NAPROXEN 250MG EC TABLETS
PL 30306/0226

UKPAR

TABLE OF CONTENTS

Lay Summary ........................................... Page 2
Scientific discussion ................................. Page 3
Steps taken for assessment ....................... Page 10
Steps taken after authorisation – summary ...... Page 11
Summary of Product Characteristics .......... Page 12
Product Information Leaflet ....................... Page 27
Labelling .............................................. Page 29
LAY SUMMARY

The MHRA granted Actavis Group PTC ehf a Marketing Authorisation (licence) for the medicinal product Naproxen 250mg EC Tablets on 25th June 2009. This product, to be available by prescription only (POM), contains naproxen and is used for the treatment of rheumatoid arthritis (including in children), osteoarthritis, ankylosing spondylitis, attacks of gout, muscle and bone disorders and painful periods.

The active ingredient naproxen is part of a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs), which are used to reduce inflammation and pain in joints and muscles.

This application is a duplicate of a previously granted application for Naproxen EC Tablets 250mg (PL 00142/0437), granted to Actavis UK Limited on 31st January 2000.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Naproxen 250mg Enteric-Coated Tablets outweigh the risks, hence a Marketing Authorisation has been granted.
NAPROXEN 250MG EC TABLETS
PL 30306/0226

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Preclinical assessment Page 8
Clinical assessment Page 9
Overall conclusions and risk benefit assessment Page 10
INTRODUCTION

The UK granted a marketing authorisation for the medicinal product Naproxen 250mg EC Tablets (PL 30306/0226) to Actavis Group PTC ehf on 25th June 2009. The product is available as a prescription-only medicine (POM).

The application was submitted as an abridged application according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Naproxen EC Tablets 250mg (PL 00142/0437), which was granted to Actavis UK Limited on 31st January 2000.

No new data were submitted nor were they necessary for this application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated for it.

The active ingredient naproxen acts as a non-steroidal anti-inflammatory, reducing the levels of prostaglandins. Naproxen 250mg EC Tablets is indicated for the treatment of juvenile rheumatoid arthritis, rheumatoid arthritis, ankylosing spondylitis, osteoarthrosis, acute gout, and acute musculoskeletal disorders (for example sprains and strains, tenosynovitis, fibrositis, lumbosacral pain, direct trauma, and cervical spondylitis), and dysmenorrhea.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 30306/0226
PROPRIETARY NAME: Naproxen 250mg EC Tablets
ACTIVE(S): Naproxen
COMPANY NAME: Actavis Group PTC ehf
LEGAL STATUS: POM

1. INTRODUCTION
This is an application for Naproxen 250mg EC Tablets submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Actavis Group PTC ehf, Reykjavíkurvegi 76-78, 220 Hafnarfjordur, Iceland.

The application cross-refers to Naproxen EC Tablets 250mg (PL 00142/0437), which was granted to Actavis UK Limited on 31st January 2000. The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed name of the product is Naproxen 250mg EC Tablets. The product has been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The product contains naproxen, equivalent to 250mg. It is to be stored in a polyvinylidene chloride/polyvinylchloride/aluminium blisters, in pack sizes of 28, 30, 56, 60, 84, 90, 100 and 112 tablets. Not all pack sizes are to be marketed, however, the marketing authorisation holder has committed to submitting mock-ups of the patient information leaflet and packaging before marketing any pack size of the product.

The proposed shelf-life (36 months) and storage conditions (store in original packaging, do not store above 25 degrees) are consistent with the details registered for the cross-reference product.

2.3 Legal status
On approval, the products will be available as prescription-only medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
Actavis Group PTC ehf, Reykjavíkurvegi 76-78, 220 Hafnarfjordur, Iceland.

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.
2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
With the exception of lactose monohydrate, no materials of animal or human origin are included in the product. This is consistent with the cross reference product.

It has been confirmed that lactose monohydrate is sourced from milk that is fit for human consumption and no animal materials, with the exception of bovine rennet, have been used in its manufacture. Any bovine rennet used complies with the criteria laid out in the CPMP Biotechnology Working Party Public Report of 22 May 2002 (EMEA/BWP/CPMP/337/02).

