NAROXIN TABLETS
(Naproxen Tablets BP 500 mg)

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the Medicinal Product

NAROXIN TABLETS

(Naproxen Tablets BP 500 mg)

2. Qualitative and Quantitative Composition

Each Unoated tablet contains:

Naproxen BP 500 mg

3. Pharmaceutical form

Uncoated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Naproxen is indicated for the treatment of:

• Rheumatoid arthritis.

• Osteoarthritis (degenerative arthritis).

• Ankylosing spondylitis.

• Juvenile rheumatoid arthritis.

• Acute gout.

• Acute musculoskeletal disorders

• Dysmenorrhoea.

4.2 Posology and method of administration

Posology

Adults

Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis

500mg-1g daily in two doses at twelve-hour intervals, or alternatively, if 1g daily is needed this can be administered as two 500mg doses or as a single dose. The size of the morning and evening doses can be adjusted on the basis of the predominant symptoms (ie night time pain or morning stiffness)

Acute gout

Initially 750mg followed by 250mg every 8 hours until the attack has passed.

Acute musculoskeletal disorders and dysmenorrhoea

Initially 500mg followed by 250mg every 6-8 hours as necessary to a maximum of 1250mg daily after the first day.

Loading Dose

As a single administration of two tablets, morning or evening, a loading dose of 750mg-1g daily for the acute phase is recommended in the following cases:

a) Patients reporting severe night time pain and/or morning stiffness.

b) Patients commencing naproxen therapy following a switch from a high dose of another antirheumatic compound.

c) Osteoarthritis where pain is the predominant symptom.

Paediatric population

For juvenile rheumatoid arthritis in children over 5 years old, 10mg/kg a day taken in two doses every 12 hours.

Elderly

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. Studies indicate that although total plasma concentration of naproxen is unchanged, unbound plasma fraction of naproxen is increased in the elderly. The implication of this finding for naproxen dosing is unknown. As with other drugs used in the elderly it is prudent to use the lowest effective dose. Dosage should be reduced in the elderly where there is an impairment of renal function.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms

Method of administration

For oral administration preferably with or after food.

4.3 Contraindications

- Hypersensitivity to naproxen, naproxen sodium or any of the excipients
- Patients with active gastrointestinal bleeding or peptic ulceration.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- 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 heart failure, hepatic failure and renal failure.
- During the third trimester of pregnancy.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

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.

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 (1000mg 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 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 ot 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 haemorrhage or perforation
- in the elderly
- when used with alcohol
- in smoking

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.

Patients with a history of GI toxicity, particularly the 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.

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.

Cardiovascular, 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, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients.

Impaired renal function:

Naproxen should be used with great caution where there is impairment of renal function as it is eliminated to a large extent (95%) via glomerular filtration; the monitoring of serum creatinine and/or creatinine clearance should be conducted in these patients.

Naproxen is not recommended in patients having baseline creatinine clearance less than 20ml/minute.

Certain patients, specifically those whose renal blood flow is compromised, because of extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure, and pre-existing renal disease, should have renal function assessed before and during naproxen therapy. Some elderly patients in whom impaired renal function may be expected, as well as patients using diuretics, may also fall within this category. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

Impaired liver function

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for naproxen dosing is unknown but it is prudent to use the lowest effective dose. The product should be used with caution in patients with a history of, or in those with impaired liver function.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Respiratory disorders

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

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.

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. 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.

Impaired 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 fertility, withdrawal of naproxen should be considered.

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 angioedema, bronchospastic reactivity (*eg*asthma), rhinitis and nasal polyps.

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

Naproxen, in common with other NSAIDs, 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 who are receiving drug therapy that affects haemostasis should be carefully observed when given naproxen.

Patients on full anticoagulant therapy (*eg* heparin or warfarin) may be at an increased risk of bleeding if given naproxen concurrently. Therefore, the benefits should be weighed against these risks.

Mild peripheral oedema has been observed in a few patients receiving naproxen. Although sodium retention has not been reported in metabolic studies, it is possible that patients with questionable or compromised function may be at a greater risk when taking naproxen.

