

**NAPROXEN EC 250MG TABLETS (PL 14894/0534)**  
**NAPROXEN EC 500MG TABLETS (PL 14894/0535)**

**UKPAR**

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**NAPROXEN EC 250MG TABLETS (PL 14894/0534)**  
**NAPROXEN EC 500MG TABLETS (PL 14894/0535)**

**LAY SUMMARY**

On 22<sup>nd</sup> February 2008, the MHRA granted Ranbaxy (UK) Limited Marketing Authorisations (licences) for the medicinal products Naproxen EC 250mg Tablets (PL 14894/0534) and Naproxen 500mg Tablets (PL 14894/0535). These are prescription only medicines (POM) that are used to treat rheumatoid arthritis, osteoarthritis, ankylosing spondylitis (causing pain and stiffness in the back), back pain, neck pain, and swollen or tender tendons. It is also used to treat sprained or strained muscles, or painful menstrual periods.

Naproxen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). These medicines help to relieve pain and joint inflammation.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Naproxen EC 250mg and 500mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.

**NAPROXEN EC 250MG TABLETS (PL 14894/0534)**  
**NAPROXEN EC 500MG TABLETS (PL 14894/0535)**

**SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Naproxen EC 250mg Tablets (PL 14894/0534) and Naproxen 500mg Tablets (PL 14894/0535) to Ranbaxy (UK) Limited on 22<sup>nd</sup> February 2008. The products are prescription-only medicines.

The applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC, claiming to be generic products to the original products Naprosyn EC 250mg and 500mg Tablets (Roche Products Limited), which have been authorised in the EEA for over 10 years.

The products contain the active ingredient naproxen and are indicated for the treatment of rheumatoid arthritis, osteoarthritis (degenerative arthritis), ankylosing spondylitis, acute musculoskeletal disorders (such as sprains and strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis) and dysmenorrhoea.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID). It is a non-selective inhibitor of the cyclo-oxygenase enzyme system.

## PHARMACEUTICAL ASSESSMENT

### DRUG SUBSTANCE

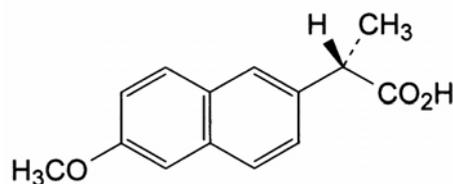
INN: Naproxen

Chemical Name: (+)-2-(6-Methoxy-2-naphthyl) propionic acid  
(S)-2-(6-Methoxynaphth-2-yl) propionic acid  
(+)-6-Methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid

CAS Registry No: 22204-53-1

Molecular Formula: C<sub>14</sub>H<sub>14</sub>O<sub>3</sub>

Structure:



Molecular Weight: 230.3

Appearance: White or almost white crystalline powder. It is lipid soluble and almost insoluble in water.

Naproxen is the subject of a European Pharmacopoeia monograph.

All aspects of the synthesis and control of the active substance are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability. These certificates are accepted as confirmation of the suitability of naproxen for inclusion in the medicinal product.

Appropriate stability data have been provided to support a retest period of 24 months and a shelf-life of 5 years, when stored in the proposed packaging.

### DRUG PRODUCT

#### Other Ingredients

Other ingredients consist of pharmaceutical excipients povidone, colloidal silicon dioxide, microcrystalline cellulose, magnesium stearate, triethyl citrate, glyceryl monostearate, methacrylic acid copolymer type C, talc, titanium dioxide E171, croscarmellose sodium and water purified.

All excipients have a respective European Pharmacopoeia monograph.

Satisfactory certificates of analysis have been provided for all ingredients showing compliance with their respective monograph.

Relevant certification on compliance with the requirements in relation to TSE/BSE has been supplied for magnesium stearate and glyceryl monostearate.

**Pharmaceutical development**

The objective of the pharmaceutical development programme was to produce products with 250mg and 500mg naproxen that are tolerable and can be considered as generic products to the originator products Naprosyn EC tablets.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Comparative *in vitro* dissolution profiles have been generated for the proposed and originator products with satisfactory results. Comparative impurity studies have also been undertaken.