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summary is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

Carton and blister
The applicant has provided the proposed wording for the packaging. No mock-ups have been provided as the applicant is not currently planning to market the product in the UK. Confirmation has been provided that mock-ups of the packaging will be provided before any marketing of the product takes place in the UK.
7. CONCLUSIONS
The data submitted with the application are acceptable. A Marketing Authorisation should be granted.
PRECLINICAL ASSESSMENT

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

As this is a duplicate application, no new clinical data have been supplied and none are required.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data are consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
This application is identical to a previously granted application for Naproxen EC Tablets 250mg (PL 00142/0437).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. 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 EC TABLETS
PL 30306/0226

STEPS TAKEN FOR ASSESSMENT

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NAME OF THE MEDICINAL PRODUCT
Naproxen 250mg EC Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains: 250mg Naproxen.

PHARMACEUTICAL FORM
Gastro-resistant tablets.
White, round, biconvex enteric-coated tablets, printed in black “C NM” on one face, blank on the reverse.

CLINICAL PARTICULARS

Therapeutic indications
Naproxen is indicated for the treatment of:
1) Rheumatoid arthritis.
2) Osteoarthritis (degenerative arthritis).
3) Ankylosing spondylitis.
4) Juvenile rheumatoid arthritis.
5) Acute gout.
6) Acute musculoskeletal disorders.
7) Dysmenorrhoea.

Posology and method of administration
Posology
Adults:
Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis: 500mg-1g daily in two doses at twelve hourly intervals, or alternatively, if 1g daily is needed this can be administered as two 500mg doses or as a single dose. The size of the morning and evening doses can be adjusted on the basis of the predominant symptoms (ie night time pain or morning stiffness)
Acute gout: Initially 750mg followed by 250mg every 8 hours until the attack has passed.
Acute musculoskeletal disorders and dysmenorrhoea: Initially 500mg followed by 250mg every 6-8 hours as necessary to a maximum of 1250mg daily after the first day.
Children over 5 years: For juvenile rheumatoid arthritis 10mg/kg a day taken in two doses every 12 hours.
Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy. Studies indicate that although total plasma concentration of naproxen is unchanged, unbound plasma fraction of naproxen is increased in the elderly. The implication of this finding for naproxen dosing is unknown. As with other drugs used in the elderly it is prudent to use the lowest effective dose. Dosage should be reduced in the elderly where there is an impairment of renal function. (See other special warnings and precautions).
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

Method of Administration
For oral administration. Tablets should be swallowed whole and not broken or crushed. To be taken preferably with or after food.
4.3 **Contraindications**

Patients with active gastrointestinal bleeding or peptic ulceration, known hypersensitivity to naproxen, naproxen sodium or any other ingredient in the formulation.

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

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

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

During the last trimester of pregnancy (see section 4.6)

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

4.4 **Special warnings and precautions for use**

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

*Cardiovascular and cerebrovascular effects*

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

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

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

*Gastrointestinal bleeding, ulceration and perforation:*

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with 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 below and section 4.5).

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

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

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).
Cardiovascular, Renal and Hepatic Impairment:
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

Impaired renal function: Naproxen should be used with great caution where there is impairment of renal function as it is eliminated to a large extent (95%) via glomerular filtration; the monitoring of serum creatinine and/or creatinine clearance should be conducted in these patients. Naproxen is not recommended in patients having baseline creatinine clearance less than 20ml/minute.

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

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

Elderly:
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2)

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

SLE and mixed connective tissue disease:
In patients with systemic lupus erythematousus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Dermatological:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Naproxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

Anaphylactic (anaphylactoid) reactions:
Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to aspirin, other non-steroidal anti-inflammatory drugs or naproxen-containing products. They may also occur in individuals with a history of angioedema, bronchospastic reactivity (eg asthma), rhinitis and nasal polyps.

Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.
Naproxen, in common with other NSAIDs, decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined. Patients who have coagulation disorders, or who are receiving drug therapy that interferes with haemostasis, should be carefully observed if they are taking naproxen. Patients on full anticoagulant therapy (e.g. heparin or warfarin) may be at an increased risk of bleeding if given naproxen concurrently. Therefore, the benefits should be weighed against these risks.

Mild peripheral oedema has been observed in a few patients. Although sodium retention has not been reported in metabolic studies, patients with questionable or compromised cardiac function may be at a greater risk when taking Naproxen.

This product contains potassium sorbate. Caution should be used in treating patients on a low potassium diet. High blood levels of potassium can cause stomach upset and diarrhoea.

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

Steroids: If steroid dosage is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Ocular effects: Studies have not shown changes in the eye attributable to naproxen administration. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilledema, have been reported in users of NSAIDs including naproxen, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with naproxen-containing products should have an ophthalmological examination.

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

The use of Naproxen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

- Naproxen is highly protein-bound hence patients receiving hydantoins, anticoagulants or a highly protein-bound sulphonamide should be closely monitored for signs of overdosage of these drugs. No interactions have been observed in clinical studies with naproxen and sulphonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.
- NSAIDs, including naproxen, have been reported to increase steady state plasma lithium levels by inhibition of renal lithium clearance. Decreased elimination of lithium. It is recommended that these levels are monitored whenever initiating, adjusting or discontinuing naproxen.
- Anti-hypertensives: Reduced anti-hypertensive effect. Concomitant administration of naproxen with beta blockers such as propranolol may reduce their antihypertensive effect 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.
- Decreased elimination of methotrexate. Caution is advised when methotrexate is administered concurrently, due to the possible enhancement of its toxicity as naproxen, like other NSAIDs, has been reported to reduce tubular secretion of methotrexate in an animal model.
- The natriuretic effect of frusemide has been reported to be inhibited by some drugs of this class. Naproxen therapy should be temporarily withdrawn 48 hours before adrenal function tests are performed as it may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxyindoleacetic acid.
• NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.
• As with all NSAIDs, caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.
• NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.
• As with all NSAIDs, caution should be taken when co-administering with corticosteroids because of the increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
• Patients taking quinolones may have an increased risk of developing convulsions.
• Other analgesics including cyclo-oxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).
• Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.
• Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).
• Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.
• Anti-platelet agents and selective serotonin reuptake inhibitors (SSRls): Increased risk of gastrointestinal bleeding (see section 4.4).
• Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
• Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haem arthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).
Dermatological: Angio-oedema, skin rashes, urticaria. Alopecia, epidermal necrolysis, erythema multiforme, Stevens Johnson syndrome, Toxic Epidermal Necrolysis (very rare) and photosensitivity reactions (including cases in which the skin resembles porphyria cutanea tarda, “pseudoporphyria”) or epidermolysis bullosa may occur rarely.

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

Haematological: Aplastic anaemia, neutropenia, granulocytopenia including agranulocytosis, haemolytic anaemia and thrombocytopenia may occur rarely.

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

Hepatic: abnormal liver function, hepatitis and jaundice.

Other: Hearing impairment, mild peripheral oedema. Anaphylactic reactions to naproxen have been reported in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs. Eosinophilic pneumonitis, hyperkalaemia, ulcerative stomatitis, vasculitis have been reported rarely.

Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggests that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke (see section 4.4).

4.9 Overdose

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

b) Therapeutic measure
Patients should be treated symptomatically as required.

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

Good urine output should be ensured.

Renal and liver function should be closely monitored.

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

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.
5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Naproxen is a non-steroidal anti-inflammatory agent.

Naproxen reduces the synthesis of prostaglandins primarily by inhibiting the enzyme cyclo-oxygenase. Naproxen has been shown to have anti-inflammatory activity in a number of experimental models. Naproxen inhibits prostaglandin E2 synthesis in vitro by human rheumatoid synovial microsomes. It also inhibits prostaglandin E2 production by phytohaemagglutin-stimulated peripheral blood mononuclear cells. At 10–4 M (23mg.l-1) naproxen inhibits neutral protease activity derived from human polymorphonuclear leucocytes. Naproxen also inhibits in vitro the activity of cathepsin-β and other hydrolytic enzymes derived from lysosomes. Naproxen is a potent inhibitor of leucocyte migration and produces effects comparable to those of colchicine.

