Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ASACARD 162.5 mg prolonged release hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains acetylsalicylic acid 162.5 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard
The capsules have a white body and red cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ASACARD 162.5 mg Capsules are indicated for secondary prophylaxis after a first coronary or cerebrovascular ischemic event:

- Myocardial infarction Stable and unstable angina
- Coronary angioplasty
- Transient ischemic attack (TIA)
- Non-haemorrhagic stroke
- Reduction of graft patency occlusion after CABG

In situations where a rapid onset of action is required (such as acute treatment of myocardial infarction or unstable angina) then conventional (immediate release acetylsalicylic acid) should be given.

4.2 Posology and method of administration

Posology

ASACARD 162.5 mg Capsules should not be taken without first seeking medical advice on the suitability of treatment. Treatment should be long-term and under medical supervision.

Adults:
One ASACARD 162.5 mg capsule per day (162.5 mg). It is recommended that the capsules are taken at the same time each day e.g. in the morning, approximately 15 minutes before food.

Elderly:
The usual adult dose is recommended in the absence of severe renal or hepatic insufficiency (see sections 4.3 and 4.4).

Paediatric population:
FLAMASACARD should not be used in children under16 years old because of safety concerns (see section 4.4).

Method of administration

Swallow the capsule with water.

4.3 Contraindications

- Peptic ulcer and/or gastrointestinal haemorrhages
- Gastric patients, and patients who have experienced gastric pain when previously using this medicine
- A history of haemorrhagic cerebrovascular accident
- Hypersensitivity to salicylic acid compounds, such as acetyl salicylic acid, or prostaglandin synthetase inhibitors (e.g. some asthma patients, who may suffer an asthma attack or faint), or to any of the excipients.
- Severe hepatic or renal insufficiency
- Haemorrhagic diathesis or coagulation disorders, such as haemophilia and hypoprothrombinaemia,
- The third trimester of pregnancy.
- Methotrexate used at doses > 15 mg/week (see section 4.5).

4.4 Special warnings and precautions for use

As ASACARD 162.6 mg Capsule is a prolonged release formulation, its use is not recommended in acute situations (see section 4.1).

ASACARD is not suitable for use as an anti-inflammatory / analgesic / antipyretic.

In patients who are being treated simultaneously with anticoagulants it is advisable to measure the International Normalisation Ratio (INR) regularly. In patients with mild or moderate disorders of the hepatic function this function must be measured regularly. Concomitant treatment with anticoagulants (coumarin derivatives, heparin) is not recommended and should generally be avoided (see section 4.5). If concurrent use cannot be avoided, frequent monitoring of the INR is indicated and patients should be cautioned to watch for signs of bleeding, especially in the gastrointestinal tract. Close medical monitoring is also necessary for patients with asthma bronchiale, allergic rhinitis (acetylsalicylic acid (ASA) may cause severe urticaria, angioedema, or bronchospasm). Patients with a history of peptic ulcer disease should avoid using ASA (which can cause gastric mucosal irritation and bleeding).

The concomitant administration of this active substance with uricosuric agents like benzbromarone, probenecid, sulphinpyrazone is not recommended (see section 4.5).

Acetylsalicylic acid must be used with care in cases of very severe menstrual bleeding. It is preferable to stop use of acetylsalicylic acid before a surgical procedure (including tooth extraction) because of the risk of a prolonged bleeding time or an aggravation of the bleeding. The length of the interruption of the treatment should be determined on a case-by-case basis, but will usually be one week.

There is possible association between acetylsalicylic acid 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 acetylsalicylic acid should not be given to children and adolescents aged under 16 years unless specifically indicated (see section 4.2).

This product should be administered with caution in patients with renal impairment.

Patients with hypertension should be monitored carefully.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

In patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, some cases of haemolytic anaemia have been reported with high doses of acetylsalicylic acid, i.e. higher than daily recommended doses.

4.5 Interaction with other medicinal products and other forms of interaction

The use of several platelet aggregation inhibitors, i.e. acetylsalicylic acid, NSAIDs, ticlopidine, clopidogrel, tirofiban, eptifibatide, increases the risk of bleeding, likewise their combination with heparin and its derivatives (hirudine, fondaparinux), oral anticoagulants (such as anti-vitamin K) and thrombolytics. Clinical and biological parameters of

haemostasis should be regularly monitored.

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).

Contraindicated combinations
Methotrexate (used at doses >15 mg /week):
The combined drugs, methotrexate and ASA, increase haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by ASA. Therefore, the concomitant use of methotrexate with ASACARD 162.5 mg Capsules is contraindicated (see section 4.3).

Associations not recommended
Uricosuric agents (benzbromarone, probenecid, and sulphinpyrazone): Reduced effect of uric acid excretion by competition of renal tubular uric acid elimination. Therefore, concomitant use of ASACARD 162.5 mg Capsules with uricosuric agents is not recommended (see section 4.4).

Combinations requiring precautions for use
Diuretics:
Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment.

