

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Naproxen Enteric Coated Tablets 250mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg of Naproxen Ph Eur.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For the management of various arthritides, such as rheumatoid arthritis, osteoarthritis, spondylitis, gout, etc., and of musculo-skeletal disorders. For the management of rheumatoid arthritis in children over the age of five years.

In the management of dysmenorrhoea.

4.2 Posology and method of administration

For oral administration.

Naproxen EC tablets should be swallowed whole and not broken or crushed.

Adults

For rheumatoid arthritis, osteoarthritis and ankylosing spondylitis the usual dose is 500mg to 1g daily, taken in two divided doses.

In the case of gout a dose of 750mg may be required as an initial dose given once, with 250mg every eight hours until the attack has passed.

For dysmenorrhoea and acute musculo-skeletal disorders the usual initial dose is 500mg and thereafter 250mg every 6 to 8 hours.

Elderly persons

The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children over the age of 5 years

In the treatment of juvenile rheumatoid arthritis, in children over 5 years of age, the usual dose is 10mg/kg/day divided into two doses taken at 12 hour intervals.

The safety of Naproxen EC tablets in children under 5 years of age has not been established and therefore use is not recommended.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance, soya, peanut or to any of the excipients listed in section 6.1..

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

Severe hepatic and renal (See section 4.4 – Special warnings and precautions for use).

During the last trimester of pregnancy (See section 4.6 – Pregnancy and lactation).

Active or previous peptic ulcer.

History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors (See section 4.5 Interactions).

Severe heart failure.

4.4 Special warnings and precautions for use

In all patients:

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (See section 4.2 – Posology and administration)

Respiratory disorders:

Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma or allergic disease since NSAIDs have been reported to precipitate bronchospasm in such patients.

Renal and Hepatic Impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function (particularly if long term dosage is under consideration), cardiac impairment, liver dysfunction, cirrhosis of the liver, sodium retention, those taking diuretics, the elderly and patient in whom renal blood flow is compromised such as in extra cellular fluid volume depletion. Renal function (serum creatinine or creatinine clearance) should be monitored in these patients (See also section 4.3 – Contraindications). Use is not recommended in patients with a creatinine clearance of less than 20ml/min.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of 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). There are insufficient data to exclude such a risk for naproxen.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity or bleeding, such as corticosteroids, or anticoagulants such as warfarin or anti-platelet agents such as aspirin (see section 4.5 Interactions).

When GI bleeding or ulceration occurs in patients receiving Naproxen, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8 – Undesirable effects).

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8 – Undesirable effects).

Female fertility:

The use of Naproxen may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Naproxen should be considered.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medical product contains lecithin derived from soya oil. Patients who are allergic to peanut or soya must not use this medicinal product (see section 4.3)

Severe cutaneous adverse reactions (SCARs):

Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with Naproxen treatment. If signs and symptoms suggestive of these reactions appear, Naproxen should be withdrawn immediately. If the patient has developed SJS, or TEN or DRESS with the use of Naproxen, treatment with Naproxen must not be restarted and should be permanently discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

The product is highly bound to plasma protein so that caution should be exercised in use in patients concomitantly receiving other drugs strongly protein bound such as anticoagulants, sulphonamides, sulphonylureas and hydantoins.

Other analgesics: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.3 Contraindications).

Acetylsalicylic acid:

Clinical pharmacodynamic data suggest that concomitant naproxen usage for more than one day consecutively may inhibit the effect of low-dose acetylsalicylic acid on platelet activity and this inhibition may persist for up to several days after stopping naproxen therapy. The clinical relevance of this interaction is not known.

Anti-hypertensives: Reduced anti-hypertensive effect of propranolol and other beta-blockers. There may be an increased risk of renal impairment with the use of ACE-inhibitors.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Cyclosporin: Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids: Increased risk of GI bleeding (see section 4.4 – Special warnings and precautions for use).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4 – Special warnings and precautions for use).

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Probenecid: Decreased excretion of Naproxen leading to increased plasma concentrations of Naproxen.

Naproxen may interfere with some tests of 17-ketogenic steroids and assays of urinary 5-hydroxyindoleacetic acid, it is advised that Naproxen therapy be temporarily discontinued for 48 hours before adrenal function and other affected tests.

