IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0281/130/002
Case No: 2035464

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

Pinewood Laboratories Ltd

Ballymacarbry, **Clonmel**, **Co. Tipperary**, **Ireland**

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

Caprin 300 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 **20/01/2009** until **22/06/2010**.

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

Caprin 300 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300mg of Acetylsalicylic Acid (Aspirin) Ph. Eur.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Caprin 300mg is an antipyretic, anti-inflammatory and analgesic agent designed to reduce the gastric side-effects of aspirin in rheumatoid arthritis and in conditions requiring continued management with aspirin.
Caprin 300mg may also be used to reduce the risk of myocardial infarction in patients with unstable angina or in patients with a previous history of myocardial infarction.

4.2 Posology and method of administration

ANALGESIC, ANTI-INFLAMMATORY, ANTIPYRETIC,

Adults (including the elderly) and children over 16 years:
3 tablets (900mg) 3-4 times daily as required.

Children and adolescents under 16 years
Do not give to children and adolescents under 16 years, except on medical advice, where the benefit outweighs the risk.

ANTITHROMBOTIC EFFECT

To reduce the risk of myocardial infarction.
One tablet daily.

Elderly: Non-steroidal anti-inflammatory drugs 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..

Route of administration - oral.
Caprin 300mg tablets must not be chewed or crushed.
The tablets are best taken before meals.

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

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
Hypersensitivity (e.g. bronchospasm, rhinitis, urticaria) to aspirin or to other non-steroidal anti-inflammatory drugs.
Coagulation deficiency disorders.

4.4 Special warnings and precautions for use

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

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 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 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 (See section 4.5).

When GI bleeding or ulceration occurs in patients receiving Caprin, 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).

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

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).

Cardiovascular and cerebrovasular 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 epidemiology 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). There are insufficient data to exclude such a risk for aspirin.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and / or cerebrovascular disease should only be treated with aspirin 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).

There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver and can be fatal. For this reason aspirin should not be given to children and adolescents aged under 16 years unless specifically indicated.

This product should be taken only when necessary. Prolonged use except on medical advice can be harmful.
The doctor should be consulted if there is no improvement in 24 hours.
If the patient is on any medication consult the doctor or pharmacist before using.

If the patient suffers from asthma, has renal or hepatic impairment, or inflammatory bowel disease then a doctor should be consulted before taking the product.

4.5 Interaction with other medicinal products and other forms of interaction

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (See section 4.4)
Anti-coagulants: 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).

Care should be taken in patients treated with any of the following drugs as interactions have been reported:
Antihypertensives: reduced antihypertensive effect.
Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.
Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.
Lithium: decreased elimination of lithium.
Methotrexate: decreased elimination of methotrexate.
Cyclosporin: increased risk of nephrotoxicity with NSAIDs.
Other NSAIDs: avoid concomitant use of two or more NSAIDs.
Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAID and metabolites. Oral hypoglycaemic agents: inhibition of metabolism of sulphonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

4.6 Pregnancy and lactation

Caution should be used in prescribing aspirin for use during pregnancy and lactation and is best avoided at term.
Aspirin may prolong labour and contribute to maternal and neonatal bleeding. The drug is excreted into breast milk.

4.7 Effects on ability to drive and use machines

Aspirin does not usually affect the ability to drive or operate machinery.

4.8 Undesirable effects

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 - Special warnings and precautions for use) have been reported following

administration. Less frequently, gastritis has been observed.

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

Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).

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).

Aspirin may precipitate bronchospasm, and induce attacks of asthma in susceptible subjects.

4.9 Overdose

Overdosage produces dizziness, tinnitus, sweating, nausea and vomiting, confusion and hyperventilation. Gross overdosage may lead to CNS depression with coma, cardiovascular collapse and respiratory depression.
Overdosage should be treated initially by aspiration and lavage and a saline purgative such as sodium sulphate, 30g in 250ml of water should be given to promote peristalsis. Otherwise treat as for aspirin poisoning, and observe for at least 72 hours to allow for possible delayed release from the enteric-coated system.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Aspirin is an analgesic and antipyretic with anti-inflammatory properties.
Aspirin inhibits prostaglandin synthetase.
Aspirin inhibits platelet aggregation.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

Aspirin is readily absorbed from the gut and rapidly distributed to all body tissues. Aspirin is excreted into breast milk and crosses the placenta. Protein binding is extensive. The rate of excretion varies with urinary pH, increasing as urinary pH rises.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised Maize Starch
Colloidal Anhydrous Silica
Zinc Stearate
Microcrystalline Cellulose
Titanium Dioxide
Red iron Oxide

Methacrylic Acid Copolymer Type C
Triethyl Citrate
Purified Talc
Macrogol 6000

Colorcon Black Ink S-1-27794 consisting of:
Shellac Glaze
Black Iron Oxide (E172)
n-Butyl Alcohol
Isopropyl Alcohol
Propylene Glycol
Industrial Methylated Spirit

6.2 Incompatibilities

None known.

6.3 Shelf Life

24 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

35 x 82 mm white polypropylene securitainer and cap, 100 pack.

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 instructions.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 281/130/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 February 1987

Date of last renewal: 03 February 2002

10 DATE OF REVISION OF THE TEXT

January 2009