

# NAXEN

## *Naproxen*

---

### Name of the Medicine

---

NAXEN  
Naproxen BP as 250 mg and 500 mg tablets

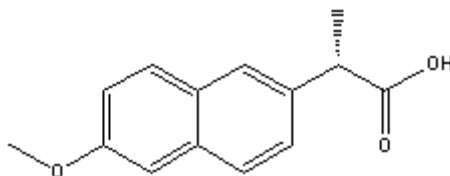
---

### Description

---

Naproxen is (+)-2-(6-methoxy-2-naphthyl)-propionic acid. Its molecular formula is  $C_{14}H_{14}O_3$  and it has a molecular weight of 230.3.

The chemical structure is:



Naxen tablets also contain lactose, maize cornflour, polyvinylpyrrolidinone, sodium starch glycolate, magnesium stearate, FD&C yellow No 6, and D&C yellow No 10.

---

### Pharmacology

---

#### *Mechanism of 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 A<sub>2</sub>. 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.

In <sup>51</sup>Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg naproxen has been demonstrated to cause significantly less gastric bleeding and erosion than 3250 mg of aspirin.

## ***Pharmacokinetics***

### **Absorption**

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

Absorption tends to occur more rapidly in fasted than non-fasted subjects, 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.

### **Distribution**

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.

### **Metabolism**

After a single dose, 70% is 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-O-desmethylnaproxen and 22% as conjugates of this metabolite.

### **Elimination**

Nearly all of a dose of naproxen is 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 is not affected by dose or by continuous administration.

### **Special Populations**

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-O-desmethyl naproxen is increased while that of conjugated naproxen is decreased. In patients treated with maintenance dialysis for terminal renal failure, the metabolite 6-O-desmethyl naproxen is dialysed but naproxen is not.

Naproxen enters breast milk achieving concentrations of approximately 1% of those in plasma.

---

## Indications

---

Naproxen is indicated for the relief of symptoms associated with rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendinitis and bursitis, acute gout and primary dysmenorrhoea.

---

## Contraindications

---

Active peptic ulceration and sensitivity to naproxen, aspirin or other non-steroidal anti-inflammatory agents. Naproxen is also contraindicated in patients with gastrointestinal ulceration, haemorrhagic diathesis, and asthma. It is relatively contraindicated in liver dysfunction.

---

## Precautions

---

### *General*

The propensity of naproxen to interact with other medicines may influence the treatment of other conditions. Caution is also required if naproxen is to be used in the treatment of patients with histories of **bronchospasm** and **allergic disease**.

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.

### *Renal Function*

Caution is required with dosage where **renal dysfunction** exists. Patients on long-term therapy should have blood chemistry and renal function checked periodically. Treatment should immediately be withdrawn if any impairment becomes evident.

### *Hepatic Function*

Naproxen should be administered to patients with **impaired liver function** only in case of necessity.

### ***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).

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.

### ***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.

### ***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 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 ulcerations occur 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 increases the risk of serious gastrointestinal adverse events.

### ***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.

### ***Use in Pregnancy***

Category C (4<sup>th</sup> Ed Medicines in Pregnancy). Naproxen inhibits prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. During late **pregnancy** naproxen is to be avoided.

### ***Use in Lactation***

Naproxen should not be used by **breast-feeding mothers** unless the benefit outweighs the potential risk.

### ***Use in the Elderly***

Caution is required with dosage in the elderly.

### ***Carcinogenicity***

The oral LD<sub>50</sub> is 543mg/kg in rats, 1234mg/kg in mice, 4110mg/kg in hamsters and >1000mg/kg in dogs.

A two year study in rats showed no evidence of carcinogenicity.

### ***Genotoxicity***

Reproduction studies in rats, rabbits and mice at doses up to 6x the human dose revealed no evidence of impaired fertility or foetal harm due to the naproxen. An increased incidence of dystocia and delayed parturition was found in the rats.

### ***Interactions with other Medicines***

The administration of antacids with naproxen has varying effects depending on the antacid. Sodium bicarbonate increases the rate of absorption of naproxen. Magnesium carbonate decreases the absorption slightly while magnesium oxide or aluminium hydroxide markedly reduce the absorption.

Concomitant administration of probenecid and naproxen results in a marked decrease in urinary excretion of unchanged naproxen and naproxen conjugates with urinary 6-O-desmethylnaproxen being increased. The plasma half-life of naproxen is increased, in one study from 14 hours to 37 hours.

The concomitant administration of aspirin with naproxen will reduce plasma levels of naproxen. The clinical significance of this is unknown.

