

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Naproxen 500 mg Tablets

2. Qualitative and Quantitative Composition

Each tablet contains 500mg of Naproxen BP

3. Pharmaceutical Form

Yellow, uncoated, deep caplet shaped tablets, marked N500 on one face and a breakline on the reverse.

Clinical Particulars

4.1. Therapeutic Indications

As an anti-inflammatory analgesic in the management of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute gout.

Also in the management of acute musculoskeletal disorders such as sprains, strains, lumbosacral pain, tenosynovitis, fibrositis and various soft tissue injuries.

4.2 Posology and method of administration

Naproxen Tablets are for oral administration. To be taken preferably with or after food.

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

Adults

For rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, the usual dose is 500mg to 1 gm daily, taken in two doses 12 hourly.

In the following cases, a loading dose of 750mg or 1 g per day may be used for the acute phase:

- (a) In patients reporting severe night time pain and/or morning stiffness.

(b) Where high-dose therapy with another anti-rheumatic agent is being replaced with naproxen.

(c) In osteoarthritis where pain is the predominant symptom.

For the patient who requires 750mg or 1g per day, the size of the morning and evening doses can be adjusted on the basis of the predominant symptoms, i.e. night time pain or morning stiffness.

In acute gout, the recommended dosage is 750mg to be taken at once, followed by 250mg 8- hourly until the attack subsides.

For the treatment of acute musculoskeletal disorders the recommended dosage is 500mg initially, followed by 250mg 6 to 8 hourly as required, with a maximum daily dose of 1250mg after the first day.

Usage in Elderly patients: Studies indicate that the unbound plasma fraction of naproxen is apparently increased in the elderly, although the total plasma concentration is unchanged. The significance of this finding for naproxen dosing is unknown. A reduction in daily dosage may be considered in some elderly patients in whom impaired renal function may be expected.

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. For the effect of reduced elimination in the elderly refer to Section 4.4.

Children (over 5 years)

For juvenile rheumatoid arthritis: 10mg/kg/day taken in 2 doses at 12-hour intervals. Naproxen Tablets are not recommended for use in any other indication in children under 16 years of age.

Renal/hepatic impairment

A lower dose should be considered in patients with renal or hepatic impairment. Naproxen Tablets are contraindicated in patients with baseline creatinine clearance less than 30 ml/minute because accumulation of naproxen metabolites has been seen in patients with severe renal failure or those on dialysis (see section 4.3).

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

4.3 Contraindications

Hypersensitivity to naproxen or to any of the excipients.

Since the potential exists for cross-sensitivity reactions, naproxen should not be given to patients in whom aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs have previously induced hypersensitivity reactions (e.g. asthma, rhinitis, angioedema, nasal polyps or urticaria). These reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.

Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

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

Severe heart failure, hepatic failure and renal failure (see section 4.4).

Naproxen is contraindicated during the last trimester of pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

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). Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

Fever and inflammation may be reduced by naproxen, thereby diminishing their usefulness as diagnostic signs.

Elderly:

The elderly and/or debilitated patients have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2) Prolonged use of NSAIDs in these patients is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

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.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients

requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

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 ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents; such as aspirin (see section 4.5).

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).

Respiratory disorders:

Caution is required if administering naproxen to patients suffering from, or with a previous history of, bronchial asthma or allergic disease, as bronchospasm may be precipitated in such patients'

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.

Renal failure linked to reduced prostaglandin production

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, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

Use in patients with impaired renal function:

Naproxen is excreted mainly through the kidney by glomerular filtration (95%) and particular care is required when using naproxen in patients with renal dysfunction. Patients with impairment of renal function should have monitoring of serum creatinine and/or creatinine clearance. Naproxen is contraindicated in patients having a baseline creatinine clearance of less than 30ml/minute.

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

Patients in whom renal blood flow is compromised, such as in extra-cellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure, or with pre-existing renal disease, should have renal function assessed before and during naproxen therapy. This category could also include some elderly patients in whom impaired renal function may be expected, as well as patients using diuretics.

Consideration should be given to reducing the daily dosage of naproxen in these patients, to avoid the possibility of accumulation of naproxen metabolites in these patients.

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.

Use in patients with impaired liver function:

In chronic alcoholic liver disease and probably in other forms of cirrhosis, the plasma concentration of unbound naproxen is increased and the total plasma concentration of naproxen is reduced. Although the significance of this finding is unknown, it is recommended that the lowest effective dose be used.

Haematological

Naproxen decreases platelet aggregation and prolongs bleeding time and this should be borne in mind when determining bleeding times.

