

Relev[®]

Naproxen 500 mg Tablets

swi[®]pha

Composition

Each tablet contains: Naproxen 500mg

Description

An oblong half scored offwhite tablet, inscribed 'swi[®]pha 500' on one side and 'NPR LLE' on the other side.

Clinical pharmacology

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID), with analgesic and antipyretic properties. As with other nonsteroidal anti-inflammatory drugs (NSAIDs), its mode of action is not fully understood; however, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

Pharmacokinetics

Absorption: Naproxen itself is rapidly and completely absorbed from the GI tract with an in vivo bioavailability of 95%. After administration of Relev[®] Tablets, peak plasma levels are attained in 2 to 4 hours. Based on the pharmacokinetic profile, the absorption phase of Relev[®] Tablets occurs in the first 4-6 hours after administration.

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 a 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. Relev[®] Tablets exhibit similar dose proportional characteristics.

Biotransformation: Naproxen is extensively metabolized to 6-O-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes. Both Naproxen and 6-O-desmethyl Naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

Elimination: The elimination half-life of Relev[®] Tablets and conventional naproxen is approximately 15 hours. Steady state conditions are attained after 2-3 doses of Relev[®] Tablets. Most of the drug is excreted in the urine, primarily as unchanged naproxen (less than 1%), 6-O-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (66-92%). A small amount of the drug is excreted in the faeces. The rate of excretion has been found to coincide closely with the rate of clearance from the plasma. In patients with renal failure, metabolites may accumulate.

Relev[®] is indicated in the following conditions:

The relief of the signs and symptoms of:

- rheumatoid arthritis
- osteoarthritis
- ankylosing spondylitis
- polyarticular juvenile idiopathic arthritis

The relief of signs and symptoms of:

- tendonitis
- bursitis
- acute gout

The management of:

- pain
- primary dysmenorrhea

Dosage and Administration

Adults:

Rheumatoid arthritis, Osteoarthritis and ankylosing spondylitis:

The usual dosage is 500 mg to 1 g per day taken in two doses at 12 — hour intervals, or alternatively as a single administration of two tablets, morning or evening.

In the following cases a loading dose of 750 mg or 1 g per day for the acute phase is recommended:

- (a) In patients reporting severe night — time pain and/or morning stiffness.
- (b) In patients being switched to Relev[®] from a high dose of another antirheumatic compound.
- (c) In osteoarthritis where pain is the predominant symptom.

For the patients who require 750 mg per day, the size of the morning and evening doses can be adjusted based on the predominant symptoms - i.e. nighttime pain or morning stiffness.

Acute gout: The recommended dosage is 750 mg initially, then 250 mg every eight hours until the attack has passed.

Acute musculoskeletal disorders and dysmenorrhea: The recommended dosage is 500 mg initially followed by 250 mg at 6 to 8-hour intervals as needed, with a maximum daily dose after the first day of 1250 mg.

Use in the elderly:

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 Relev[®] dosing is unknown. As with other drugs used in the elderly, it is prudent to use the lowest effective dose. For the effect of reduced elimination in the elderly refer to the section – "Use in patients with impaired renal function".

Children: Relev[®] is effective in the treatment of juvenile rheumatoid arthritis in children over five years of age, at a dose of 10mg/kg/day taken in two doses at 12—hour intervals. Relev[®] is not recommended for use in any other indication in children under 16 years of age.

Interactions

Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking Relev[®] with drugs that interfere with hemostasis. Concomitant use of Relev[®] Tablets and analgesic doses of aspirin is not generally recommended. Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

ACE inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with Relev[®] Tablets, may diminish the antihypertensive effect of these drugs. Monitoring of blood pressure is recommended.

ACE Inhibitors and ARBs: Concomitant use with Relev[®] in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high-risk patients, monitor for signs of worsening renal function.

Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects.

Digoxin: Concomitant use with Relev[®] tablets can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels.

Contraindication

Relev[®] is contraindicated in patients with known hypersensitivity to naproxen.

Relev[®] should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

Relev[®] is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Warnings and Precautions

Cardiovascular Effects

Cardiovascular Thrombotic Events: Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible.

Hypertension: **Relev** can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of cardiovascular events.

Congestive Heart Failure and Edema: **Relev** should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects

Risk of Ulceration, Bleeding, and Perforation: Nonsteroidal anti-inflammatory drugs (NSAIDs), including **Relev**, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the 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. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly.

Skin Reactions

NSAIDs, including **Relev**, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Exacerbation of Asthma Related to Aspirin Sensitivity

Relev tablets is contraindicated in patients with aspirin-sensitive asthma. Monitor use in patients with preexisting asthma (without aspirin sensitivity).

Hematologic Toxicity

Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia.

Anaphylactic Reactions

Discontinue drug, seek emergency care if an anaphylactic reaction occurs

Adverse Reaction

The most common adverse reactions to naproxen as reported from clinical trials are dyspepsia, abdominal pain, nausea, headache, rash, ecchymosis, and edema.

Dermatological/hypersensitivity:

Skin rashes, urticaria, angio-oedema. Anaphylactic reactions to naproxen and naproxen sodium formulations, eosinophilic pneumonitis, photosensitive dermatitis in which the skin resembles porphyria cutanea tarda ('pseudoporphyria'), and/or epidermolysis bullosa may occur rarely.

CNS:

Headache, insomnia, inability to concentrate and cognitive dysfunction have been reported.

Haematological:

Thrombocytopenia, granulocytopenia, aplastic anaemia and haemolytic anaemia may occur rarely

Other:

Tinnitus, hearing impairment, vertigo, mild peripheral oedema, jaundice, fatal hepatitis, nephropathy, haematuria, visual disturbances, vasculitis and ulcerative stomatitis have been reported rarely.

Use in Specific Populations

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation.

Breastfeeding: The Naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum Naproxen concentration in plasma. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for **Relev** Tablets and any potential adverse effects on the breastfed infant from the **Relev** Tablets or from underlying maternal condition.

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of **Relev** Tablets in women who have difficulties conceiving.

Renal Impairment: Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min).

Symptoms of overdose and Management

Significant naproxen overdose may be characterized by drowsiness, heartburn, 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 unclear if these were drug related or dose specific. The oral LD50 of the drug is 500 mg/kg in rats, 1200 mg/kg in mice, 4000 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

Management

In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen. Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalization of urine or hemoperfusion may not be useful due to high protein binding.

Storage Condition

Store below 30°C
Protect from light.

Pack sizes: 2 x 10, 10 x 10

KEEP MEDICINE OUT OF REACH OF CHILDREN

swi^opha

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NAFDAC REG NO.: 04-9829