Systemic glucocorticoids (except hydrocortisone used as a replacement therapy in Addison's disease):
The concomitant use of ASA with glucocorticoids can lead to a decrease in blood salicylate level during corticosteroid treatment and a risk of salicylate overdose after this treatment is stopped via increased elimination of salicylate by corticosteroids. This combination requires precaution. Furthermore, risk of blood loss in the gastrointestinal tract is enhanced.
Therefore, doses of ASA should be adjusted during the combination and after glucocorticoid treatment is stopped.

Methotrexate used at doses lower than 15 mg / week:
The combined drugs, methotrexate and ASA, increased haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring in the presence of even mildly impaired renal function, as well as in elderly.

Heparin used at curative dosage or in elderly patients:
When ASA is co-administered with heparin at curative dosage or in elderly patients, there is an increased risk of bleeding. Close monitoring of the INR, aPTT and/or bleeding time should be performed in the case of concomitant administration of both drugs, ASACARD 162.5 mg Capsules and heparin.

Combinations to be taken into account
Other anticoagulants (coumarin derivatives, heparin at preventive dosage), other platelet anti-aggregants, anti-vitamin K, and other thrombolytics:
Increased risk of bleeding.

NSAIDS:
Increased risk of bleeding and of damage on gastrointestinal mucosa and enhancement of prolonged bleeding time

Antacids:
Antacids can increase the renal excretion of ASA by alkalinizing the urine.
Sulphonylureas and insulins: The hypoglycaemic effect may be potentiated by ASA

Alcohol:
Addition of their own damage on gastrointestinal mucosa and enhancement of prolonged bleeding time.

4.6 Fertility, pregnancy and lactation

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 recommendations 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 a prostaglandin synthesis inhibitor has been shown to result 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
Acetylsalicylic acid passes into breast milk; therefore ASACARD 162.5 mg capsules should be avoided during breast feeding.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. On the basis of the pharmacodynamic profile and/or adverse reactions profile it is unlikely that acetylsalicylic acid affects the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects are often dose-dependent and are due to the pharmacological effect of acetylsalicylic acid (see section 5.1). Most undesirable effects are usually associated with the gastrointestinal tract.
The frequencies of the adverse reactions below are defined as follows: Very common (>1/10), Common (>1/100, <1/10), Uncommon (>1/1,000, <1/100), Rare (>1/10,000, <1/1,000), Very rare (< 1/10,000).

Effects on the gastrointestinal tract:
Very common: gastric complaints such as hyperacidity and nausea
Common: vomiting, gastritis, mild to moderate blood loss in the gastrointestinal tract, diarrhoea. With long-term or

repeated use this blood loss can lead to anaemia.
Uncommon: gastric bleeding, gastric ulcers.

Very rare including isolated reports: gastrointestinal perforation

Effects on the central nervous system:
Rare: dizziness, headache, tinnitus. These are usually the first indications of overdose (see also section 4.9)

Haematological effects:
Common: prolongation of the bleeding time. This effect can persist for several days after stopping the treatment and can give rise to haemorrhagic risks in the event of surgery or can lead to heavier menstruation
Uncommon: intracranial bleeding, blood in urine
Rare: haemorrhagic syndrome (nosebleeds, bleeding gums, bloody vomiting and bloodloss via the faeces, etc.)

Hypersensitivity reactions:
Uncommon: urticaria, skin rash, angio-oedema, rhinitis, bronchial spasms

Very rare including isolated reports: anaphylactic shock, aggravation of the allergic symptoms of food allergy

Skin and subcutaneous tissue disorders:
Very rare including isolated reports: severe skin reactions (e.g. erythema exsudativum multiforme).

Endocrine disorders:
Very rare including isolated reports: hypoglycaemia.

Hepatobiliary disorders:
Very rare including isolated reports: liver impairment.

Renal and urinary disorders:
Very rare including isolated reports: Acute renal insufficiency, especially in patients with existing renal insufficiency, heart decompensation, nephritic syndrome or concomitant treatment with diuretics.

Metabolism and nutrition disorders:
Very rare including isolated reports: Low-dose ASA can reduce the excretion of uric acid (which can lead to acute gout in pre-disposed patients).

Reporting of suspected adverse reaction
Reporting of 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 the HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie. E-mail: medsafety@hpra.ie.

4.9 Overdose

The following are associated with moderate intoxication: dizziness, headache, tinnitus, confusion and gastrointestinal symptoms (nausea, vomiting and gastric pain).
With severe intoxication, serious disturbances of the acid-base equilibrium occur. Initial hyperventilation leads to respiratory alkalosis. Subsequently a respiratory acidosis also occurs as a result of a suppressive effect on the respiratory centre. A metabolic acidosis also arises due to the presence of salicylate. Given that children, infants and toddlers are often only seen at a late stage of intoxication, they will usually have already reached the acidosis stage.