**Manufacturing Process**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

**Finished Product Specification**

The finished product specifications proposed for both strengths are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container-Closure System**

Product is packaged in blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**

Stability studies were performed on pilot-scale batches of all strengths of finished product and all packaging types, in accordance with current guidelines. All results from stability studies on pilot batches were within specified limits. These data support a shelf-life of 4 years, with storage conditions 'Do not store above 25°C' and 'Store in the original package'.

**Bioequivalence/bioavailability**

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

**SPC, PIL, Labels**

The SPC, PIL and Labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**CONCLUSION**

It is recommended that Marketing Authorisations are granted for these applications.

The proposed products are considered to be generic medicinal products to the reference product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

## **PRECLINICAL ASSESSMENT**

In these applications, the products are claiming to be generic medicinal products of Naprosyn EC 250mg and 500mg Tablets (Roche Products Limited), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

## **CLINICAL ASSESSMENT**

### **1. INTRODUCTION**

These are abridged applications for Marketing Authorisations in the UK submitted under Article 10.1 of Directive 2001/83 (as amended), first paragraph so called generic application.

The original product is Naprocoat 250mg Tablets first authorised on the 14<sup>th</sup> October 1992 to Roche/Syntex in The Netherlands. The reference medicinal product is listed as Naprosyn EC 250mg Tablets, PL 00031/0467 granted 31<sup>st</sup> May 1996 which was a change of ownership from PL 00286/0113 granted 12<sup>th</sup> July 1991. The medicinal product used in bioequivalence was Naprocoat 500 sourced from The Netherlands.

Naproxen is a non-steroidal anti-inflammatory drug (NSAID). It is a non-selective inhibitor of the cyclo-oxygenase enzyme system.

Naproxen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis. It is also used in dysmenorrhoea, headache including migraine, postoperative pain, soft-tissue disorders, acute gout, and to reduce fever. The adverse effects and precautions, for naproxen, are as for any other NSAID in general.

### **2. INDICATIONS**

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

The indications proposed are consistent with that for the originator product and are, therefore, satisfactory.

### **3. DOSE & DOSE SCHEDULE**

Adults:

Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis: The usual dose is 500 mg to 1 g per day taken in two doses at 12 hour intervals. Where 1 g per day is needed, the suggested regime is 500 mg twice daily.

In the following cases a loading dose of 750 mg or 1 g per day for the acute phase is recommended:

1. In patients reporting severe night-time pain and/or morning stiffness.
2. In patients being switched to naproxen from a high dose of another anti-rheumatic compound.
3. In osteoarthritis where pain is the predominant symptom.

For the patient who requires 750 mg 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.

Acute gout: The recommended dosage is 750 mg at once, then 250 mg every eight hours until the attack has passed.

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

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID (non-steroidal anti-inflammatory drug) is considered necessary, the lowest dose should be used and the patient should be monitored for gastrointestinal bleeding for 4 weeks following initiation of NSAID therapy.

Children: For the treatment of juvenile rheumatoid arthritis in children over five years of age, the usual dosage is 10 mg per kg bodyweight per day taken in two doses at 12 hour intervals.

Method of administration: Oral; the tablets should be swallowed with a drink of water.

The dose and dose schedule proposed are consistent with that for the originator product and are, therefore, satisfactory.

## 4 CLINICAL PHARMACOLOGY

### 4.1 PHARMACOKINETICS

Naproxen is fully absorbed when administered orally. The rapidity, but not the extent, of absorption is influenced by the presence of food in the stomach. Peak concentrations in plasma occur within 2 to 4 hours and may be achieved more rapidly after administration of naproxen sodium. Absorption may be accelerated by the concurrent administration of sodium bicarbonate or reduced by magnesium oxide or aluminium hydroxide.

Naproxen and its metabolites are almost entirely excreted in the urine. About 30% of the drug undergoes 6-methylation and most glucuronide or other conjugates. Naproxen is almost completely (99%) bound to plasma protein following normal therapeutic doses. Naproxen crosses the placenta and appears in the milk of lactating women at approximately 1% of the maternal plasma concentration.

### 4.2 BIOEQUIVALENCE

#### 4.2.1 Study design

Open randomised, two treatments (R and T), two periods, two sequence, crossover steady-state bioavailability study of two 500 mg naproxen gastroresistant formulations in 24 male volunteers. Treatments were separated by a one week washout period.