4.6. Pregnancy and lactation

Pregnancy:

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriosus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3 Contraindications). NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

From the 20th week of pregnancy onward, Naproxen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Naproxen should not be given unless clearly necessary. If Naproxen is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Naproxen for several days from gestational week 20 onward. Naproxen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Naproxen is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Lactation:

In limited studies so far available, NSAIDs including Naproxen can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7. Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery

4.8 Undesirable effects

Gastrointestinal: The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, sometimes with haemorrhage and perforation and non-peptic gastrointestinal ulceration or GI bleeding, sometimes fatal, particularly in the elderly,

may occur (see section 4.4). Nausea, vomiting, epigastric distress, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm, eosinophilic pneumonitis, or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema, alopecia and more rarely exfoliative, porphyria cutanea tarda and bullous dermatoses (including epidermal necrolysis, erythema multiforme and Stevens-Johnson syndrome).

Cardiovascular: Oedema, hypertension, cardiac failure and rarely vasculitis have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4). Although data suggest that the use of naproxen (1000 mg/d) may be associated with a lower risk, some risk cannot be excluded.

Other adverse events reported less commonly include:

Renal: Nephrotoxicity in various forms, including glomerular nephritis, interstitial nephritis, nephrotic syndrome, haematuria, papillary necrosis and renal failure.

Hepatic: Abnormal liver function, hepatitis and jaundice.

Neurological and special senses: Visual disturbance, optic neuritis, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, convulsion, confusion, hallucinations, hearing impairment, tinnitus, vertigo, dizziness, insomnia, malaise, fatigue, drowsiness, lack of concentration and cognitive dysfunction.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia and hyperkalemia.

Dermatological: photosensitivity.

Skin and subcutaneous tissue disorders: Frequency: Not known - Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4) and fixed drug eruption

4.9. Overdose

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, heartburn, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure

Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Naproxen is a non steroidal anti-inflammatory agent and also has analgesic and antipyretic activity in man. Naproxen reduces the synthesis of prostaglandins by inhibiting the cyclo-oxygenase enzyme. The exact mechanism of its anti-inflammatory action is not known.

5.2. Pharmacokinetic properties

Naproxen is completely absorbed following oral administration. Peak plasma concentrations are seen after about 2 hours. Absorption rate, but not extent, is diminished by concomitant administration with food or antacids.

Naproxen is highly protein bound (>99%) resulting in a volume of distribution of 0.91kg^{-1} .

Naproxen is extensively metabolised by the liver, and excretion is primarily by the kidneys. Less than 10% of a dose is excreted unchanged.

Plasma half life is 12 - 15 hours.

5.3. Pre-clinical safety data

Naproxen does not have mutagenic potential. There is no evidence of carcinogenicity in two year studies in rats. There is no evidence of teratogenicity in mice, rats or rabbits. Naproxen has been shown to delay parturition in animals and to affect the closure of the ductus arteriosus in the human foetal cardiovascular system.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The tablet contains:

Lactose monohydrate Ph Eur
Maize starch Ph Eur
Povidone Ph Eur
Crospovidone Ph Eur
Purified talc Ph Eur
Colloidal anhydrous silica Ph Eur
Magnesium stearate Ph Eur

The enteric coat contains:

Cellulose Ph Eur
Diethylphthalate Ph Eur
Acetone Ph Eur

The printing ink Opacode S - 1 - 8152HV Black contains:

Industrial Methylated Spirit 74 OP BP
Shellac (E094) EP
Iron Oxide Black (E172)
N-Butyl Alcohol
Soya Lecithin (E322) USNF
Antifoam DC 1510

6.2. Incompatibilities

None known.

6.3. Shelf life

4 years.

6.4. Special precautions for storage

Store below 25°C.

6.5. Nature and content of container

Naproxen EC tablets are available in PVC/aluminium foil blister packs.

The pack sizes available are 5, 7, 10, 14, 15, 20, 21, 25, 28, 30, 56, 60, 84, 90, 100, 112, 120, 168 and 180

6.6. Instructions for use/handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Generics [UK] Limited t/a Viatrix
Station Close,
Potters Bar,
Hertfordshire,
EN6 1TL,
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 4569/0281

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF
AUTHORISATION**

15 May 1998

10 DATE OF REVISION OF THE TEXT

15/05/2026