The following can also arise: hyperthermia and perspiration, leading to dehydration, restlessness, convulsions,

hallucinations and hypoglycaemia. Depression of the nervous system can lead to coma, cardiovascular collapse and respiratory arrest. The lethal dose of acetylsalicylic acid is 25-30 gram. Plasma salicylate concentrations above 300 mg/l (1.67 nmol) suggest intoxication.

If a toxic dose has been ingested then admission to hospital is necessary. With moderate intoxication an attempt can be made to induce vomiting; if this fails, gastric lavage is indicated. Activated charcoal (adsorbent) and sodium sulphate (laxative) are then administered. Alkalising of the urine (250 mmol $NaHCO_3$ for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for sever intoxication. Treat other signs of intoxication symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Phamacotherapeutic group -- Platelet aggregation inhibitors.
ATC Code - B01AC06

ASACARD 162.5 mg Capsules are a novel formulation of acetylsalicylic acid (ASA) made up of microparticles each separately coated with a thin, neutral, non-toxic film based on ethylcellulose. This film prevents direct contact between the particles of acetylsalicylic acid and the gastric mucosa (the ethylcellulose film-coating acts as a semi-permeable membrane that allows the acetylsalicylic acid to diffuse progressively, particularly in the intestine). This progressive diffusion results in a longer duration of absorption.

The antithrombotic effect of ASACARD 162.5 mg Capsules has not been demonstrated in clinical trials. It has been shown to exert an antiplatelet effect ex vivo similar to other acetylsalicylic acid formulations by irreversible acetylation of cyclooxygenase. This results in the inhibition of the synthesis of thromboxane A2, an aggregatory and vasoconstrictive agent. The anti-platelet effect lasts for 4 to 8 days after treatment withdrawal. Acetylsalicylic acid essentially blocks the trigger reaction in the coagulation system but not the entire system. However, high doses decrease the synthesis of coagulation factors in the liver.

Acetylsalicylic acid also shows analgesic, anti-inflammatory and antipyretic activities, but at doses higher than those recommended here.

With chronic administration of ASACARD 162.5 mg Capsules the percentage thromboxane inhibition is greater than 90% and is similar to that seen with conventional acetylsalicylic acid formulations. Thromboxane inhibition, as measured by serum thromboxane, collagen-induced release reaction and collagen-induced platelet aggregation was demonstrated in a clinical study of ASACARD 162.5 mg Capsules versus immediate release acetylsalicylic acid 75mg and 150mg. Over a four week period the changes in thromboxane were statistically significantly different between ASACARD 162.5 mg Capsules and 75 mg acetylsalicylic acid in two out of three measurements.

It was not significantly different compared to the 150 mg dose. ASACARD 162.5 mg Capsules do not significantly inhibit prostacyclin over a 28 day treatment period or significantly modify bleeding time.

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 hours before or within 30 minutes after immediate release aspirin (81 mg), a decreased effect of aspirin 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

The coating of the microparticles in the capsules ensure that acetylsalicylic acid is released throughout the day.

Following administration of ASACARD 162.5mg capsules blood levels of acetylsalicylic acid are virtually

undetectable and pharmacokinetic parameters cannot be calculated for ASA.

Levels of salicylic acid (SA), the principal metabolite of ASA peak at around 3 hours after administration of ASACARD 162.5 mg capsules. The peak levels of SA are between 2.35 and 2.80 mcg/ml around one third of the levels seen with conventional acetylsalicylic acid. The mean residence-time for SA is between 9 and 12 hours, approximately three times longer than that of conventional acetylsalicylic acid.

5.3 Preclinical safety data

Acetylsalicylic acid has not been found to have a mutagenic or a carcinogenic potential.

A comparative, acute toxicity study was conducted in rats that received ASACARD 162.5 mg capsules in comparison with non-film-coated acetylsalicylic acid. No LD50 values could be determined at a dose of 2500 mg/kg, though the LD50 in the rat when dosed with acetylsalicylic acid starting material was 1400 mg/kg. No clinical signs were observed.

Anatomopathological examination did not show any lesions, even in the stomach.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules contain:
Ethylcellulose
Povidone
Castor oil
Magnesium stearate
Colloidal anhydrous silica
Tartaric acid
Talc

Capsule shell contains:
Gelatin
Titanium dioxide (E171)
Erythrosine (E127)
Indigotin (E132)

6.2 Incompatibilities

Acetylsalicylic acid is incompatible with alkalizing agents that increase its solubilisation. In addition, aluminium salts form insoluble hydroxides. Similarly, acetylsalicylic acid is incompatible with calcium carbonate.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original packaging.

6.5 Nature and contents of container

Box of 4, 10, 28, 30 or 100 capsules packaged in a heat-sealed PVC/PVDC/Foil blister pack.
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

New Haven Pharma (UK) Limited
1 Park Row
Leeds LS1 5AB
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1966/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 October 1999

Date of last renewal: 20 January 2008

10 DATE OF REVISION OF THE TEXT

May 2016