IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0073/090/001
Case No: 2049103

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

Antigen Pharmaceuticals Ltd

Chandler House, **Castle Street**, **Roscrea**, **Co Tipperary**, **Ireland**

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

Genoxen 250 mg Tablets

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 **28/01/2009**.

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

Genoxen 250 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of Naproxen.

Excipient: Each tablet contains 45mg lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Yellow, flat, round, uncoated tablet with bevelled edges and embossed with 'N/250' on one side and 'a' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an anti-inflammatory analgesic in the management of osteoarthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis and acute gout. Also in tenosynovitis, fibrositis, sprains and various soft tissue injuries.

4.2 Posology and method of administration

Genoxen tablets are for oral administration only.

Adults:

For rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, the usual dose is 500mg to 1g daily taken in two doses at 12-hour intervals or as a single administration of two tablets, morning or evening. The dose of 1g per day should not be given for more than six months.

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 and/or morning stiffness.
(b) In patients being switched to Genoxen from a high dose of another anti-rheumatic compound.
(c) In osteoarthritis where pain is the predominant symptom.

For the patient who requires 750mg 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.

In acute gout, the recommended dosage is 750mg at once, then 250mg every eight hours until the attack has passed.
For the treatment of acute musculoskeletal disorders, the recommended dose is 500mg initially followed by 250mg at 6 - 8 hour intervals as needed, with a maximum daily dose after the first day of 1250mg.

Use in the 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 Genoxen dosing is unknown. As with other drugs used in the elderly, it is prudent to use the lowest effective dose. For the effect of reduced elimination in the elderly, refer to the section 'Use in patients with impaired renal function'.

Children:

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

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

4.3 Contraindications

Use in active peptic ulceration or gastro-intestinal inflammation. History of gastro-intestinal bleeding or perforation, related to previous NSAIDs Therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more episodes of proven ulceration or bleeding). Severe heart failure. Hypersensitivity to naproxen and naproxen sodium formulations. Since the potential exists for cross-sensitivity reactions, genoxen should not be given to pateints in whom aspirin or other non-steroidal anti-inflammatory/analgesic drugs induce asthma, rhinitis or urticaria.

4.4 Special warnings and precautions for use

Use of Genoxen with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

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

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)

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

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with hemorrhage 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 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 Genoxen, 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).

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.

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.

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

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.

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, such as in 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 could 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.

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 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. Genoxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose –galactose malabsorption should not take this medication.

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). 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.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the high plasma protein binding of naproxen patients simultaneously receiving hydantoins, anti-coagulants 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 anti-coagulants or sulphonylureas, but caution is nevertheless advised since interaction has 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 anti-hypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increase 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.

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-hydroxyindoleacetic acid.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (See section 4.4)

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

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4)

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, thus use of this class of therapeutic agent requires cautious balancing of possible benefit against potential risk to the mother and foetus, especially in the first and third trimesters. The use of naproxen should be avoided in patients who are breast-feeding.

4.7 Effects on ability to drive and use machines

Nil.

4.8 Undesirable effects

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

Disorders of blood & the Lymphatic system disorder: 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).

CNS:

Headache, insomnia, inability to concentrate and cognitive dysfunction have been reported.

Hematological :
Thrombocytopenia, granulocytopenia, aplastic anaemia and haemolytic anaemia may occur rarely.

Gastro-intestinal:
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.

Dermatological/hypersensitivity:
Skin rashes, urticaria, angio-oedema. Anaphylactic reactions to naproxen and naproxen sodium formulations, eosinophilic pneumonitis, alopecia, erythema multiforme. Bullous reactions including Stevens Johnson syndrome and toxic epidermal necrolysis (very rare) and photosensitivity reactions including photosensitive dermatitis and rare cases in which skin resembles porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa may occur rarely.

Other:
Tinnitus, hearing impairment, vertigo, mild peripheral oedema. Jaundice, fatal hepatitis, nephropathy, haematuria, visual disturbances, vasculitis, aseptic meningitis and ulcerative stomatitis have been reported rarely.

4.9 Overdose

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea or vomiting. A few patients have experienced seizures, but it is not 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 is a non-steroidal anti-inflammatory agent with analgesic and antipyretic properties.

5.2 Pharmacokinetic properties

It is readily absorbed from the gastro-intestinal tract, metabolised in the liver and excreted mainly in the urine, with a half life of 12 - 15 hours.

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Sodium starch glycollate
Povidone
Magnesium stearate
Quinoline yellow E104

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in original package in order to protect from light.

6.5 Nature and contents of container

Blister packs containing 28 tablets in strips of 2 x 14 tablets. The strips are of hard PVC and are foil lidded.

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

Antigen Pharmaceuticals Limited
Chandler House
Castle Street
Roscrea
County Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 73/90/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th July 1986

Date of last renewal: 4th July 2006

10 DATE OF REVISION OF THE TEXT

January 2009