Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Caprin 75 mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 mg of Aspirin (acetylsalicylic acid).
Excipients with known effect
Each tablet contains 62 mg of Anhydrous Lactose.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablets.

Pink enteric coated, round, biconvex tablets printed with "75" in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CAPRIN 75mg may be used to reduce the risk of myocardial infarction in patients with unstable angina or ischaemic stroke and in patients with a previous history of myocardial infarction. The enteric coating makes Caprin unsuitable for short term pain relief.

4.2 Posology and method of administration

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

Adults (including the elderly)
One tablet daily.
In cases where a rapid onset of action is required e.g. immediately following acute myocardial infarction, then three tablets should be given for the first two days of treatment.

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.

CAPRIN 75 mg tablets must not bechewed or crushed.
The tablets are best taken before meals.

Method of administration
For oral use.

4.3 Contraindications

CAPRIN 75 mg tablets are contraindicated in the following:

Hypersensitivity to aspirin (e.g. bronchospasm, rhinitis, urticaria), to non-steroidal anti-inflammatory drugs or to any of the excipients listed in section 6.1.

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.

Coagulation deficiency disorders: hypoprothrombinaemia, haemophilia, haemorrhagic disease or a history of bleeding disorders, cerebral haemorrhage and active peptic ulceration.

Doses >100 mg/day during the third trimester of pregnancy (see section 4.6).

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). Where prolonged therapy is required, patients should be reviewed regularly.

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 such as clopidogrel and dipyridamole (see section 4.5).

Aspirin should be used with caution in patients with a history of peptic ulceration, inflammatory bowel disease or coagulation abnormalities. They may also induce gastro-intestinal haemorrhage, occasionally major.

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 NSAIDs (see section 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 associated with non-steroidal anti-inflammatory drugs (NSAIDs) may be reduced by using the minimum effective dose for the shortest possible duration. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

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.

Care should be taken when stopping therapy in those patients with multiple risk factors as the risk of a cerebrovascular event in the four weeks after aspirin discontinuation is significant. The risk/benefit of stopping aspirin therapy in the case of patients undergoing surgery should be considered.

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.

Aspirin should be used with caution in patients with impaired renal, cardiac or hepatic function (avoid if severe), or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

Aspirin can reduce uric acid excretions and so should be used with care in patients with gout or a history of gout.

In patients with strokes, aspirin should not be given until the possibility of cerebral haemorrhage has been excluded.

Aspirin may also precipitate bronchospasm or induce attacks of asthma in susceptible subjects.

High doses of aspirin may precipitate acute haemolytic anaemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency.

Aspirin decreases platelet adhesiveness and increases bleeding time. Haematological and haemorrhagic effects can occur, and may be severe. Patients should report any unusual bleeding symptoms to their physician.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Aspirin may enhance the effects of anticoagulants, antiplatelet agents and fibrinolytics leading to increased risk of bleeding.

Concomitant use of alcohol with aspirin may increase the risk of gastrointestinal bleeding.

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

CAPRIN 75 mg may enhance the effects of phenytoin and sodium valproate. However, no special precautions are needed.

Methotrexate: the activity of methotrexate may be markedly enhanced and its toxicity increased.

CAPRIN 75 mg may inhibit action of uricosurics.

The toxicity of sulphonamides may also be increased.

Anti-hypertensives: CAPRIN 75 mg may reduce the efficacy of antihypertensive drugs.

Aspirin is pharmaceutically incompatible with iron salts and alkalis.

Antacids: Patients using enteric-coated aspirin should be advised against ingesting antacids simultaneously, to avoid premature drug release.

<u>Care should be taken in patients treated with any of the following drugs as interactions have been reported:</u>
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).
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.
Corticosteroids: Plasma salicylate concentrations may be reduced by concurrent use of corticosteroids, and salicylate toxicity may occur following withdrawal of the corticosteroids. The risk of gastrointestinal ulceration and bleeding may be increased when aspirin and corticosteroids are co-administered (see Section 4.4).
Ciclosporin: 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.

Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardioprotection.