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 papilledema, 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.

Combination with other NSAIDs

The combination of naproxen-containing products and others NSAIDs is not recommended, because of the cummulative risks of inducing serious NSAID-related adverse events.

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

The antipyretic and anti-inflammatory activities of naproxen may reduce fever and inflammation thereby diminishing their utility as diagnostic signs.

Interference in tests:

Naproxen therapy should be temporarily withdrawn 48 hours before adrenal function tests are performed as it may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxyindoleacetic acid.

Sporadic abnormalities in laboratory tests (e.g. liver function test) have occurred in patients on naproxen therapy, but no definite trend was seen in any test indicating toxicity.

Medication Overuse Headache (MOH)

After long term treatment with analgesics, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH - medication-overuse headache) should be suspected in patients who have frequent or daily headaches despite (or because of) regular use of analgesics. Patients with medication overuse headache should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

Contains Lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

• Naproxen is highly protein-bound hence patients receiving hydantoins, anticoagulants or a highly protein-bound sulphonamide should be closely monitored for signs of overdosage of these drugs. No interactions have beern observed in clinical studies with naproxen or sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

• NSAIDs, including naproxen, have been reported to increase steady state plasma lithium levels by inhibition of renal lithium clearance. Decreased elimination of lithium. It is recommended that these levels are monitored whenever initiating, adjusting or discontinuing naproxen.

• Anti-hypertensives: Reduced anti-hypertensive effect. Concomitant administration of naproxen with beta blockers may reduce their antihypertensive effect and may increase the risk of renal impairment associated with the use of ACE inhibitors or angiotensin II receptor antagonist.

• Probenecid given concurrently increases naproxen plasma levels and extends its half-life considerably.

• Decreased elimination of methotrexate. Caution is advised when methotrexate is administered concurrently, due to the possible enhancement of its toxicity as naproxen, like other NSAIDs, has been reported to reduce tubular secretion of methotrexate in an animal model.

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

• NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides..

• As with all NSAIDs, caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.

• NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

• As with all NSAIDs, caution should be taken when co-administering with corticosteroids because of the increased risk of gastrointestinal ulceration or bleeding.

• 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 .

• Diuretics: NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g. dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

• Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin.

• 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.

• Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.

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

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

• Bisphosphonates: concomitant use of bisphosphonates and NSAIDs may increase the risk of gastric mucosal damage.

• Colestyramine: colestyramine delays the absorption of naproxen. Naproxen should be taken at least one hour before or four to six hours after colestyramine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post- implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. 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.

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

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

- renal dysfunction, which may progress to renal failure with oligo-hydramniosis; 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 last trimester of pregnancy.

Lactation

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

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

System Organ Class	Common (≥ 1/100 < 1/10)	Uncommon (≥ 1/1000 < 1/100)	Rare (≥ 1/10,000 < 1/1000)	Very Rare (< 1/10,00)	Frequency not known (cannot be estimated from the available data)
Blood and lymphatic system disorders			haemolytic anaemia	granulocyctopenia, thrombocytopenia, agranulocytosis	aplastic anaemia, neutropenia
Immune system disorders			allergic and hyper-sensitivity reactions, anaphylaxis		
Endocrine disorders					
Metabolism and nutrition disorders			hyperkalaemia		
Psychiatric disorders		depression, cognitive dysfunction, insomnia, loss of concentration, abnormal dreams			hallucinations
Nervous system disorders	confusion, dizziness, drowsiness, headache			convulsions, aseptic meningitis*	vertigo, paraesthesia, malaise, exacerbation of Parkinson's disease
Eye disorders	visual disturbances				optic neuritis, papilloedema
Ear and labyrinth disorders	tinnitus		hearing impairment		
Cardiac disorders		palpitations			cardiac failure
Vascular disorders			vasculitis	arterial thrombotic events e.g. myocardial infarction or stroke	hypertension
Respiratory, thoracic and mediastinal disorders			aggravated asthma, eosinophilic pneumontitis		bronchospasm, dyspnoea, rhinitis, pulmonary oedema
Gastrointestinal disorders				pancreatitis	thirst, peptic ulcers, perforation or GI bleeding**, nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia,

					abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease gastritis
Hepatobiliary			hepatitis (sometimes fatal), jaundice		abnormal liver function,
Skin and subcutaneous tissue disorders	rash, pruritis, purpura	urticaria, photo-sensitivity	alopecia, pseudo-porphyria	erythema multiforme, Stevens Johnsons syndrome, toxic epidermal necrosis, epidermolysis bullosa	angio-oedema, epidermal necrosis, exfoliative and bullous dermatoses, lichen planus
Musculoskeletal and connective tissue disorders			myalgia, muscle weakness		
Renal and urinary disorders				glomerular nephritis, haematuria, interstitial nephritis, nephritic syndrome, renal papillary necrosis	renal failure, nephropathy, increase in serum creatinine
Reproductive system and breast disorders					impaired female fertility
General disorders and administration site complications	fatigue				mild peripheral oedema, pyrexia

*especially in patients with existing auto-immune disorders, such as system lupus erythematosus, mixed connective tissue disease, with symptoms such as stiff neck headache, nausea, vomiting, fever and disorientation.

** sometimes fatal, particularly in the elderly, may occur

Clinical trial and epidemiological data suggests 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

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

Treatment

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

Pharmacotherapeutic group: Antiinflammatory and antirheumatic products, nonsteroids.Propionic acid derivatives.

ATC code: M01AE02

Naproxen is a non-steroidal anti-inflammatory agent.

Mechanism of action

Naproxen reduces the synthesis of prostaglandins primarily by inhibiting the enzyme cyclo-oxygenase. Naproxen has been shown to have anti-inflammatory activity in a number of experimental models. Naproxen inhibits prostaglandin E_2 synthesis in vitro by human rheumatoid synovial microsomes. It also inhibits prostaglandin E_2 production by phytohaemagglutin-stimulated peripheral blood mononuclear cells. At 10^{-4} M ($23mg.1^{-1}$) naproxen inhibits neutral protease activity derived from human polymorphonuclear leucocytes. Naproxen also inhibits in vitro the activity of cathepsin-β and other hydrolytic

enzymes derived from lysosomes. Naproxen is a potent in inhibitor of leucocyte migration and produces effects comparable to those of colchicine.

5.2 Pharmacokinetic properties

Absorption

Naproxen is readily absorbed from the gastrointestinal tract.

Distribution

Peak plasma concentrations are attained 2-4 hours after ingestion. Plasma concentrations of naproxen increase proportionally with dose up to about 500mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. At therapeutic concentrations naproxen is more than 99% bound to plasma proteins and has a plasma half-life of about 13 hours.

Elimination

Approximately 95% of a dose is excreted in urine as naproxen and 6-O-desmethylnaproxen and their conjugates. Less than 3% of a dose has been recovered in the faeces. Naproxen crosses the placenta and is excreted in breast milk.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

Also contains: lactose, magnesium stearate, maize starch, polyvidone, E172, E463.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf-life

3 years from the date of manufacture.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4 Special precautions for storage

Store below 25°C in a dry place. Protect from light.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs and cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-6g/M^2 PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 20s, 28s, 30s, 50s, 56s, 60s, 84s, 90s, 100s, 112s, 120s, 168s, 180s, 250s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for *temporary* storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Administrative data

6. Pharmaceutical particulars

6.1 List of excipients

1. LACTOSE BP
2. STARCH BP
3. POLYVINYLPYRROLIDINE K-30 BP
4. MAGNESIUM STEARATE BP
5. SODIUM STARCH GLYCOLATE BP
6. COLLOIDAL ANHYDROUS SILICA BP
7. PURIFIED WATER BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a Cool, dry place.

6.5 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.6 Nature and contents of container

Noraxin Tablet are available in Blister pack of 2 x 10 tablets in a carton.

Pack size: Blister pack of 2 x 10 Tablets in a carton

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer name

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