

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Naprosyn EC 500mg Gastro-resistant Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg naproxen  
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Gastro-resistant film-coated tablets.

*Product imported from the UK:*

Capsule-shaped, white tablet marked 'NPR EC 500' in black ink on one side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Naprosyn EC is indicated for the treatment of rheumatoid arthritis, osteoarthritis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, acute musculo-skeletal disorders (such as sprains and strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis) and dysmenorrhoea.

### 4.2 Posology and method of administration

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

#### **Adults:**

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

#### ***Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis:***

The usual dose is 500mg to 1g daily taken in two doses at 12-hour intervals. Where 1g per day is needed one 500mg tablet twice daily or two 500mg tablets in a single administration (morning or evening) is recommended.

#### ***Acute gout:***

The recommended dosage is 750mg initially, then 250mg every eight hours until the attack has passed.

#### ***Acute musculo-skeletal disorders and dysmenorrhoea:***

The recommended dose is 500mg initially followed by 250mg at 6 - 8 hour intervals as needed, with a maximum daily dose after the first day of 1250mg.

#### ***Elderly:***

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. The implication of this finding for Naprosyn EC dosing is unknown. As with other drugs used in the elderly it is prudent to use the lowest effective dose as elderly patients are more prone to adverse events. For the effect of reduced elimination in the elderly see section 4.4.

**Children:**

Naprosyn EC is effective in the treatment of juvenile rheumatoid arthritis in children over 5 years of age at a dose of 10mg/kg/day taken in two doses at 12-hour intervals. Naprosyn EC is not recommended for use in any other indication in children under 16 years of age.

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

**4.3 Contraindications**

Active or a history of gastrointestinal bleeding or perforation, related to previous NSAID therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

Hypersensitivity to naproxen and naproxen sodium formulations. Since the potential exists for cross-sensitivity reactions, Naprosyn EC should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce asthma, rhinitis or urticaria.

Naprosyn EC tablets are contraindicated in patients with severe heart failure.

**4.4 Special warnings and precautions for use**

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

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

The elderly 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 the NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

***Gastrointestinal ulceration, bleeding and perforation***

GI bleeding, ulceration or perforation which can be fatal has been reported with all NSAIDs at anytime 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 haemorrhage 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 Section 4.5).

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8). 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. When GI bleeding or ulceration occurs in patients receiving Naprosyn the treatment should be withdrawn. Episodes of gastro-intestinal bleeding have been reported in patients with naproxen therapy. Naprosyn EC should be given under close supervision to patients with a history of gastro-intestinal disease.

Serious gastro-intestinal adverse reactions, can occur at any time in patients on therapy with non-steroidal anti-inflammatory drugs. The risk of occurrence does not seem to change with duration of therapy. Studies to date have not identified any subset of patients not at risk of developing peptic ulcer and bleeding. However, elderly and debilitated patients tolerate gastro-intestinal ulceration or bleeding less well than others. Most of the serious gastro-intestinal events associated with non-steroidal anti-inflammatory drugs occurred in this patient population.

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

Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

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

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

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 cardiac function may be at a greater risk when taking Naprosyn EC.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Caution should be advised in patients receiving concomitant medication which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-uptake inhibitors or anti-platelet agents such as aspirin (see section 4.5).

### ***Skin reactions***

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

### ***Use in patients with impaired renal function:***

As naproxen is eliminated to a large extent (95%) by urinary excretion via glomerular filtration, it should be used with great caution in patients with impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Naprosyn EC is not recommended in patients having a baseline creatinine clearance of 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 Naprosyn EC 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.

### ***Use in patients with 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 Naprosyn EC dosing is unknown but it is prudent to use the lowest effective dose.

### ***Haematological:***

Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen-containing products are administered.

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

***Precautions related to 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.

***Combination with other NSAIDs:***

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

**4.5 Interaction with other medicinal products and other forms of interaction**

Concomitant administration of an 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.

Due to the high plasma protein binding of naproxen, patients simultaneously receiving hydantoin, anticoagulants or a highly protein-bound sulphonamide should be observed for signs of overdose of these drugs. It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

No interactions have been observed in clinical studies with naproxen and anticoagulants or sulfonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class. NSAIDs may enhance the effects of anti-coagulants such as warfarin.

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

Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported.

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

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

Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, since naproxen, in common with 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 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 cortico-steroids because of the increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

The concomitant administration of two or more NSAIDs should be avoided.

Patients taking quinolones may have an increased risk of developing convulsions.