Probenecid: reduction in metabolism and elimination of NSAIDs and metabolites.

Oral hypoglycaemic agents: inhibition of metabolism of sulphonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

Ibuprofen: 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).

Gold: risk of increased hepatotoxicity with aspirin.

Thiopental: Aspirin may potentiate the effects of thiopental anaesthesia.

Carbonic anhydrase inhibitors: Concurrent administration of carbonic anhydrase inhibitors such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.

Aspirin can interfere, to varying degrees, with some urine tests for catecholamines, dopa, glucose, ketones, hippuric acid, homogentisic acid, homovallinic acid, 17- hydroxycorticosteroids, 5-hydroxyindoleacetic acid, urine pregnancy tests and with some serum or plasma tests for albumin, barbiturates, calcium, propylthiouracil, tyrosine and uric acid.

4.6 Fertility, pregnancy and lactation

Fertility:
Women attempting to conceive should not use any NSAID, including aspirin, because of the findings in a variety of animal models that indicate these agents block blastocyst implantation.

Pregnancy:
Low doses (up to 100 mg/day):
Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100-500 mg/day:
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendation below for doses of 500 mg/d and above apply also for this dose range.

Doses of 500 mg/day and above:
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy. In animals, administration of prostaglandin synthesis inhibitor has been shown to results in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a

woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

Lactation:
As aspirin is secreted into breast milk, Caprin should not be taken by patients who are breast-feeding, as there is a risk of Reye's syndrome in the infant. High maternal doses may impair platelet function in the infant.

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

Summary of the safety profile
The most commonly observed adverse events are gastrointestinal in nature.

Tabulated list of adverse reactions
Undesirable effects are listed by MedDRA System Organ Classes.
Assessment of undesirable effects is based on the following frequency groupings:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000
Not known: cannot be estimated from the available data.

System Organ Class	Undesirable Effect
Blood and lymphatic system disorders	*Not Known:* Bleeding disorders Anaemia[1] Thrombocytopenia
Immune system disorders	*Not Known:* Hypersensitivity reactions including skin rashes, urticaria, angioedema, asthma attacks, bronchospasm and anaphylaxis.
Nervous system disorders	*Not Known:* Cerebral haemorrhage Stroke
Ear and labyrinth disorders	*Not Known:* Tinnitus
Cardiac disorders	*Not Known:* Cardiac failure Myocardial infarction
Vascular disorders	*Not Known:* Hypertension Haemorrhages[2] Haematoma[2]
Respiratory thoracic and mediastinal disorders	*Not Known:* Epistaxis Haemoptysis

Gastrointestinal disorders[3]	*Not Known:* Peptic ulcers[4] GI Perforation[4] GI Bleeding[4] Nausea Vomiting Diarrhoea Flatulence Constipation Dyspepsia Abdominal pain Melaena Haematemesis Ulcerative stomatitis Exacerbation of colitis Exacerbation of Crohn's disease Gastritis Gastrointestinal ulcer
Skin and subcutaneous tissue disorders	*Very rare:* Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome. *Not Known:* Purpura Ecchymoses
Renal and urinary disorders	*Not Known:* Haematuria Urate kidney stones
General disorders and administration site disorders	*Not Known:* Oedema
Investigations	*Not Known:* Bleeding time prolonged
Hepatobiliary disorders	*Not Known:* Transaminases increased

[1]May occur following chronic GI blood loss or acute haemorrhage
[2]May occur in various organ systems and may be fatal
[3]The special coating of Caprin helps to reduce the incidence of side effects resulting from gastric irritation.
[4]Sometimes fatal, particularly in the elderly

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Salicylate toxicity (> 100 mg/kg/day over 2 days may produce toxicity) may result from chronic, therapeutically acquired, intoxication, and from, potentially life-threatening, acute intoxications (overdose), ranging from accidental ingestions in children to incidental intoxications.

If overdosage is suspected, the patient should be kept under observation for at least 24 hours, as symptoms and salicylate blood levels may not become apparent for several hours. With the gastro-resistant formulation, peak plasma levels may not occur for up to 12 hours.