#### Results

##### *Results for main pharmacokinetic parameters:*

Summary of the bioequivalence analysis for naproxen after single dose administration. Means of log transformed data:

Parent drug: Naproxen

|                            | Test Agent      | Reference       | Point estimate<br>(90% CI) |
|----------------------------|-----------------|-----------------|----------------------------|
| C <sub>max</sub> (ng/mL)   | 62.8            | 58.5            | 1.07 (0.98-1.17)           |
| AUC <sub>t</sub> (ng.h/mL) | 0.94            | 0.90            | 1.04 (1.00-1.08)           |
| AUC <sub>∞</sub> (ng.h/mL) | 1.09            | 1.06            | 1.03 (1.00-1.06)           |
| T <sub>max</sub> (h)       | 12.0 (5.0-15.0) | 12.0 (5.0-24.0) |                            |

Summary of the bioequivalence analysis for naproxen after multiple dose administration. Means of log transformed data:

Parent drug: Naproxen

|                            | Test            | Reference      | Point estimate<br>(90% CI) |
|----------------------------|-----------------|----------------|----------------------------|
| C <sub>max</sub> (ng/mL)   | 94.1            | 94.2           | 0.99 (0.95-1.04)           |
| AUC <sub>t</sub> (ng.h/mL) | 0.79            | 0.81           | 0.98 (0.94-1.02)           |
| T <sub>max</sub> (h)       | 12.0 (0.0-12.0) | 5.0 (1.5-12.0) |                            |

The test/reference 90% confidence interval results lay within the acceptance criteria. The acceptance criteria were pre-defined and satisfactory.

PK parameters were in line with published values.

The appearance of individual plasma concentration and time curves are in line with the results.

The validated range of assay is satisfactory.

#### 4.2.2 Assessor's Conclusions

Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria and can be approved.

The multiple-dose waiver criteria are met and hence this study is accepted as demonstrating bioequivalence for the other product strength.

The data support bioequivalence for the test drug and the reference. This is consistent with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98). Since naproxen pharmacokinetics seems to be linear up to 500 mg, this bioequivalence study is acceptable for both strengths: 500 mg and 250 mg.

### 4.3 PHARMACODYNAMICS

Naproxen has analgesic, anti-inflammatory and antipyretic properties. It is an inhibitor of prostaglandin synthetase. Naproxen is used in rheumatic disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis, in mild to moderate pain such as dysmenorrhoea, migraine, and some musculoskeletal disorders, and in acute gout

### 5. EFFICACY

No new data are submitted and none are required for this type of application.

### 6. SAFETY

No new data on the safety of entronap are submitted and none are required for this type of application.

**7. EXPERT REPORTS**

A clinical expert report is provided, written by an appropriately qualified medical doctor. It is satisfactory.

**8. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The SPCs are consistent with the approved SPCs of the reference product and are satisfactory.

**9. PATIENT INFORMATION LEAFLET (PIL)**

The PIL has been provided and is consistent with the SPC.

**10. LABELLING**

Labelling has been provided and these are satisfactory.

**11. APPLICATION FORM (MAA)**

The MAA form is satisfactory.

**12. DISCUSSION**

Bioequivalence has been satisfactorily demonstrated for the 500mg product in accordance with CPMP criteria. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500mg strength can be extrapolated to the other strength tablet.

The SPC, PIL and Labelling are consistent with those approved in the UK for the originator product and are satisfactory.

**13. MEDICAL CONCLUSION**

Marketing authorisations may be granted for these products.

## OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

### QUALITY

The important quality characteristics of Naproxen EC 250mg and 500mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

### EFFICACY

Bioequivalence has been demonstrated between the applicant's Naproxen EC 500mg tablets and Naprocoat 500mg Tablets. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 500mg strength can be extrapolated to the other strength tablet.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent.

### RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with naproxen is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**NAPROXEN 250MG TABLETS (PL 14894/0534)**  
**NAPROXEN 500MG TABLETS (PL 14894/0535)**

**STEPS TAKEN FOR ASSESMENT**

|   |                                                                                                                                            |
|---|--------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | The MHRA received the marketing authorisation applications on 25 <sup>th</sup> October 2007                                                |
| 2 | Following standard checks and communication with the applicant the MHRA considered the applications valid on 6 <sup>th</sup> November 2007 |
| 3 | Following assessment of the applications the MHRA requested no further information relating to the quality and clinical dossiers.          |
| 4 | The applications were determined on 22 <sup>nd</sup> February 2008                                                                         |

**NAPROXEN 250MG TABLETS (PL 14894/0534)**  
**NAPROXEN 500MG TABLETS (PL 14894/0535)**

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

| <b>Date submitted</b> | <b>Application type</b> | <b>Scope</b> | <b>Outcome</b> |
|-----------------------|-------------------------|--------------|----------------|
|                       |                         |              |                |
|                       |                         |              |                |
|                       |                         |              |                |
|                       |                         |              |                |
|                       |                         |              |                |

**SUMMARY OF PRODUCT CHARACTERISTICS****1 NAME OF THE MEDICINAL PRODUCT**

Naproxen EC 250mg Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Naproxen EC 250mg Tablets: each tablet contains 250mg naproxen.

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Gastro-resistant film-coated tablets.

Naproxen EC 250mg Tablets: a round, biconvex, white or almost white, film-coated tablet with a smooth surface containing 250mg of naproxen

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications**

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

**4.2 Posology and method of administration**

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

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

**Adults***Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis*

The usual dose is 500mg to 1g daily taken in 2 doses at 12-hour intervals. Where 1g per day is needed either one 500mg tablet twice daily or two 500mg tablets in a single administration (morning or evening) is recommended. In the following cases a loading dose of 750mg or 1g per day for the acute phase is recommended:

- a) In patients reporting severe night-time pain/or morning stiffness.
- b) In patients being switched to Naproxen from a high dose of another anti-rheumatic compound.
- c) In osteoarthritis where pain is the predominant symptom.

*Acute musculoskeletal disorders and dysmenorrhoea*

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 Naproxen 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 Use in patients with impaired renal function.

**Children**

Naproxen EC is not recommended for use 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 history of peptic ulceration or active gastrointestinal bleeding.
- Hypersensitivity to naproxen and naproxen sodium formulations, or to any of the excipients.
- Since the potential exists for cross-sensitivity reactions, Naproxen EC should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce asthma, rhinitis, nasal polyps or urticaria.
- Severe heart failure.

**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 cardiovascular risks below).

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

Elderly patients are particularly susceptible to the adverse events of NSAIDs. Prolonged use of the NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Episodes of gastro-intestinal bleeding have been reported in patients with naproxen therapy. Naproxen 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 Naproxen 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 Naproxen EC.

*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. Naproxen 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 Naproxen 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 Naproxen 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.

*Precautions related to fertility*

The use of naproxen, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or 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.

*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, smoking).

#### **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.

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 overdosage 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 sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

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 corticosteroids because of the increased risk of bleeding.

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 Naproxen 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.

#### 4.6 Pregnancy and lactation

##### *Pregnancy*

As with other drugs of this type, naproxen produces delay in parturition in animals and also affects the human foetal cardiovascular system (closure of ductus arteriosus). Therefore, naproxen should not be used during pregnancy unless clearly needed.

##### *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, thus increasing the risk of uterine haemorrhage.

##### *Nursing mothers*

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

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

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of Naproxen. If patients experience these or similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

#### 4.8 Undesirable effects

*Gastrointestinal* : The more frequent reactions are nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal discomfort and epigastric distress. More serious reactions which may occur occasionally are gastro-intestinal bleeding, peptic ulceration (sometimes with haemorrhage and perforation), non-peptic gastro-intestinal ulceration and colitis. Jaundice, fatal hepatitis, ulcerative stomatitis, abnormal liver function tests, oesophagitis and pancreatitis have been reported rarely.

*Dermatological* : Skin rashes including fixed drug eruption, itching (pruritis), urticaria, ecchymoses, purpura, sweating. Alopecia, erythema multiforme, Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis and photosensitivity reactions (including cases in which the skin resembles porphyria cutanea tarda, "pseudoporphyria") or epidermolysis bullosa-like reactions may occur rarely.

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

*CNS* : Convulsions, dizziness, headache, lightheadedness, insomnia, drowsiness, dream abnormalities, depression, vertigo, aseptic meningitis, inability to concentrate and cognitive dysfunction have been reported.

*Cardiovascular* : Dyspnoea, oedema, palpitations, congestive heart failure and hypertension have been reported 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 a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

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

*Respiratory* : Asthma, eosinophilic pneumonitis and pulmonary oedema.

