NAPREX

Tablets & Suppositories

Composition

Naprex Suppositories
Each suppository contains Naproxen 500 mg.

Naprex 250 Tablets
Each tablet contains Naproxen 250 mg

Naprex 500 Tablets
Each tablet contains Naproxen 500 mg

Action

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

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

Naproxen is capable of providing benefit to patients suffering from: rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendonitis and bursitis and acute gout. It is comparable to aspirin and indomethacin in controlling disease activity with less frequent and milder side effects. Clinical improvement induced by naproxen is not dependent on age, sex, severity, or duration of disease.

Naprex suppositories are particularly useful when relief of night pain and early morning stiffness is desired and when oral administration is not feasible for whatever reason.

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

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

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

After a single dose, 70% eliminated as naproxen either unchanged (10%) or conjugated with glucuronic acid (60%). Approximately 28% of the dose undergoes 6-demethylation. 5% of the original dose, therefore, appears in the urine as the inactive metabolite 6-0-desmethylnaproxen and 22% as conjugates of this metabolite. Nearly all of a dose of naproxen excreted in the urine, only 0.1-3% appears in the faeces. The renal clearance is 2-3 times the glomerular filtration rate indicating active tubular secretion is involved.

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

In patients with mild to moderate renal impairment (C_{cr} 15-60 ml/min), there is little change in the pharmacokinetics of naproxen, but changes are more marked when the creatinine clearance is between 1-10 ml/min. There is a reduction in total AUC and urinary recovery. The excretion of total, free, and conjugated 6-0-desmethylnaproxen increased while that of conjugated naproxen decreased. In patients treated with maintenance dialysis for terminal renal failure, the metabolite 6-0-desmethylnaproxen is dialyzed but naproxen is not.

Indications

- Relief of the signs and symptoms of rheumatic diseases including osteoarthritis, ankylosing spondylitis and rheumatoid arthritis, both in the treatment of acute flares and in the long-term management of the disease. Juvenile rheumatoid arthritis. Periarticular and musculoskeletal disorders relief of pain in bursitis, tendinitis, synovitis, tenosynovitis and lumbago.
- Relief of pain, swelling, tenderness and fever in acute gouty arthritis.
- Relief of the symptoms of primary dysmenorrhea.

Contraindications

- Hypersensitivity to Naproxen or Naproxen sodium.
- Because the potential exists for cross-sensitivity reactions, Naproxen is also contraindicated in patients in whom aspirin or other NSAID's induce serious allergic manifestations, such as asthma, rhinitis or nasal polyps.
- Naproxen suppositories are contraindicated in patients with a history of proctitis or recent rectal bleeding.

Warnings

Naproxen should not be given to patients with active peptic ulcer. In other patients with a history of gastrointestinal disease, Naproxen should be given under close supervision. Serious gastrointestinal adverse reactions can occur at any time in patients on NSAID therapy. The cumulative incidence of serious gastrointestinal adverse reactions, including gross bleeding and perforation increases approximately linearly with duration of use of Naproxen (or other NSAID's). As with other NSAID's, there is probably a higher risk of adverse reactions associated with the use of higher doses of this drug.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. However, elderly and debilitated patients tolerate gastrointestinal ulceration or bleeding less well than other individuals do. Most of the fatal gastrointestinal events associated with NSAID's have occurred in this population of patients. Studies to date are inconclusive concerning the relative risk of various NSAID's in causing such reactions.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has been reported, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with this drug. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with this drug, as with other NSAID's, although such reactions are rare, if abnormal liver tests persist or worsen, clinical signs and symptoms consistent with liver disease develop, or systemic manifestations occur (e.g. eosinophilia, rash, etc.), use of this drug should be discontinued.

Pregnancy

Category B (1st and 2nd trimesters)

Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category D (If used in 3rd trimester)

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing Mothers
Naproxen anion has been found in the milk of lactating women. Therefore, use in nursing mothers should be avoided.

Paediatric Use
Rheumatoid arthritis in children over 5 years of age is the only pediatric indication for which other dosage forms of Naproxen approved.
There are no adequate data on the effectiveness or dose response for other pediatric indications.

Elderly Use
Studies indicate that although total plasma concentration of Naproxen is unchanged, the unbound plasma fraction of Naproxen increased in the elderly. The implication of this finding for Naproxen dosing is unknown. As with other drugs used in the elderly, it is prudent to use the lowest effective dosage.

Anaphylactic Reactions
Anaphylactic reactions usually occur in patients with a history of hypersensitivity to aspirin, other NSAID's or Naproxen. They may however also occur in patients without known previous exposure or hypersensitivity to these agents. Both types of anaphylactic reactions have the potential for being fatal.

