IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0408/020/001
Case No: 2034081

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Ranbaxy Ireland Limited

Spafield, Cork Road, **Cashel**, **Co. Tipperary**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

RIMOXYN NAPROXEN Tablets BP 250 mg

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **29/06/2007** until **17/11/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rimoxyn Naproxen Tablets BP 250 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Naproxen 250 mg.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablet

Flat yellow bevelled edge, round (11 mm) tablet, marked ‘RN250’ on one face with a breakline on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the symptomatic management of various arthritides, such as rheumatoid arthritis, osteoarthrosis, spondylitis, gout, etc., and of musculoskeletal disorders. For the management of juvenile polyarthritis and rheumatoid arthritis in children over the age of 5 years.

4.2 Posology and method of administration

For oral administration

Adults:
The usual dose is 250mg twice daily, with a maximum daily dose of 1000mg
In the case of gout a dose of 750mg may be required as an initial dose given once, with 250mg every 8 hours thereafter for a maximum of 72 hours. Subsequently use may be made of the usual regimen if necessary.

Elderly:
NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events.

The lowest dose compatible with adequate safe clinical control should be employed. See also Section 4.4.

Children over the age of 5 years:
The usual total daily dose is 10mg/kg body weight in divided doses every 12 hours.

The safety of the drug in children under the age of 5 years has not been demonstrated and its use cannot therefore be recommended in this group.
Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

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

4.3 Contraindications

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

Severe heart failure.
Patients with active peptic ulceration, active gastrointestinal bleeding or intestinal inflammation.

Patients with a history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to Naproxen or naproxen sodium formulations, Aspirin or other non-steroidal anti-inflammatory drugs.

4.4 Special warnings and precautions for use

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration necessary to control symptoms (see section 4.2 and GI and cardiovascular risks below). Patients treated with NSAIDs long term should undergo regular medical supervision to monitor for adverse events.

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

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

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).

Episodes of gastro-intestinal bleeding have been reported in patients with naproxen therapy. Naproxen 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 have occurred in this patient population.

The antipyretic and anti-inflammatory activities of Naproxen 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 was seen in any test indicating toxicity.

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

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 greater risk when taking Naproxen.

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 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.

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 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 the 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 a ophthalmological examination.

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.

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.

Gatrointestinal effects:
Gastrointestinal bleeding, ulceration and perforation; GI bleeding, ulceration or perforation,which can be fata, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher when 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 pateints requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 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 their condition may be exacerbated (see section 4.8- undesirable effects).

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

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 infraction or stroke). Although data suggests that the use of naproxen (100mg 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).

Dermatological effects:
Severe 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 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Naproxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

4.5 Interaction with other medicinal products and other forms of interaction

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

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Concomitant administration of an antacid of cholestyramine can delay the absorption of naproxen but does not affect its extent. Concomitant administration of food can delay the absorption of naproxen, but does no affect its extent.

Due to the high plasma protein binding of naproxen, patients simultaneously receiving hydantoins, anticoagulants or a highly protein-bound sulphonamide should be observed for signs of overdosage of these drugs. No interactions have been observed in clinical studies with naproxen and anticoagulants or sulphonylureas, but caution is nevertheless advised since interaction had been seen with other non-steroidal agents of this class.

The natriuretic effect of frusemide 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, among other non-steroidal anti-inflammatory drugs, has been reported to reduce the tubular secretion of methotrexate in an animal model.

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

As with all NSAIDs caution is advised when cyclosporin 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.

A reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations when co-administering aminoglycosides.

As with all NSAIDs, caution should be taken when co-administering with cortico-steroids because of the increased risk of bleeding or gastrointestinal ulceratoin. (see section 4.4).

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

Patients taking oral hypoglycaemic agents may experience an inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

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

4.6 Pregnancy and lactation

Teratology studies in rats and rabbits at dose levels equivalent on a human multiple basis to those which have produced foetal abnormality with certain other non-steroidal anti-inflammatory agents, e.g. aspirin, have not produced evidence of foetal damage with naproxen. As with other drugs of this type, naproxen delays parturition in animals (the relevance of this finding to human patients is unknown) and also affects the human foetal cardiovascular system (closure of the ductus arteriosus). Good medical practice indicates minimal drug usage in pregnancy and use of this class if therapeutic agents requires cautious balancing possible benefit against potential risk to the mother and foetus especially in the first and third trimesters.

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

4.7 Effects on ability to drive and use machines

Nothing stated.

4.8 Undesirable effects

Gastro-intestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation of 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 stomatits, exacerbation of colitis and Crohn's disease (see section 4.4- Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

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

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

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

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

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

Oedema, hypertension and cardiac failure have been reported in association 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 infraction or stroke) (see section 4.4).

4.9 Overdose

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea, or vomiting. A few patients have experienced seizures, but it is not clear 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 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 analgesic, anti-inflammatory and anti-pyretic actions.

5.2 Pharmacokinetic properties

Naproxen is a non-steroidal anti-inflammatory agent, readily absorbed from the gastrointestinal tract, metabolised in the liver and excreted mainly in the urine with a half-life of 12 to 15 hours.

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

Lactose
Starch (maize)
Quinoline yellow (E104)
Povidone
Magnesium stearate
Sodium starch glycolate (Type A).

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep in the original container. Keep the container tightly closed.

6.5 Nature and contents of container

Polypropylene/polyethylene containers and closures.

100, 250, 500 and 1000 tablets.
Not all pack sizes may be marketed

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy Ireland Ltd.
Spafield
Cork Road
Cashel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 408/20/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th November 1988
Date of last renewal: 18th November 2003

10 DATE OF REVISION OF THE TEXT

June 2007