

Data Sheet

NOFLAM

Naproxen

Presentation

Noflam 250mg Tablets: Yellow flat bevel edged tablet, 11.1mm in diameter, imprinted NP/250 on one side.

Noflam 500mg Tablets: Yellow capsule shaped tablet, 17mm x 9mm, imprinted NP 500 on one side, with a bisect on the other side.

Uses

Actions

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

Naproxen is a propionic acid derivative related to the arylacetic acid class of medicines. The chemical name of naproxen is (+)-6-methoxy- α -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.

Mechanism of Action

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 administration of naproxen tablets, peak plasma levels are attained in 2 to 4 hours depending on food intake.

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-O-desmethyl naproxen.

Elimination

Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-O-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 faeces.

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.

Preclinical Safety

Carcinogenicity

Naproxen was administered with food to Sprague-Dawley rats for 24 months at doses of 8, 16 and 24 mg/kg/day. Naproxen was not carcinogenic in rats.

Mutagenicity

Mutagenicity was not seen in *Salmonella typhimurium* (5 cell lines), *Sachharomyces cerevisiae* (1 cell line), and mouse lymphoma tests.

Fertility

Naproxen did not affect the fertility of rats when administered orally at doses of 30mg/kg/day to males and 20mg/kg/day to females.

Teratogenicity

Naproxen was not teratogenic when administered orally at doses of 20mg/kg/day during organogenesis to rats and rabbits.

Perinatal/Postnatal Reproduction

Oral administration of naproxen to pregnant rats at doses of 2, 10 and 20 mg/kg/day during the third trimester of pregnancy resulted in difficult labour. These are known effects of this class of compounds and were demonstrated in pregnant rats with aspirin and indomethacin.

Indications

NOFLAM is indicated for its anti-inflammatory and analgesic action in the treatment of rheumatoid arthritis, osteoarthritis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, acute musculoskeletal disorders, post-operative pain and dysmenorrhoea.

Dosage and Administration

General

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

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. Naproxen is not recommended in patients with baseline creatinine clearance less than 30 mL/minute because accumulation of naproxen metabolites has been seen in such patients.

During long-term administration the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. In patients who tolerate lower doses well, the dose may be increased to 1000mg per day when a higher level of anti-inflammatory/analgesic activity is required. When treating patients with naproxen 1000 mg/day, the physician should observe sufficient increased clinical benefit to offset the potential increased risk (see Precautions).

The morning and evening doses do not have to be equal in size and administration of the medicine more frequently than twice daily does not generally make a difference in response.

Standard Dosage

Recommended Formulations

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

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

Caution is required with dosage in the elderly and also in patients with renal impairment.

ADULTS

For rheumatoid arthritis, osteoarthritis and ankylosing spondylitis

Initial Therapy

The usual dose is 500-1000mg per day taken in two doses at 12 hour intervals. The tablets should be swallowed whole with liquid preferably after meals. Where 1000mg per day is needed, the suggested regimen is one naproxen 500mg tablet twice daily.

Maintenance Treatment

The maintenance dose is usually 500mg per day taken in two doses at 12 hour intervals, i.e. 250mg on awakening and 250mg before retiring. The tablets should be swallowed whole with liquid preferably after meals. Dosage adjustments within the range of 500-1000mg per day, maintaining 12 hour interval administration, may be employed. The size of the morning and evening doses should be adjusted on the basis of predominant symptoms, i.e. night time pain or morning stiffness.

Alternatively, patients stabilised on a daily maintenance dose of 500mg, 750mg or 1000mg may administer their daily requirements as a single dose as naproxen has been shown to be effective when administered as a single daily dose.

The total daily dose of naproxen should not exceed 1000mg maintaining 12 hour interval administration.

For acute gout

750mg should be given initially, followed in 8 hours with 500mg, and thereafter 250mg at 8 hour intervals until the attack has passed.

For dysmenorrhoea

500mg should be given initially, followed by 250mg at 6-8 hour intervals for up to 5 days, if necessary.

For adult usage in other indications (analgesic and acute muscular skeletal disorders)

500mg should be given initially, followed by 250mg at 6-8 hour intervals, if necessary.

CHILDREN

For juvenile rheumatoid arthritis

The usual dose for children over 5 years is 10mg/kg/day given as two divided doses at 12 hour intervals. Therapy in children under 5 years of age is not recommended.

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/ analgesics 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, patients with asthma and in patients with haemorrhagic diathesis.

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 and Precautions

The use of naproxen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Cardiovascular Thrombotic Events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Dosage and Administration).

Clinical trial and epidemiological data suggest that the use of coxibs and some NSAIDs (particularly at high doses or long-term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg/d) may be associated with lower risk, some risk cannot be excluded.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Gastrointestinal events

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation, which may increase with dose or duration of use, but can occur at any time without warning. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated with for 3-6 months and in about 2-4% patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulceration occurs in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increase the risk of serious gastrointestinal adverse events.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension, and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart failure

Fluid retention and oedema have been observed in some patients taking NSAIDs; therefore caution is advised in patients with fluid retention or heart failure.

Precautions related to elderly patients

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. In elderly patients the clearance is reduced. Use of the lower end of the dosage range is recommended (see Dosage and Administration).