*Reproductive, femal* : Infertility

*Special senses* : Tinnitus, hearing disturbances including impairment, visual disturbances, corneal opacity, papillitis, retrobulbar optic neuritis and papilloedema.

*Other* : Thirst, pyrexia, mild peripheral oedema, malaise, myalgia, muscle weakness. Anaphylactic reactions to naproxen and naproxen sodium formulations including angioneurotic oedema, have been reported in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs.

#### **4.9 Overdose**

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea, renal dysfunction or vomiting.

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

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 Naproxen 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.

ATC code: M01A E02 (anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives).

### **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**

Tablet core : polyvidone, colloidal silicon dioxide, microcrystalline cellulose, croscarmellose sodium, magnesium stearate

Tablet coating : triethyl citrate, glycerol monostearate, methacrylic acid copolymer (type C), talc, titanium dioxide (E171)

**6.2 Incompatibilities**

None known.

**6.3 Shelf life**

48 months.

**6.4 Special precautions for storage**

Store below 25°C.

Blisters : keep blister in the outer carton in order to protect from light

**6.5 Nature and contents of container**

Transparent or coloured PVC/PVDC blister with aluminium foil in cartons containing 56 tablets.

**6.6 Special precautions for disposal**

None applicable.

**7 MARKETING AUTHORISATION HOLDER**

Ranbaxy (UK) Limited

20 Balderton Street

London

W1K 6 TL

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 14894/0534

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION****10 DATE OF REVISION OF THE TEXT****11 DOSIMETRY (IF APPLICABLE)****12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

**1 NAME OF THE MEDICINAL PRODUCT**

Naproxen EC 500mg Tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Naproxen EC 500mg Tablets: each tablet contains 500mg naproxen.

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Gastro-resistant film-coated tablets.

Naproxen EC 500mg Tablets: an oblong, biconvex, white or almost white, film-coated tablet with a smooth surface containing 500mg of naproxen

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications**

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

**4.2 Posology and method of administration**

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

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

**Adults***Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis*

The usual dose is 500mg to 1g daily taken in 2 doses at 12-hour intervals. Where 1g per day is needed either one 500mg tablet twice daily or two 500mg tablets in a single administration (morning or evening) is recommended. In the following cases a loading dose of 750mg or 1g per day for the acute phase is recommended:

- a) In patients reporting severe night-time pain/or morning stiffness.
- b) In patients being switched to Naproxen from a high dose of another anti-rheumatic compound.
- c) In osteoarthritis where pain is the predominant symptom.

*Acute musculoskeletal disorders and dysmenorrhoea*

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 Naproxen 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 Use in patients with impaired renal function.

*Children*

Naproxen EC is not recommended for use 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 history of peptic ulceration or active gastrointestinal bleeding.
- Hypersensitivity to naproxen and naproxen sodium formulations, or to any of the excipients.
- Since the potential exists for cross-sensitivity reactions, Naproxen EC should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce asthma, rhinitis, nasal polyps or urticaria.
- Severe heart failure.

**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 cardiovascular risks below).

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

Elderly patients are particularly susceptible to the adverse events of NSAIDs. Prolonged use of the NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Episodes of gastro-intestinal bleeding have been reported in patients with naproxen therapy. Naproxen 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 Naproxen 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 Naproxen EC.

*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. Naproxen 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 Naproxen 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 Naproxen 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.

*Precautions related to fertility*

The use of naproxen, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or 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.

*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, smoking).

#### **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.

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 overdosage 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 sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

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 corticosteroids because of the increased risk of bleeding.

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 Naproxen 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.

#### 4.6 Pregnancy and lactation

##### *Pregnancy*

As with other drugs of this type, naproxen produces delay in parturition in animals and also affects the human foetal cardiovascular system (closure of ductus arteriosus). Therefore, naproxen should not be used during pregnancy unless clearly needed.

##### *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, thus increasing the risk of uterine haemorrhage.

##### *Nursing mothers*

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

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

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of Naproxen. If patients experience these or similar undesirable effects, they should exercise caution in carrying out activities that require alertness.