It is suggested that Naprosyn EC 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.

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.

#### **4.6 Fertility, pregnancy and lactation**

Teratology studies in rats and rabbits at dose levels equivalent on a human multiple basis to those which have produced foetal abnormality with certain other non-steroidal anti-inflammatory agents, e.g. aspirin, have not produced evidence of foetal damage with naproxen. As with other drugs of this type naproxen delays parturition in animals (the relevance of this finding to human patients is unknown) and also affects the human foetal cardiovascular system (closure of the ductus arteriosus).

Good medical practice indicates minimal drug usage in pregnancy, and the use of this class of therapeutic agent requires cautious balancing of possible benefit against potential risk to the mother and foetus, especially in the first and third trimesters.

Naproxen has been found in the milk of lactating mothers. The use of Naprosyn EC should therefore be avoided in patients who are breast-feeding.

#### **4.7 Effects on ability to drive and use machines**

None known.

#### **4.8 Undesirable effects**

**Gastro-intestinal:** The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal particularly in the elderly (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of ulcerative colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently gastritis has been observed.

**Dermatological:** Skin rashes, urticaria, angio-oedema. Alopecia, erythema multiforme, bullous reactions including Stevens Johnson syndrome, very rarely toxic epidermal necrolysis, photosensitivity reactions (including cases in which the skin resembles porphyria cutanea tarda, "pseudoporphyria") or epidermolysis bullosa may occur rarely.

**Renal:** Including but not limited to glomerular nephritis, interstitial nephritis, nephrotic syndrome, haematuria, renal papillary necrosis and renal failure.

**CNS:** Convulsions, headache, insomnia, inability to concentrate and cognitive dysfunction have been reported.

**Haematological:** Thrombocytopenia, granulocytopenia including agranulocytosis, aplastic anaemia and haemolytic anaemia may occur rarely.

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

**Other:** Tinnitus, hearing impairment, vertigo, mild peripheral oedema. Anaphylactic reactions to naproxen and naproxen sodium formulations have been reported in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs. Jaundice, fatal hepatitis, visual disturbances, eosinophilic pneumonitis, vasculitis, hyperkalaemia, aseptic meningitis and ulcerative stomatitis have been reported rarely.

## 4.9 Overdose

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea or vomiting. A few patients have experienced seizures, but it is not known whether these were naproxen-related or not. It is not known what dose of the drug would be life-threatening.

Should a patient ingest a large amount of Naprosyn EC accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. Animal studies indicate that the prompt administration of activated charcoal in adequate amounts would tend to reduce markedly the absorption of the drug.

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Naproxen has been shown to have anti-inflammatory, analgesic and antipyretic properties when tested in classical animal test systems. It exhibits its anti-inflammatory effect 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 agents. As with other agents, however, the exact mechanism of its anti-inflammatory action is not known.

### 5.2 Pharmacokinetic properties

Naproxen is completely absorbed from the gastro-intestinal tract, and peak plasma levels are reached in 2 to 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. Excretion is almost entirely via the urine, mainly as conjugated naproxen, with some unchanged drug. 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.

When naproxen is administered in the enteric-coated form, the peak plasma levels are delayed compared to those seen with standard tablets. However, the mean areas under the plasma concentration-time curves, and hence bioavailability, are equivalent. The tablets, therefore, perform as one would anticipate for a drug which does not disintegrate until it reaches the small intestine, where dissolution is rapid and complete.

### **5.3 Preclinical safety data**

No evidence of carcinogenicity was found in rats. Reproduction studies performed in rats, rabbits and mice at doses up to 6 times the human dose revealed no evidence of impaired fertility or harm to the foetus. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Povidone  
Croscarmellose sodium  
Magnesium stearate  
Methacrylic acid copolymer (Type C)  
Purified talc  
Sodium hydroxide  
Triethyl citrate  
Simeticone emulsion  
Iron oxide, black (E172)  
Shellac  
Propylene glycol

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

### **6.4 Special precautions for storage**

Store below 30°C.  
Keep the blister in the outer carton in order to protect from light.

### **6.5 Nature and contents of container**

Blisters of 56 tablets in an over labelled outer carton.

### **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

## **7 PARALLEL PRODUCT AUTHORISATION HOLDER**

B&S Healthcare  
Unit 4  
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UK

**8 PARALLEL PRODUCT AUTHORISATION NUMBER**

PPA1328/97/2

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

Date of First Authorisation: 3rd April 2009

**10 DATE OF REVISION OF THE TEXT**

August 2011