5.2 Pharmacokinetic properties
Naproxen is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are attained 2-4 hours after ingestion. Plasma concentrations of naproxen increase proportionally with dose up to about 500mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. At therapeutic concentrations naproxen is more than 99% bound to plasma proteins and has a plasma half-life of about 13 hours. Approximately 95% of a dose is excreted in urine as naproxen and 6-O-desmethylnaproxen and their conjugates. Less than 3% of a dose has been recovered in the faeces. Naproxen crosses the placenta and is excreted in breast milk.

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Methacrylic acid-ethylacrylate copolymer (1:1), lactose, magnesium stearate, maize starch, crospovidone, propylene glycol, shellac glaze, sodium hydroxide, triethyl citrate, titanium dioxide (E171), iron oxide black (E172), potassium sorbate (E202), sodium citrate (E331), xanthan gum (E415), hydroxypropyl cellulose (E463), purified talc (E553), beeswax.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Shelf-life
36 months from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.

Shelf-life after first opening
Not applicable.

6.4 Special precautions for storage
Do not store above 25°C.
Store in the original package.

6.5 Nature and contents of container
PVC/PVdC/Aluminium blister. Pack sizes of 28, 30, 56, 60, 84, 90, 100, 112 tablets.

6.6 Special precautions for disposal
Not applicable.
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NAPROXEN 250MG EC TABLETS
PL 30306/0226

Naproxen 250mg EC tablets

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 get 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 tablets are and what they are used for
2. Before you take Naproxen EC tablets
3. How to take Naproxen EC tablets
4. Possible side effects
5. How to store
6. Further information

1. What Naproxen EC tablets are and what they are used for
Naproxen belongs to a group of medicines called non-steroidal anti-inflammatory drugs (NSAIDs), which are used to reduce inflammation and pain in joints and muscles.

Naproxen EC tablets are used to treat:
- diseases of joints such as rheumatoid arthritis (including in children), osteoarthritis and ankylosing spondylitis. Naproxen EC tablets cannot cure arthritis but is used to give relief of some of the symptoms such as inflammation, swelling, stiffness and joint pain.
- attacks of gout.
- muscle and bone disorders.
- painful periods.

2. Before you take Naproxen EC tablets
Do not take Naproxen EC tablets if you:
- are allergic to naproxen or to any of the other ingredients in Naproxen EC tablets (see section 6)
- are allergic to aspirin or other non-steroidal anti-inflammatory medicines (NSAIDs), or you have developed signs of asthma (wheezing), runny nose, swelling of the skin or rash when taking this medicine
- have or have had stomach or duodenum (gut) ulcers, bleeding in the stomach or intestines (gastrointestinal bleeding) or have had two or more episodes of peptic ulcers, stomach bleeding or perforation
- are in the last three months of pregnancy or if you are breast feeding
- have severe liver, kidney or heart failure.

If you are not sure about any of the above conditions, please ask your doctor.

Check with your doctor before taking Naproxen EC tablets if you:
- are on a low potassium diet, as this product contains potassium sorbate. High blood levels of potassium can cause stomach upset and diarrhoea
- use other non-steroidal anti-inflammatory medicines (NSAIDs) or any medication which may cause bleeding or ulcers in the stomach
- have a history of gastrointestinal disease e.g. ulcerative colitis, Crohn's disease
• are elderly
• have or have had high blood pressure or any liver, kidney or heart problems
• have or have had bronchial asthma, other breathing problems or nasal polyps
• have systemic lupus erythematosus or other connective tissue disorders
• are a women trying to become pregnant or undergoing investigation of infertility.