Severe Skin Reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

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 medicines 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.

Renal effects

There have been reports of impaired renal function, renal failure, acute interstitial nephritis, haematuria, 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, hypovolaemia, heart failure, liver dysfunction, salt depletion, those taking diuretics 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. 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 30 mL/min because accumulation of naproxen metabolites has been seen in such patients.

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

Hepatic effects

Naproxen is relatively contraindicated in liver dysfunction.

As with other non-steroidal anti-inflammatory medicines, 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 medicine as with other non-steroidal anti-inflammatory medicines. Cross reactivity has been reported.

Haematological

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 therapy that interferes with haemostasis 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.

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 papilloedema, 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.

Precautions related to fertility

The use of naproxen, as with any medicine known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have

difficulty conceiving or are undergoing investigation of infertility withdrawal of naproxen should be considered.

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 and Lactation

Pregnancy

As with other medicines of this type, naproxen produces delay in parturition in animals and also affects the human foetal cardiovascular system (closure of ductus arteriosus). 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 foetal circulation and inhibit uterine contractions, thus increasing the risk of uterine haemorrhage.

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

Effects on Ability to Drive and Use Machines

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of naproxen. If patients experience these or similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

Adverse Effects

Post-Marketing

The following are the adverse events that have been reported with NSAIDs and with naproxen:

Gastrointestinal

Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal particularly in the elderly (see Warnings and Precautions); heartburn, nausea, oesophagitis, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, non-peptic gastrointestinal ulceration, melaena, haematemesis, stomatitis, ulcerative stomatitis, exacerbation of ulcerative colitis and Crohn's disease, pancreatitis, gastritis

Infections

Aseptic meningitis

Blood and lymphatic system disorders

Agranulocytosis, aplastic anaemia, eosinophilia, haemolytic anaemia, leucopenia, thrombocytopenia

Immune system disorders

Anaphylactoid reactions

Metabolic and nutrition disorders

Hyperkalaemia

Psychiatric disorders

Depression, dream abnormalities, insomnia

Nervous system disorders

Dizziness, drowsiness, headache, light-headedness, retrobulbar optic neuritis, convulsions, cognitive dysfunction, inability to concentrate

Eye disorders

Visual disturbances, corneal opacity, papillitis, papilloedema

Ear and labyrinth disorders

Hearing impairment, hearing disturbances, tinnitus, vertigo

Cardiac disorders

Palpitations, cardiac failure has been reported in association with NSAIDs treatment, congestive heart failure

Vascular disorders

Hypertension, 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 (1000mg/d) may be associated with a lower risk, some risk cannot be excluded.

Respiratory, thoracic and mediastinal disorders

Dyspnoea, pulmonary oedema, asthma, eosinophilic pneumonitis

Hepatobiliary disorders

Hepatitis (some cases of hepatitis have been fatal), jaundice

Skin and subcutaneous tissue disorders

Ecchymoses, itching (pruritus), purpura, skin eruptions, sweating, alopecia, epidermal necrolysis, very rarely toxic epidermal necrolysis, erythema multiforme, bullous reactions, including Stevens-Johnson syndrome, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, skin rashes, systemic lupus erythematosus, urticaria, photosensitivity reactions including rare cases resembling porphyria cutanea tarda ("pseudoporphyria"), or epidermolysis bullosa, and angioneurotic oedema.

If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Musculoskeletal and connective tissue disorders

Myalgia, muscle weakness

Renal and urinary disorders

Haematuria, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis

Reproductive system and breast disorders

Female infertility

General disorders and administration site conditions

Oedema, thirst, pyrexia (chills and fever), malaise

Investigations

Abnormal liver function tests, raised serum creatinine

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 medicines such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs and aspirin. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Although no significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants, NSAIDs may enhance the effects of anticoagulants, such as warfarin. Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

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 medicines 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 medicines, 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 naproxen 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, naproxen therapy may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

There is an increased risk of gastrointestinal bleeding (see Warnings and Precautions) when anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

Overdosage

Symptoms

Significant naproxen overdosage may be characterised by dizziness, drowsiness, epigastric pain, abdominal discomfort, indigestion, nausea, transient alterations in liver function, hypoprothrombinaemia, renal dysfunction, metabolic acidosis, apnoea, disorientation or vomiting. A few patients have experienced convulsions, but it is not clear whether or not these were naproxen related.

Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression and coma may occur after the ingestion of NSAIDs but are rare.

Anaphylactoid reactions have been reported with therapeutic ingestions of NSAIDs, and may occur following an overdose.

Treatment

Patients should be managed by symptomatic and supportive care following NSAIDs overdose. There are no specific antidotes. Prevention of further absorption (eg. activated charcoal) may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinisation of urine, haemodialysis, or haemoperfusion may not be useful due to high protein binding.

Pharmaceutical Precautions

Store below 30°C. Protect from light.

Medicine Classification

Prescription Medicine.

Package Quantities

NOFLAM 250mg tablets: Bottles of 100's and 500's

NOFLAM 500mg tablets: Bottles of 50's and 250's

Not all pack sizes may be marketed.

Further Information

Nil.

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