#### 4.8 Undesirable effects

*Gastrointestinal* : The more frequent reactions are nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal discomfort and epigastric distress. More serious reactions which may occur occasionally are gastro-intestinal bleeding, peptic ulceration (sometimes with haemorrhage and perforation), non-peptic gastro-intestinal ulceration and colitis. Jaundice, fatal hepatitis, ulcerative stomatitis, abnormal liver function tests, oesophagitis and pancreatitis have been reported rarely.

*Dermatological* : Skin rashes including fixed drug eruption, itching (pruritis), urticaria, ecchymoses, purpura, sweating. Alopecia, erythema multiforme, Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis and photosensitivity reactions (including cases in which the skin resembles porphyria cutanea tarda, "pseudoporphyria") or epidermolysis bullosa-like reactions may occur rarely.

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*CNS* : Convulsions, dizziness, headache, lightheadedness, insomnia, drowsiness, dream abnormalities, depression, vertigo, aseptic meningitis, inability to concentrate and cognitive dysfunction have been reported.

*Cardiovascular* : Dyspnoea, oedema, palpitations, congestive heart failure and hypertension have been reported 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 a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

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

*Respiratory* : Asthma, eosinophilic pneumonitis and pulmonary oedema.

*Reproductive, femal* : Infertility

*Special senses* : Tinnitus, hearing disturbances including impairment, visual disturbances, corneal opacity, papillitis, retrobulbar optic neuritis and papilloedema.

*Other* : Thirst, pyrexia, mild peripheral oedema, malaise, myalgia, muscle weakness. Anaphylactic reactions to naproxen and naproxen sodium formulations including angioneurotic oedema, have been reported in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs.

#### **4.9 Overdose**

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea, renal dysfunction or vomiting.

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

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 Naproxen 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.

ATC code: M01A E02 (anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives).

### **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**

Tablet core : polyvidone, colloidal silicon dioxide, microcrystalline cellulose, croscarmellose sodium, magnesium stearate

Tablet coating : triethyl citrate, glycerol monostearate, methacrylic acid copolymer (type C), talc, titanium dioxide (E171)

**6.2 Incompatibilities**

None known.

**6.3 Shelf life**

48 months.

**6.4 Special precautions for storage**

Store below 25°C.

Blisters : keep blister in the outer carton in order to protect from light

**6.5 Nature and contents of container**

Transparent or coloured PVC/PVDC blister with aluminium foil in cartons containing 56 tablets.

**6.6 Special precautions for disposal**

None applicable.

**7 MARKETING AUTHORISATION HOLDER**

Ranbaxy (UK) Limited

20 Balderton Street

London

W1K 6 TL

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 14894/0535

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

22/02/2008

**10 DATE OF REVISION OF THE TEXT****11 DOSIMETRY (IF APPLICABLE)****12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)**

PACKAGE LEAFLET: INFORMATION FOR THE USER

# **R** Naproxen EC 250mg and 500mg Tablets Naproxen

**Read all of this leaflet carefully before you start taking this medicine**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**

1. What Naproxen EC is and what it is used for
2. Before you take Naproxen EC
3. How to take Naproxen EC
4. Possible side effects
5. How to store Naproxen EC
6. Further information

**1. WHAT NAPROXEN EC IS AND WHAT IT IS USED FOR**

Naproxen EC tablets contain the active ingredient naproxen, which belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). These medicines help to relieve pain and joint inflammation.

Naproxen EC can be used to treat rheumatoid arthritis, osteoarthritis, ankylosing spondylitis (causing pain and stiffness in the back), back pain, neck pain, and swollen or painful tendons. It is also used to treat sprained or strained muscles or painful menstrual periods.

**2. BEFORE YOU TAKE NAPROXEN EC****Do not take Naproxen EC if you:**

- are **allergic** (hypersensitive) to **Naproxen EC** or **any of the ingredients** it contains (see Section 6).
- have a **stomach ulcer**, or **bleeding of the stomach or intestine**.
- have had **wheeziness** (asthma), **hay fever**, **itchiness** or **skin rash** (urticaria) **after taking aspirin or other NSAIDs** (non-steroidal anti-inflammatory drugs).
- are attempting to become **pregnant**.
- are **under sixteen years** of age.
- suffer from **severe heart failure**.