Chronic salicylate poisoning can be insidious as signs and symptoms are non-specific. Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses.

Symptoms

Common features include dizziness, vomiting, nausea, dehydration, tinnitus, vertigo, deafness, sweating, headache, confusion, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Symptoms may be controlled by reducing the dosage. Tinnitus can occur at plasma concentrations of 150 to 300 micrograms/mL. More serious adverse events occur at concentrations above 300 micrograms/mL.

The principle feature of acute intoxication is severe disturbance of the acid-base balance, which may vary with age and severity of intoxication. The most common presentation for a child is metabolic acidosis. The severity of poisoning cannot be estimated from plasma concentration alone. Absorption of acetylsalicylic acid can be delayed due to reduced gastric emptying, formation of concretions in the stomach, or as a result of ingestion of enteric-coated preparations. Management of acetylsalicylic acid intoxication is determined by its extent, stage and clinical symptoms and according standard poisoning management techniques. Predominant measures should be the accelerated excretion of the drug as well as the restoration of the electrolyte and acid-base metabolism.

Uncommon features include tachypnoea, diaphoresis, haematemesis, hyperpyrexia, hypoglycaemia, hyperglycaemia, increased ketone levels, hypokalaemia, hypernatraemia, hypoprothrombina, thrombocytopenia, increased INR/PTR, intravascular coagulation, dehydration, oliguria, renal failure, GI bleeding non-cardiogenic pulmonary oedema, asphyxation, respiratory arrest, dysarrhythmias, hypotension, and cardiovascular arrest.

Central nervous system features including confusion, disorientation, lethargy, coma, convulsions and toxic encephalopathy are less common in adults than in children.

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.

Management
Gastric lavage or repeated administration of activated charcoal if an adult present within one hour of ingestion of more than 125 mg/kg. The plasma salicylate concentration should be measured for patients who have ingested >125mg/kg. However, the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account.

Urea and electrolytes, INR/PTR, blood pressure, ECG alteration and blood glucose should be monitored. Elimination is increased by urinary alkalisation, which is achieved by the administration of intravenous sodium bicarbonate. The urine pH should be monitored, and further intravenous sodium bicarbonate may be required to maintain urinary pH 7.5-8.5 (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years and over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Salicylic Acid & Derivatives
ATC Code: B01A C06

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 400 mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81 mg), 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

Absorption: Aspirin is rapidly absorbed after oral administration, with some hydrolysis to salicylate before absorption.
Absorption is delayed by the presence of food and is impaired in patients suffering migraine attacks.
Absorption is more rapid in patients with achlorhydria and also following administration of polysorbates and antacids.
To prevent stomach irritation, CAPRIN 75mg tablets have a special enteric coating so that aspirin is not released until it has passed through the stomach.

Distribution: Aspirin is found in the saliva, milk, plasma and synovial fluid at concentration less than blood and crosses the placenta.
Salicylate/extensive protein binding.
Aspirin/protein binding to a small extent.

Metabolism: In the blood, rapid hydrolysis to salicylic acid; glucuronic acid/glycine conjugation to form glucuronides and salicyluronic acid, oxidation of a small proportion.

Excretion: Excreted in the urine mainly as salicyluronic acid. Salicylate reabsorbed by renal tubules in acid urine, and alkaline diuresis will increase the rate of excretion; 85% of dose excreted as free salicylate.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Lactose
Collodial Anhydrous Silica
Pregelatinised Starch
Zinc Stearate
Titanium Dioxide (E171)
Polyvinyl Acetate Phthalate
Acetylated Vegetable Oil Monoglyceride
Hydroxypropyl Cellulose
Red Iron Oxide (E172)

Colorcon Black Ink S-1-17823 consisting of:
Shellac glaze
Black iron oxide (E172)
n-Butyl alcohol
Isopropyl alcohol
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C.

Keep the container tightly closed to protect from moisture.

6.5 Nature and contents of container

White polypropylene container (securitainer) and lid, containing 20 or 100 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

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/130/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 June 2000

Date of last renewal: 23 June 2010

10 DATE OF REVISION OF THE TEXT

January 2023