Other warnings
• Medicines such as naproxen 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 high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.
• If you are elderly or frail, you have a higher risk of getting side effects, especially of the stomach. If you experience any unusual symptoms from the stomach you must tell your doctor about it.
• Naproxen EC tablets may hide the symptoms of an infection.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken, any other medicines, including medicines obtained without a prescription. Especially:
• other NSAIDs such as aspirin or COX II inhibitors
• medicines which thin the blood or which prevent blood clotting (e.g. heparin or warfarin)
• corticosteroids (e.g. prednisolone), if needed the doctor will reduce the dose of the steroid slowly and monitor for side effects.
• diuretics (‘water tablets’) such as furosemide
• medicines to treat high blood pressure (e.g. captopril, ramipril or propranolol)
• ciclosporin or tacrolimus
• mifepristone – do not take NSAIDs 8-12 days after mifepristone
• SSR1 antidepressants
• zidovudine
• quinolones (e.g. ciprofloxacin)
• probenecid
• methotrexate
• lithium
• hydantoins (e.g. phenytoin)
• sulphonamides (e.g. sulfamethoxazole)
• sulphonylureas (e.g. glibenclamide or gliclazide)
• cardiac glycosides (e.g. digoxin)

Pregnancy and breast-feeding
Naproxen may make it more difficult to become pregnant. You should inform your doctor if you are planning to become pregnant or if you have problems becoming pregnant.
You should not take Naproxen EC in the first 6 months of pregnancy and must not take Naproxen EC in the last 3 months of pregnancy or during labour.
If you are breast-feeding, you should not take Naproxen EC tablets.

Driving and using machines
Naproxen EC tablets may cause dizziness, drowsiness or affect your vision. Make sure you are not affected before you drive or operate machinery.

Sugar intolerance
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine, as it contains lactose.

Tests
If you need any blood or urine tests tell your doctor you are taking Naproxen EC tablets. The tablets may need to be stopped 48 hours before a test, as they may interfere with the results.

3. How to take Naproxen EC tablets
Always take Naproxen EC tablets exactly as your doctor has told you. If you are not sure, check with your doctor or pharmacist.

Swallow whole with or after food with water. Do not crush or break them.

Dosage:

Your doctor should prescribe as low a dose as possible. This will reduce any side effects you may experience.

Adults:
- Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis: 500mg-1g a day in two doses at twelve hourly intervals. If 1g a day is needed this can be given as two 500mg doses or as a single dose.
- Attack of gout: Initially 750mg as a single dose then 250mg every 8 hours until the attack has passed.
- Muscle and bone disorders and painful periods: Initially 500mg as a single dose then 250mg every 6-8 hours as necessary. Up to a maximum of 1250mg a day may be given after the first day.

Children over 5 years for juvenile rheumatoid arthritis:
10mg per kg of body weight a day, taken in two doses at twelve hourly intervals.

Elderly with kidney disease:
Dosage may be reduced in the elderly.

If you take more Naproxen EC tablets than you should
It is important not to take too many tablets. Contact your doctor, pharmacist or nearest hospital casualty department immediately if you have taken more tablets than you should. Symptoms of an overdose are feeling or being sick, heartburn, drowsiness, fits and indigestion.

If you forget to take Naproxen EC tablets
If you forget to take your tablets, take your next dose as soon as you remember, unless it is nearly time for your next dose. Do not take a double dose to make up for one you have missed.

4. Possible side effects
Like all medicines, Naproxen EC tablets can cause side-effects, although not everybody gets them. If any of the side effects get worse, or if you notice any not listed in this leaflet, please tell your doctor or pharmacist.
Stop taking Naproxen tablets and contact your doctor immediately if you
- develop stomach or intestinal ulcers or bleeding, indigestion, heartburn or abdominal pain (pains in your stomach) or other abnormal stomach symptoms
- Pass blood in your faeces (stools/motions)
- Pass black tarry stools
- Vomit any blood or dark particles that look like coffee grounds.