Patients with coagulation disorders, or who are receiving drug therapy that interferes with haemostasis, should be monitored carefully while taking naproxen.

Patients at high risk of bleeding or those on full anti-coagulation 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 angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

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.

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 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 suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded.

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 events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

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).

Dermatological

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8) Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the

first month of treatment. Naproxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Precautions related to fertility

The use of naproxen as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis 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.

Combination with other NSAIDs

The combination of naproxen-containing products and other NSAIDs, including cyclooxygenase-2 selective inhibitors, is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of antacid or colestyramine 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.

It is considered unsafe to take NSAIDs in combination with anti-coagulants such as warfarin or heparin unless under direct medical supervision, as NSAIDs may enhance the effects of anti-coagulants (see Section 4.4).

Other analgesics including cyclooxygenase - 2 selective inhibitors. Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4. 4)

Naproxen is highly bound to plasma protein and patients simultaneously receiving anticoagulants, highly protein-bound sulphonamides, other NSAIDs, aspirin and hydantoins should be monitored for signs of overdose of these drugs. Patients simultaneously receiving Naproxen Tablets and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required. No interactions have been observed in clinical studies with naproxen and anticoagulants or sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

Caution is advised when Naproxen is co-administered with diuretics as there can be a decreased diuretic effect. The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Diuretics can increase the risk of nephrotoxicity of non-steroidal anti- inflammatory drugs.

Inhibition of renal clearance of lithium leading to increased plasma levels of lithium has been reported.

Naproxen and other non-steroidal anti-inflammatory drugs can reduce the antihypertensive effect of anti-hypertensives. Naproxen may increase the risk of renal impairment associated with the use of ACE inhibitors.

Probenecid increases plasma levels of naproxen and extends its plasma half-life.

Caution is advised where methotrexate is given concurrently because of possible enhancement of its toxicity, since naproxen, among other non-steroidal anti-inflammatory drugs, has been reported to reduce the tubular secretion of methotrexate in an animal model.

NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma glycoside levels when co-administered with cardiac glycosides.

There is an increased risk of nephrotoxicity when NSAIDs are used in patients receiving cyclosporine.

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

As with all NSAIDs, there is an increased risk of GI bleeding or ulceration when an NSAID and a corticosteroid are used concurrently.

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

There is an increased risk of gastrointestinal bleeding (see section 4.4) when anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

There is a possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus

There is an increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

It is suggested that Naproxen therapy be temporarily discontinued 48 hours before adrenal function tests are performed, because naproxen may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5- hydroxyindoleacetic acid.

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 of Naproxen in the last trimester of pregnancy is contraindicated (see Section 4.3)

Naproxen should not be used during the first two trimesters of pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.

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 contractions, with an increased bleeding tendency in both mother and child.

Lactation:

Naproxen has been found in the milk of lactating women. The use of naproxen should be avoided in patients who are breast-feeding.

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, vertigo, insomnia, fatigue, depression and visual disturbances are possible after taking naproxen. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The following adverse events have been reported with NSAIDs and with naproxen.

Gastrointestinal disorders: The most commonly observed adverse events are gastrointestinal in nature. Nausea, vomiting heartburn, diarrhoea, flatulence, constipation, dyspepsia, epigastric distress and abdominal discomfort have been reported. More serious reactions which may occur are gastro-intestinal bleeding, which is sometimes fatal, particularly in the elderly (see section 4.4), peptic ulceration, perforation, non-peptic gastro-intestinal ulceration, melaena, haematemesis, stomatitis, ulcerative stomatitis, exacerbation of ulcerative colitis and Crohn's disease (See section 4.4), oesophagitis, gastritis and pancreatitis.

Blood and lymphatic system disorders: Thrombocytopenia, neutropenia, granulocytopenia including agranulocytosis, aplastic anaemia, eosinophilia, leucopenia and haemolytic anaemia.

Immune System disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs, in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) various skin disorders, including different types of rashes, pruritus, urticaria, angio-oedema, purpura and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Metabolic and nutrition disorders: hyperkalaemia

Psychiatric disorders: Insomnia, dream abnormalities, depression, confusion, hallucinations.

Nervous System Disorders: Convulsions, dizziness, headache, lightheadedness, drowsiness, paraesthesia, retrobulbar optic neuritis, inability to concentrate and cognitive dysfunction have been reported. Aseptic meningitis (especially in patients with existing auto immune 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).

Eye Disorders: Visual disturbances, corneal opacity, papillitis and papilloedema.