**Take special care with Naproxen EC (and talk to your doctor) if you:**

- suffer from stomach problems. It is known that bleeding in the stomach or gut can occur in patients taking Naproxen EC. If you find you have black, tarry stools while taking these tablets you must stop taking them and tell your doctor at once.
- have asthma, hayfever or allergies as these tablets can cause breathing difficulties (bronchospasm).
- have ever suffered any allergic reactions after taking aspirin or other NSAIDs or if you have a history of swelling of the tongue or larynx (angioedema), asthma, inflammation of the nose (rhinitis), or nasal polyps.
- are having liver or adrenal function tests as taking these tablets can change the results.
- suffer from any blood clotting disorders or are taking anti-coagulant therapy (blood thinning medicines) e.g. heparin or warfarin, as naproxen decreases the ability of your blood to clot and will increase the length of time you bleed if you get a cut.
- have heart problems. Occasionally patients have reported swollen feet or hands while taking these tablets and this is more likely in patients who have heart problems.
- have kidney problems. Your doctor may wish to check your kidney function before and during treatment and/or use a lower dose than normal.
- have liver problems, including alcohol-related disease or other forms of cirrhosis of the liver, as you should then take the least number of tablets needed.

**Please note:**

Medicines such as Naproxen EC may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke. Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment.

If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have a high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

**Taking other medicines**

Please tell your doctor or pharmacist if are taking other medicines, including any you have bought without a prescription. This is important because Naproxen EC could alter how other medicines work. These include medicines for:

- epilepsy (hydantoins)
- blood clots (anti-coagulants)
- oral diabetic drugs (sulphonylureas)
- infections (sulphonamides or quinolone antibiotics)
- heart failure (furosemide or cardiac glycosides such as digoxin)
- depression (lithium)
- high blood pressure (propranolol and other beta-blockers, ACE inhibitors e.g. cilazapril)
- gout (probenecid) and psoriasis (methotrexate)
- arthritis (steroids)
- other NSAIDs (such as aspirin)
- acute organ rejection (cyclosporin)
- mifepristone (a drug usually prescribed through hospitals)

**Pregnancy and breast-feeding**

You must tell your doctor if you are pregnant or if you think you may be pregnant. Your doctor will then discuss this with you and decide whether you should take this medicine.

If you are breast -feeding you should not take these tablets.

Ask your doctor or pharmacist for advice before taking any medicines.

**Driving and using machines**

You should not drive or operate machinery if you are affected by dizziness, tiredness, abnormal vision or depression when taking Naproxen EC.

**3. HOW TO TAKE NAPROXEN EC****Dosage**

Always take Naproxen EC exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The number of tablets you should take depends on the type of pain you have.

Read the following section carefully. It tells you how the tablets are usually taken. Do not take more than you are told to, as this increases the chances of side-effects (especially in the elderly).

For rheumatoid arthritis, osteoarthritis or ankylosing spondylitis

Take between 500mg and 1g each day in two separate doses, 12 hours apart. Where 1g per day is needed, you can take 500mg twice each day, or 1g in one single dose (morning or evening).

In some people, a larger dose of between 750mg and 1g per day may be taken to start with to control the pain. This is in patients with:

- severe night-time pain and/or morning stiffness.
- if your tablets have recently been changed from a high dose of another treatment for pain.
- osteoarthritis where pain is your main problem.

For strained or sprained muscles or painful periods

Take 500mg to start with, then 250mg every 6 to 8 hours as needed. Do not take more than 1250mg a day after the first day.

**If you take more Naproxen EC than you should**

If you take too many tablets, contact your doctor, pharmacist or nearest hospital straight away.

**If you forget to take Naproxen EC**

If you should forget to take your tablets, take the normal dosage as soon as you remember and then wait for the normal interval before taking the next dose. Do not take a double dose to make up for a forgotten one.

**If you stop taking Naproxen EC**

Your doctor will advise you when to stop taking the medicine.

If you have any further questions on the use of this product, ask your doctor or pharmacist

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Naproxen EC can cause side effects, although not everybody gets them.

**If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

Tell your doctor if you have any of the following problems which do not go away: nausea, vomiting, stomach discomfort or heartburn.

**Stop taking your tablets and talk to your doctor urgently if you have any of the following problems: passing of black, tarry stools or blood, mouth or stomach ulcers, severe diarrhoea and lower abdominal pains (colitis).**

Other problems may include:

**Allergies**

Allergic reactions to naproxen.

