practice.

Therefore, naproxen should not be used during pregnancy unless clearly needed.

Labour and delivery
Naproxen-containing products are not recommended in labour and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

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 drugs on neonates, use in nursing mothers is not recommended.

Undesirable effects
The following are the adverse events observed most frequently in association with Synflex:
Gastrointestinal: inflammation, bleeding (sometimes fatal, particularly in the elderly), ulceration, perforation and obstruction of the upper or lower gastrointestinal tract, abdominal pain, constipation, diarrhea, dyspepsia, heartburn, nausea, gastritis, stomatitis, exacerbation of ulcerative colitis and Crohn's disease.

Central nervous system: dizziness, drowsiness, headache, lightheadedness, vertigo.

Dermatologic: ecchymoses, itching (pruritus), purpura, skin eruptions, sweating.

Special senses: hearing disturbances, tinnitus, visual disturbances.

Cardiovascular: dyspnea, edema, palpitations.

General: thirst.

The following adverse events have also been reported:
Gastrointestinal: abnormal liver function tests, colitis, esophagitis, hematemesis, hepatitis (some cases of hepatitis have been fatal), jaundice, melena, pancreatitis, vomiting.

Renal: hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine.

Hematological: agranulocytosis, aplastic anemia, eosinophilia, hemolytic anemia, leukopenia, thrombocytopenia.

Central nervous system: aseptic meningitis, cognitive dysfunction, convulsions, depression, dream abnormalities, inability to concentrate, insomnia, malaise, myalgia, muscle weakness.

Dermatologic: alopecia, epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, skin rashes, SLE, Stevens-Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), urticaria, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda ("pseudoporphyria") or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Special senses: hearing impairment.

Cardiovascular: congestive heart failure, hypertension, pulmonary edema, vasculitis. Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and 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/d) may be associated with a lower risk some risk cannot be excluded.

Respiratory: asthma, eosinophilic pneumonitis.

General: anaphylactoid reactions, angioneurotic edema, pyrexia.

Special senses: corneal opacity, papillitis, retrobulbar optic neuritis and papilledema.

Interactions
Concomitant administration of antacid orcholestyramine 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 drugs such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs and aspirin. Patients simultaneously receiving the drug and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants, however caution is advised since interactions have been seen with other nonsteroidal agents of this class, the free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function.

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 drugs have been reported to reduce the clearance of methotrexate, and thus possibly enhance its toxicity.

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

As with other non-steroidal anti-inflammatory drugs, 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 Synflex 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, Naprosyn or Synflex therapy may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

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

Overdosage
Significant naproxen overdosage may be characterised by dizziness, drowsiness, epigastric pain, abdominal discomfort, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Because Synflex 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.

Should a patient ingest a large amount of naproxen-containing products, accidentally or purposefully, the stomach should be emptied and the usual supportive measures employed. Animal studies indicate that the prompt administration of 50-100 g of activated charcoal as an aqueous slurry over 15 minutes within 2 hours of the overdose would tend to reduce markedly the absorption of the drug. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

Special remarks
Incompatibilities
None known.

Stability and storage conditions
Protect from light.
This medicine must not be used after the expiry date (EXP) shown on the pack. See also outer pack for storage remark.

Packs
Tablets 275 mg 100
Medicine: keep out of reach of children

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