Adverse Reactions
Naproxen is generally well tolerated. However, the following adverse reactions have been reported.

Gastrointestinal
Heartburn, nausea, abdominal pain, dyspepsia, constipation, diarrhea, stomtatitis.

Central Nervous System
Headache, dizziness, drowsiness, light-headedness, vertigo.

Dermatological
Itching, skin eruptions, ecchymoses, sweating.

Cardiovascular
Edema, palpitations, dyspnea.

Special Senses
Tinnitus, hearing and visual disturbances.

Adverse Reactions of lower incidence (less than 1%) include convulsions, peptic ulceration with bleeding and/or perforation, gastrointestinal bleeding and/or perforation, colitis, vomiting, jaundice, hepatitis, nephropathy, hematuria, thrombocytopenia, granulocytopenia, inability to concentrate, cognitive dysfunction, depression, insomnia, alopecia, erythema multiforme, Stevens-Johnson syndrome, epidermal necrolysis, photosensitivity reactions (including rare cases in which skin resembles perphyria cutanea tarda or epidermolysis bullosa), vasculitis and eosinophilic pneumonitis. Anaphylactic reactions, whether of the true allergic type or the pharmacological idiosyncratic (e.g. aspirin syndrome) type, usually (but not always) occur in patients with a known history of such reactions.

The following have also been reported rarely: fatal hepatitis, hyperkalemia, renal disease (including but not limited to glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome, and renal failure), ulcerative stomtatitis.

Other reactions have been reported in circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility of a causal relationship cannot be excluded. Therefore, these observations listed below, to serve as alerting information to the physician.

Hematological
Agranulocytosis, aplastic anemia, hemolytic anemia.

Dermatological
Urticaria.

Gastrointestinal
Non-peptic gastrointestinal ulceration, ulcerative stomtatitis.

General
Angioneurotic edema, hyperglycemia, hypoglycemia, aseptic meningitis.

Precautions

Naproxen should not be used concomitantly with the related drug Naproxan (Naproxen sodium), since they both circulate in plasma as the Naproxen anion.

In patients with a history of gastrointestinal tract disease, Naproxen usage should be carefully monitored. Although Naproxen has been found to be better tolerated by patients exhibiting dyspepsia with similar agents, the possibility of peptic ulceration and/or episodes of gastrointestinal bleeding with Naproxen usage should be borne in mind.

Patients with initial hemoglobin values of 10 grams or less who are to receive, long-term therapy should have hemoglobin values determined frequently.

Peripheral edema has been observed in some patients receiving Naproxen. Although sodium retention has not been found in metabolic studies with this drug, as with other NSAID's, caution is required in patients with compromised cardiac function. Patients experiencing drowsiness, vertigo or depression during Naproxen therapy should be warned that their ability to perform potentially hazardous tasks requiring mental alertness or physical coordination, such as driving a vehicle or operating machinery, may be impaired.

Studies to date have not shown changes in the eye attributable to Naproxen administration. However, because of adverse findings in animal studies with drugs of this class, it is recommended that ophthalmological studies be carried out within a reasonable period after starting Naproxen therapy. These studies should be repeated at periodic intervals thereafter, if the drug is to be used for an extended period. The antipyretic and anti-inflammatory activities of Naproxen may reduce fever and inflammation, thereby diminishing their utility as diagnostic signs.

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 is administered. Patients on full anticoagulation therapy (e.g. heparin or dicumarol derivatives) may be at increased risk of bleeding if given Naproxen concurrently. Thus, the benefits should be weighed against these risks.

Impaired Renal Function
Since Naproxen and its metabolites are eliminated to a large extent (95%) by urinary excretion via glomerular filtration, this drug should be used with particular caution in patients with significantly impaired renal function. When used in such patients, it is recommended to monitor their serum

creatinine and/or creatinine clearance. In such cases, a reduction in daily dosage should be considered, to avoid the possibility of excessive drug accumulation.

Naproxen should not be used chronically in patients with a baseline creatinine clearance less than 20 ml/min.

Certain patients, specifically those where renal blood flow is compromised, such as in extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure, and pre-existing renal disease, should have renal function assessed before and during Naproxen therapy. Some elderly patients, in whom impaired renal function may be expected, could also fall within this category. The lowest effective dosage should be considered, to avoid the possibility of excessive accumulation of Naproxen metabolites in these patients.