Ear and Labyrinth disorders: Tinnitus, hearing disturbances including impairment and vertigo.

Cardiac disorders: Oedema, palpitations, cardiac failure and congestive heart failure have been reported

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) (see section 4.4)

Vascular disorders: Hypertension, vasculitis

Respiratory, thoracic and mediastinal disorders: Dyspnoea, asthma, eosinophilic pneumonitis and pulmonary oedema.

Hepatobiliary disorders: Abnormal liver function tests, fatal hepatitis and jaundice have been reported.

Skin and subcutaneous tissue disorders: Skin rashes including fixed drug eruption, itching (pruritus), urticaria, ecchymoses, purpura, sweating. Alopecia, erythema multiforme, Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis, very rarely toxic epidermal necrolysis, photosensitivity reactions (including cases in which skin resembles porphyria cutanea tarda “pseudoporphyria”) or epidermolysis bullosa-like reactions which may occur rarely.

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 and muscle weakness.

Renal and urinary disorders: Nephrotoxicity in various forms including but not limited to, glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome, raised serum creatinine, renal failure and haematuria.

Reproductive system and breast disorders: Female infertility.

General disorders and administration site conditions: Thirst, pyrexia, fatigue and malaise.

4.9 Overdose

a) Symptoms

Symptoms of overdose include headache, nausea, vomiting, heartburn, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting and respiratory depression.

In cases of significant poisoning acute renal failure and liver damage are possible.

In one case of naproxen overdose, transient prolongation of the prothrombin time due to hypoprothrombinaemia may have been due to selective inhibition of the synthesis of vitamin-K dependent clotting factors.

b) Therapeutic measures

The life threatening dose of naproxen is unknown.

Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered as it may reduce the absorption of naproxen. Alternatively, in adults, gastric lavage and general supportive measures 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.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding. However, it may be appropriate in a patient with renal failure who has taken naproxen.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Naproxen has anti-inflammatory, analgesic and antipyretic properties. It exhibits its anti-inflammatory affect even in adrenalectomised animals, indicating that its action is not mediated through the pituitary - adrenal axis. It inhibits prostaglandin synthetase, as do other non-steroidal anti-inflammatory drugs, although the exact mechanism of its anti-inflammatory action is unknown.

5.2 Pharmacokinetic properties

Naproxen appears to be completely absorbed from the gastro-intestinal tract after oral administration and peak plasma levels occur within 2-4 hours. Naproxen is present in the blood mainly as unchanged drug, extensively bound to plasma proteins. The plasma half-life is between 12 and 15 hours, enabling a steady state to be achieved within 3 days of initiation of therapy on a twice daily dose regimen. The degree of absorption is not significantly affected by either foods or most antacids

Approximately 95 % of a dose is excreted in the urine, mainly as conjugated naproxen, but with some unchanged drug. The remainder is excreted via faeces. Biliary excretion is minimal. The rate of excretion correlates closely with the rate of drug disappearance from plasma.

Metabolism in children is similar to that in adults. Chronic alcoholic liver disease reduces the total plasma concentration of naproxen but the concentration of unbound naproxen increases. In the elderly, the unbound plasma concentration of naproxen is increased although total plasma concentration is unchanged.

5.3 Preclinical safety data

Carcinogenicity

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

Mutagenicity

Mutagenicity was not seen in *Salmonella typhimurium* (5 cell lines), *Saccharomyces 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 20mg/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.

Pharmaceutical Particulars

6.1 List of Excipients

Lactose BP
Maize Starch BP
Sodium Starch Glycollate BP
Quinoline Yellow E104 C.I. 14031
Povidone BP
Industrial Methylated Spirits BP
Purified Water BP
Magnesium Stearate BP

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months

6.4. Special precautions for storage

For Securitainer - Do not store above 25°C.

For Blister pack - Do not store above 30°C.

Store in original container/package in order to protect from light.

6.5. Nature and contents of container

Polypropylene securitainers with tamper evident polypropylene caps.

Pack size: 100 tablets.

Blister packs of 250 micron clear PVC/PVDC laminated non toxic film with 90 gsm PVDC coating and 0.02 mm thick hard tempered Aluminium foil with matt finish with assigned shelf life of 36 months.

Pack size: 28 tablets

6.6 Instructions for Use/Handling

Use as directed by the physician.

Keep out of reach of children.

Administrative Data

7. Marketing Authorisation Holder

Goldshield Pharmaceuticals Limited

12-16 Addiscombe Road

Croydon

Surrey

CR0 0XT

United Kingdom

8. Marketing Authorisation Number

PL 12762/0125

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