

NAPROXAN

Tablets

Composition

Each tablet contains Naproxen sodium 275 mg.

Action

Naproxen sodium, the active principle of Naproxan, has been developed as an analgesic because it is more rapidly absorbed than Naproxen.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The Naproxen anion inhibits prostaglandin synthesis, but beyond this, its mode of action is unknown.

By virtue of its prostaglandin synthetase inhibitory activity, Naproxen has proved valuable in markedly decreasing uterine contractility in primary dysmenorrhea, thus offering relief from the associated pain and discomfort.

Pharmacokinetics

Naproxen sodium is freely soluble in water, and is rapidly and completely absorbed from the gastrointestinal tract. Because of this rapid and complete absorption, significant plasma levels and onset of pain relief obtained in patients within 20 minutes of administration. Peak plasma levels of Naproxen anion attained at 1-2 hours, depending on food intake, with steady state conditions normally achieved after 4-5 doses. The mean biological half-life of the anion in humans is approximately 13 hours, and at therapeutic levels it is greater than 99% albumin bound.

Approximately 95% of a given dose is excreted in the urine, primarily as Naproxen, 6-O-desmethylnaproxen or their conjugates. The rate of excretion has been found to coincide closely with the rate of drug disappearance from the plasma. The drug does not induce metabolizing enzymes.

Indications

- Relief of mild to moderate pain, and for the treatment of primary dysmenorrhea.
- Treatment of the signs and symptoms of mild to moderately severe acute musculoskeletal and soft tissue inflammation, such as bursitis, tendinitis, synovitis, tenosynovitis and lumbago.

Contraindications

- Hypersensitivity to Naproxen sodium or Naproxen.
- 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.

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

Apart from the approved use of Naproxen in juvenile rheumatoid arthritis in children over 5 years of age, 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 is 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, however, may 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, stomatitis.

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 porphyria 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 stomatitis.

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 are listed below, to serve as alerting information to the physician.

Hematological

Agranulocytosis, aplastic anemia, hemolytic anemia.

Dermatological

Urticaria.

Gastrointestinal

Non-peptic gastrointestinal ulceration, ulcerative stomatitis.

General

Angioneurotic edema, hyperglycemia, hypoglycemia, aseptic meningitis.

Precautions

Naproxen sodium should not be used concomitantly with the related drug Naproxen, 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. Since each Naproxen sodium tablet contains approximately 25 mg (about 1 mEq) of sodium, this should be taken into account in patients whose overall intake of sodium must be markedly restricted. Naproxen should therefore be used with caution in patients with fluid retention, hypertension or heart failure.

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, might 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 largely (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, reduces 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, sulfonyleureas, hydantoin, coumarin anticoagulants, and methotrexate) from their protein-binding sites. Patients should be observed for signs of overdose 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/ β -Blockers

As with other NSAID's, the antihypertensive effect of propranolol and other β -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

The recommended starting dose is 2 tablets, followed by 1 tablet every 6-8 hours, as required. The total daily dose should not exceed 5 tablets (1,375 mg).

Over Dosage

Manifestations

Significant over dosage may be characterized by drowsiness, heartburn, and indigestion nausea or vomiting. Because Naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced seizures, but it is not clear whether they were Naproxen-related. No evidence of toxicity or late sequelae have been reported 5-15 months after ingestion of doses equivalent of up to 3.3 grams/day of Naproxen sodium, for 3-7 days. One patient ingested a single dose equivalent to 27.5 grams of Naproxen sodium, 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

Box of 10 tablets