Impaired Hepatic Function
Chronic alcoholic liver disease, and probably other forms of cirrhosis reduce the total plasma concentration of Naproxen, but the plasma concentration of unbound Naproxen is increased. The implication of this finding for Naproxen dosing is unknown, but it is prudent to use the lowest effective dosage.

As with other NSAID's, borderline elevations of one or more liver tests may occur. Symptoms and/or signs suggesting liver dysfunction or the appearance of abnormal liver tests require periodic liver evaluation during therapy with this drug.

Drug Interactions

Drug Interactions caused by Drug Displacement
Because of its affinity for protein, Naproxen may displace other drugs (such as sulphonamides, sulfonylureas, hydantoins, coumarin anticoagulants, and methotrexate) from their protein-binding sites. Patients should be observed for signs of overdosage to these drugs when receiving them concomitantly with Naproxen.

Patients on full anticoagulation therapy (e.g. heparin or dicumarol derivatives) may be at increased risk of bleeding if given Naproxen concomitantly.

Naproxen/ ß-Blockers
As with other NSAID's, the antihypertensive effect of propranolol and other ß-blockers may be reduced.

Naproxen/ Angiotensin Converting Enzyme (ACE) Inhibitors
As with other NSAID's, Naproxen may increase the risk of renal impairment associated with the use of ACE inhibitors.

Naproxen/ Probenecid
Concurrent administration with probenecid increases Naproxen anion plasma levels and extends its plasma half-life significantly.

Naproxen/ Lithium
Concurrent administration may cause inhibition of lithium renal clearance, leading to an increase in plasma lithium concentration.

Naproxen/ Furosemide
The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class.

Naproxen/ Methotrexate
Caution should be exercised when Naproxen and methotrexate are administered concomitantly, because Naproxen has been reported, along with other NSAID's, to reduce the tubular secretion of methotrexate in an animal model, and thus possibly enhance its toxicity.

Naproxen/ Zidovudine
In vitro studies have shown that Naproxen may interfere with the metabolism of zidovudine, resulting in higher zidovudine plasma levels. Therefore, consideration should be given to reducing zidovudine doses to avoid the potential of increased side effects associated with increased zidovudine plasma levels.

Diagnostic Interference
Since Naproxen may interfere with some tests for 17-ketogenic steroids, it is suggested that Naproxen therapy be temporarily discontinued 72 hours before adrenal function tests are performed.

Naproxen may also interfere with some urinary assays of 5-hydroxyindoleacetic acid.

Dosage and Administration

Rheumatic Diseases
The recommended daily dosage is 500 mg or 1 gram, taken as a single dose in the morning or in the evening. Alternatively, 250 mg or 500 mg may be taken twice daily at 12-hour intervals, morning and evening.
In patients who tolerate lower doses well, and have no history of gastrointestinal disease, the dosage may be increased to 1,500 mg/day for flare-ups or acute exacerbations of disease for no longer than 2 weeks. Increased gastrointestinal side effects have been reported with these higher dosages.

Juvenile Rheumatoid Arthritis
In children over 5 years of age, the recommended dosage is 10 mg/kg body weight/day taken in 2 doses at 12-hour intervals.

Periarticular and Musculoskeletal Disorders
500 mg initially, followed by 250 mg every 8-12 hours.

Acute Gouty Arthritis
750 mg initially, followed 8 hours later by 500 mg and thereafter by 250 mg at 8-hour intervals, until the attack has passed.

Primary Dysmenorrhea
500 mg initially, at the onset of menstrual pain, followed by 250 mg every 6 hours until symptoms have subsided, up to a total of 1,250 mg daily.

Over Dosage

Manifestations
Significant over dosage may be characterized by drowsiness, heartburn, indigestion, and nausea or vomiting. A few patients have experienced seizures, but it is not clear whether they were Naproxen-related. No evidence of toxicity or late sequelae has been reported 5-15 months after ingestion of doses of up to 3 grams/day, for 3-7 days. One patient ingested a single dose of 25 grams of Naproxen, and experienced mild nausea and indigestion. It is not known what dose of the drug would be life threatening.

Treatment
Should a patient ingest a large quantity of Naproxen, accidentally or deliberately, the stomach may be emptied and usual supportive measures employed. Animal studies indicate that the prompt administration of activated charcoal, in adequate amounts, tends to markedly reduce the absorption of the drug. It is not known if the drug is dialyzable.

Presentation

Naprex 500 mg Suppositories
Box of 6 suppositories.

Naprex 250 mg Tablets
Box of 20 tablets.

Naprex 500 mg Tablets
Box of 8 tablets.