The natriuretic effect of frusemide has been reported to be inhibited by some non-steroidal anti-inflammatory agents. Inhibition of renal lithium clearance with increases in plasma lithium concentrations has also been reported.

Naproxen administered to patients on warfarin has been shown to modestly but significantly increase the serum free fraction of warfarin in-vitro. In-vivo, however, one trial showed no apparent effect on the steady state serum concentrations of free or total warfarin or on the prothrombin times of 5 subjects receiving a constant maintenance dose of warfarin. Patients who require concomitant warfarin and naproxen should, however, be observed closely.

Theoretically, naproxen could displace sulphonylurea hypoglycaemic agents from protein binding sites and regular blood sugar checks should be made where naproxen is given to patients already stabilised on oral hypoglycaemic medication.

Naproxen may reduce the tubular secretion of methotrexate.

Naproxen may interfere with some tests for 17-ketogenic steroids and urinary assay of 5-hydroxy indole acetic acid (5-HIAA).

---

## **Adverse effects**

---

The following are the adverse events observed most frequently in association with naproxen:

*Gastrointestinal:* abdominal pain, constipation, diarrhoea, dyspepsia, heartburn, nausea, stomatitis.

*Central nervous system:* dizziness, drowsiness, headache, light-headedness, vertigo.

*Dermatologic:* ecchymoses, itching (pruritus), purpura, skin eruptions, sweating.

*Special senses:* hearing disturbances, tinnitus, visual disturbances.

*Cardiovascular:* dyspnoea, oedema, palpitations.

*General:* thirst.

The following adverse events have also been reported:

*Gastrointestinal:* abnormal liver function tests, colitis, oesophagitis, gastrointestinal bleeding and/or perforation, haematemesis, hepatitis (some cases of hepatitis have been fatal), jaundice, melena, nonpeptic gastrointestinal ulceration, pancreatitis, peptic ulceration, ulcerative stomatitis, vomiting.

*Renal:* haematuria, hyperkalaemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine.

*Haematological:* agranulocytosis, aplastic anaemia, eosinophilia, haemolytic anaemia, 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 (systemic lupus erythematosus), 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.

*Cardiovascular:* congestive heart failure, hypertension, pulmonary oedema, vasculitis.

*Reproductive, female:* infertility.

*Respiratory:* asthma, eosinophilic pneumonitis.

*General:* anaphylactoid reactions, angioneurotic oedema, pyrexia (chills and fever).

*Special senses:* corneal opacity, papillitis, retrobulbar optic neuritis and papilloedema.

---

## **Dosage and Administration**

---

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

A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients. Naxen is not recommended in patients with baseline creatinine clearance less than 20 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 1000 mg 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.

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***

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

##### ***Maintenance treatment***

The maintenance dose is usually 500 mg per day taken in two doses at 12 hour intervals, i.e. 250 mg on awakening and 250 mg before retiring. The tablets should be swallowed whole with liquid preferably after meals. Dosage adjustments within the range of 500-1000 mg 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 stabilized on a daily maintenance dose of 500 mg, 750 mg or 1000 mg 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 1000 mg maintaining 12 hour interval administration.

##### ***For acute gout***

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

##### ***For dysmenorrhoea***

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

#### **For adult usage in other indications (analgesia and acute muscular skeletal disorders)**

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

### ***Children***

#### **For juvenile rheumatoid arthritis**

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

---

## **Overdosage**

---

Studies show that doses of up to 4 g can be handled without saturation of elimination mechanisms.

Overdosage is, therefore, unlikely but if a case arises, empty the stomach by inducing emesis or performing gastric lavage. Administer activated charcoal to reduce the absorption of naproxen and treat other symptoms as they arise

---

## **Presentation and Storage conditions**

---

Naproxen BP in:

**250 mg tablet:** Yellow, biconvex, round tablet of 11mm diameter with one face engraved NX250 and having a bisecting score.

**500 mg tablet:** Yellow, biconvex, oval tablet of 19mm length, one face engraved NX500 with a bisecting score and the other face plain.

### ***Storage***

Store below 30°C. The shelf life of the tablets is 36 months.

### ***Pack quantities***

250 mg tablets: 100s and 500s.

500 mg tablets: 100s and 500s

---

## **Medicine Classification**

---

Prescription medicine.

---

## **Name and Address of Sponsor**

---

Douglas Pharmaceuticals Ltd  
P O Box 45 027  
Auckland 0651  
New Zealand

Phone:(09) 835 0660

Fax: (09) 835 0665

---

## **Date of Preparation**

---

July 2007