**Gastro-Intestinal**

Constipation, inflammation of the pancreas.

**Skin**

Skin rash, red scaly rash on the face, itchiness (urticaria), bruising, bluish/black marks or spots on the skin, tender bruise like swellings (erythema nosodum), swelling of the neck and face (angioedema), redness of the skin (erythema multiforme), blistering of hands or feet (Stevens Johnson syndrome), pus containing spots, peeling skin (epidermal necrolysis), rare reactions due to exposure to light including inflammation of the skin and blistering eruptions (pseudoporphyria or epidermolysis bullosa-like reactions), swelling of the hands or feet (peripheral oedema), sweating or yellow skin (jaundice).

**Hair**

Loss of hair (alopecia).

**Liver**

Life-threatening inflammation of the liver (hepatitis), changes in liver function tests.

**Kidney**

Inflammation of the kidney (glomerular or interstitial nephritis), protein in the urine (nephrotic syndrome), blood in urine (haematuria), death of part of the tissue of your kidneys (renal papillary necrosis), changes in kidney function tests or kidney failure.

**Lung**

Asthma, inflammation of the lung (eosinophilic pneumonitis), fluid on the lungs (pulmonary oedema).

**Heart**

Breathlessness, high blood pressure (hypertension), irregular heartbeat (palpitations), heart failure, oedema.

Medicines such as Naproxen EC may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke (swelling).

**Head**

Convulsions, headache, tiredness, inability to sleep (insomnia), change in dream patterns, inability to concentrate or remember things (cognitive dysfunction), ringing or buzzing in the ears (tinnitus), problems with hearing, light-headedness, dizziness (vertigo), depression, ulcers or inflammation in the inside of the mouth (ulcerative stomatitis) or non-infectious inflammation of the membranes of the brain (aseptic meningitis).

**Blood**

A reduction in the number of platelets (thrombocytopenia), an increase or decrease in white blood cells, a reduction of the quantity of the oxygen-carrying pigment haemoglobin in the blood (anaemia) caused by decreased production (aplasia) or increased destruction (haemolysis) of red blood cells, high levels of potassium in the blood (hyperkalaemia) or inflammation of blood vessels (vasculitis).

**Eyes**

Visual disturbances or problems with sight. If you do develop any visual disturbances during treatment, then you should talk to your doctor who may arrange for you to have an eye examination.

**Fertility**

As with other NSAIDs, Naproxen EC may make it difficult to become pregnant. You should inform your doctor if you are attempting to become pregnant or if you have problems becoming pregnant.

**General**

These tablets may cause muscle weakness or pain, swelling (oedema), thirst or fever.

If you are concerned about these or any other unwanted effects talk to your doctor.

**If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

**5. HOW TO STORE NAPROXEN EC**

- Store below 25°C
- Keep blister in the outer carton in order to protect from light
- Keep pack in a dry place
- Keep this medicine out of the reach and sight of children.
- This medicine must not be used after the date (EXP) printed on the pack. The expiry date refers to the last day of the month. Consult your pharmacist if you have any doubts about the shelf life.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**6. WHAT NAPROXEN EC CONTAINS****What Naproxen EC contains**

- The active substance is naproxen
  - Naproxen EC 250 mg tablets contain 250 mg naproxen
  - Naproxen EC 500 mg tablets contain 500 mg naproxen

- The other ingredients are povidone, colloidal silicon dioxide, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, triethyl citrate, glycerol monostearate, methacrylic acid copolymer (type C), talc, titanium dioxide (E171), as inactive ingredients.

**What Naproxen EC looks like and contents of pack**

Naproxen EC 250 mg tablets: round, biconvex, white or almost white, film-coated, smooth surface  
 Naproxen EC 500 mg tablets: oblong, biconvex, white or almost white, film-coated, smooth surface

Both strengths of Naproxen EC are supplied in blister packs of 56 tablets.

**Marketing Authorisation Holder and Manufacturer**

Ranbaxy (UK) Limited  
 20 Balderton Street  
 W1 6 TL London  
 United Kingdom

**This medicinal product is authorised under the following names :**

Naproxen EC 250 mg Tablets: PL ...  
 Naproxen EC 500 mg Tablets: PL ...

**This leaflet was last approved in**