Tell your doctor if you notice any of the following side effects:
- Allergic reaction: an itchy skin rash, blood spots, bruising or discolouring of the skin, red patches (erythema multiforme), a severe rash with reddening, peeling and swelling of the skin that resembles burns (epidermal necrolysis), or any other severe reactions like swelling of the face, mouth, tongue or airways, feeling and being sick, difficulty breathing or wheezing.
- Nervous system: fits, headache, ringing in the ears, a spinning sensation, difficulty concentrating and sleeping, inflammation of the optic nerve, disturbed vision, tingling or "pins and needles", depression, confusion, sensing things that are not there, dizziness, feeling of general discomfort and illness, tiredness, drowsiness, septic meningitis (may cause fever, feeling or being sick, disorientation, headache, neck stiffness and light intolerance).
- Skin: rashes which may be red, itchy or blisters, hair loss, swelling of the face or body, sensitivity of the skin to light, red patches (erythema multiforme), severe skin rash with flushing, fever, blisters or ulcers (Stevens-Johnson syndrome) or a severe rash with reddening, peeling and swelling of the skin that resembles burns (epidermal necrolysis).
- Stomach and intestine: stomach, duodenal or intestinal bleeding, ulcers or perforation, feeling or being sick, diarrhoea, wind, constipation, inflammation of the stomach lining (gastritis), worsening of colitis and Crohn’s disease.
- Kidneys: kidney damage or failure and blood in the urine.
- Other: changes in the numbers and types of blood cells (if you develop sore throats, nose bleeds or infections consult your doctor), water retention, hearing difficulties, swelling of the hands and feet, lung damage, jaundice (yellow skin or eyes), high blood potassium levels, mouth ulcers, inflammation of blood vessels, inflammation of the liver, heart failure.
- Medicines such as naproxen may be associated with a small increased risk of heart attack (myocardial infarction) or stroke.

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

5. How to store
Keep out of the reach and sight of children.
Do not store above 25°C. Store in the original package.
Do not use Naproxen EC tablets after the expiry date stated on the label/carton/bottle. The expiry date refers to the last day of that month.
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. Further information
What Naproxen EC tablets contain
- The active substance (the ingredient that makes the medicine work) is 250mg, 375mg or 500mg of naproxen.
- The other ingredients are methacrylic acid-ethylacrylate copolymer (1:1), lactose, magnesium stearate, maize starch, crospovidone, propylene glycol, shellac glaze, sodium hydroxide, triethyl citrate, titanium dioxide (E171), iron oxide black (E172), potassium sorbate (E202), sodium citrate (E331), xanthan gum (E415), hydroxypropyl cellulose (E463), purified talc (E553), beeswax.

What Naproxen EC tablets look like and contents of the pack

250mg tablets are white, round, biconvex, enteric-coated tablets.

Pack sizes: 28, 30, 56, 60, 84, 90, 100, 112.

Marketing Authorisation Holder

Actavis Group PTC ehf
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland.

Manufacturer

Actavis, Bamstead, EX32 8NS

This leaflet was last revised in October 2008.
NAPROXEN 250MG EC TABLETS
PL 30306/0226

LABELLING

a) Cartons
Front panel:
NAPROXEN 250mg EC TABLETS
Quantity of tablets per container

For oral use

Flap
NAPROXEN 250mg EC TABLETS
*tablets
Braille (Naproxen 250mg EC Tablets)

Back panel
NAPROXEN 250mg EC TABLETS
Quantity of tablets per container

Each tablet contains 250mg Naproxen
Also contains: propylene glycol, potassium sorbate (E202), lactose.
Please read enclosed leaflet.
For oral use.
Use as directed by physician.
Keep out of the reach and sight of children.
Do not store above 25 °C
Store in the original package.
PL 30306/0226

Marketing Authorisation Actavis Group PTC ehf,
Reykjavikurvegi 76-78, 220 Hafnarfjordur
Iceland.
Place dispensing label here

Flap
Batch
Manufd
Exp

Side panel
NAPROXEN 250mg EC TABLETS
Quantity of tablets per container.
Barcode

Pack sizes of 28, 30, 56, 60, 84, 90, 100, 112 tablets
*not all pack sizes will be marketed

b) Foil:
Actavis logo
NAPROXEN 250mg EC TABLETS
Batch number
Expiry date