Information for Health Professionals

Apranax® 550mg Tablets اپرینکس ۵۵۰ ملی گرام گولیاں

(Naproxen Sodium)

WARNING:
RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
Cardiovascular Thrombotic Events
(NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
Naproxen sodium tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery.
Gastrointestinal Bleeding, Ulceration and Perforation
NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

Composition:
Each film coated tablet contains: Naproxen Sodium (USP).....550mg

Indications:
Apranax is indicated for the treatment of:
• Rheumatoid arthritis,
• Osteoarthritis,
• Ankylosing spondylitis,
• Gout,
• Juvenile rheumatoid arthritis,
• Dysmenorrhea,
• Migraine treatment and prophylaxis,
• Analgesic and antipyretic use in adults including postpartum non-nursing mothers,
• Analgesic and antipyretic use in children,
• Periarticular and musculoskeletal indications-such as bursitis, tendinitis, synovitis, tenosynovitis, low back pain,
• For the relief of acute and/or chronic pain states in which there is an inflammatory component,
• Surgical manipulations and trauma - sprains, strains orthopedic manipulations, dental extractions, surgery,
• Menorrhagia.

Properties and effects:
Apranax is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties. The onset of pain relief is more rapid with Apranax than with Naprosyn, therefore Apranax 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. 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 sodium is 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 sodium, but does not affect its extent. After oral administration of Apranax 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 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
Hepatic Impairment:
Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency.
Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased.
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.
Geriatric:
Although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is <1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects.
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.

Dosage and administration:
General
Naproxen-sodium containing product circulates in the plasma as naproxen. Onset of pain relief can begin within 30 minutes in patients taking naproxen sodium. 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.
Recommended formulations
Because the sodium salt of naproxen is more rapidly absorbed, Apranax is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. Apranax may be given orally either in fasting state or with meals and/or antacids.
Dose in adults
Acute conditions
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, Apranax is recommended for the management of acute painful conditions when prompt onset of pain relief is desired.
The recommended starting dose is Apranax 550 mg followed by Apranax 275 mg every 6-8 hours as required.
Acute gout: The recommended starting dose is 825 mg of Apranax followed by 275 mg every 8 hours as needed.
Menorrhagia: Apranax 825-1375 mg per day taken in 2 doses on the first day of menstrual bleeding. Thereafter, the total daily dose should not exceed 1100 mg.
Migraine: For treatment of acute migraine headache, the dose is Apranax 825 mg at the first symptom of an impending attack. An additional dose of Apranax 275 mg to 550 mg can be taken throughout the day, if necessary, but not before half an hour after the initial dose.
For prophylaxis of migraine headache, the dose of Apranax is 550 mg twice daily. If no improvement is seen within 4-6 weeks, the drug should be discontinued.
Dose in children
Safety and effectiveness in children below the age of 2 years have not been established.

Contraindications:
Naproxen sodium is contraindicated in the following patients:
• Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to naproxen or any components of the drug product.
• History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients.
• In the setting of coronary artery bypass graft (CABG) surgery.

Warnings and Precautions:
Cardiovascular Thrombotic Events
COX-2 selective and nonselective NSAIDs have an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.
The concurrent use of aspirin and an NSAID, such as naproxen, increases the risk of serious gastrointestinal (GI) events
Post-MI Patients
Avoid the use of naproxen sodium tablets in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events including signs of cardiac ischemia.
Gastrointestinal ulceration, bleeding and perforation
NSAIDs, including naproxen, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in of patients treated for one year. However, even short-term NSAID therapy is not without risk.
Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.
Strategies to Minimize the GI Risks in NSAID-treated patients:
• Use the lowest effective dosage for the shortest possible duration.
• Avoid administration of more than one NSAID at a time.
• Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.

180mm

140mm

180mm

140mm

• Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
• If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue naproxen sodium until a serious GI adverse event is ruled out.
• In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding.

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.

Sodium
A 275 mg tablet of Apranax 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. This should be considered in patients whose overall intake of sodium should be markedly restricted.

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 a greater risk when taking naproxen.

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

Labour and deliver
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 Apranax: *Gastrointestinal:* abdominal pain, constipation, diarrhea, dyspepsia, heartburn, nausea, stomatitis. *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 and palpitations.
General: thirst.
The following adverse events have also been reported:
Gastrointestinal: abnormal liver function tests, colitis, esophagitis, gastrointestinal bleeding and/or perforation, hematemesis, hepatitis (some cases of hepatitis have been fatal), jaundice, melena, nonpeptic gastrointestinal ulceration, pancreatitis, peptic ulceration, ulcerative stomatitis, 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, 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, corneal opacity, papillitis, retrobulbar optic neuritis and papilledema.
Cardiovascular: congestive heart failure, hypertension, pulmonary edema, vasculitis.
Respiratory: asthma, eosinophilic pneumonitis.
General: anaphylactoid reactions, angioneurotic edema, pyrexia (chills and fever).

Interactions:
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 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 furosemide.
Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has been reported.
It is suggested that Apranax therapy should be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used because naproxen may artefactually interfere with some tests for 17-ketogenic steroids. Similarly, Apranax 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, hypoprothrom-binemia, renal dysfunction, metabolic acidosis, apnea, disorientation or vomiting. Because Apranax 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.

Stability:
See expiry on the pack

Packs:
Apranax is supplied in the following dosage forms, strengths and pack sizes:
Tablets (scored) 550mg 20's

INSTRUCTIONS:
Keep all medicines out of the reach of children.
Protect from light, heat and moisture. Store below 30°C.

To be sold on prescription of a registered medical practitioner only.

ہدایات:
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
روشنی، گرمی اور نمی سے محفوظ رکھیں۔
۳۰° گری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کی جائے۔

Manufactured by:
Martin Dow Limited
Plot 37, Sector 19, Korangi Industrial Area,
Karachi-74900, Pakistan.

Martin Dow