

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Ascal Brisper Cardio-Neuro 100 mg effervescent tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One effervescent tablet contains 100 mg carbasalate calcium, corresponding to 78 mg acetyl salicylic acid.

Excipient: contains Lactose Monohydrate 150.0 mg.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Effervescent tablet.

White- to cream-coloured, round, flat tablet with bevelled edge.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Ascal is indicated for secondary prevention after a first myocardial or cerebrovascular event linked to atherosclerosis :

- Myocardial infarction
- Unstable and stable angina pectoris
- Stroke and transient ischaemic attack provided that intracranial haemorrhages are excluded.
- Graft occlusion after aorta-coronary bypass.

### 4.2 Posology and method of administration

*Secondary prevention of myocardial infarction:*

In acute cases a loading dose of an initial 2 effervescent tablets (200 mg carbasalate calcium, corresponding to 156 mg acetylsalicylic acid) per day should be taken on the first day, followed by 1 to 2 effervescent tablets (100 mg carbasalate calcium, corresponding to 78 mg acetylsalicylic acid, to 200 mg carbasalate calcium, corresponding to 156 mg acetylsalicylic acid) per day. In acute cases, the first dose must be taken as soon as possible after the diagnosis.

*Secondary prevention of unstable and stable angina pectoris:*

In acute cases a loading dose of an initial 2 effervescent tablets (200 mg carbasalate calcium, corresponding to 156 mg acetylsalicylic acid) per day should be taken on the first day, followed by 1 to 2 effervescent tablets (100 mg carbasalate calcium, corresponding to 78 mg acetylsalicylic acid, to 200 mg carbasalate calcium, corresponding to 156 mg acetylsalicylic acid) per day. In acute cases, the first dose must be taken as soon as possible after the diagnosis.

*Secondary prevention of stroke and transient ischaemic attack provided that intracranial haemorrhages are excluded:*

In acute cases a loading dose of an initial 2 effervescent tablets (200 mg carbasalate calcium, corresponding to 156 mg acetylsalicylic acid) per day should be taken on the first day, followed by 1 effervescent tablet (100 mg carbasalate calcium, corresponding to 78 mg acetylsalicylic acid) per day. In acute cases, the first dose must be taken as soon as possible after the diagnosis.

*Secondary prevention of graft occlusion after aorta-coronary bypass:*

In acute cases a loading dose of an initial 2 effervescent tablets (200 mg carbasalate calcium, corresponding to 156 mg acetylsalicylic acid) per day should be taken on the first day, followed by 1 to 2 effervescent tablets (100 mg carbasalate calcium, corresponding to 78 mg acetylsalicylic acid, to 200 mg carbasalate calcium, corresponding to 156 mg acetylsalicylic acid) per day. In acute cases, the first dose must be taken as soon as possible after the aorta-coronary bypass.

Ascal 100 mg must be taken in solution. Dissolve the effervescent tablet in a glass of water until the solution is clear and then drink. Do not give to children and adolescents aged under 16 years (see section 4.4)

### 4.3 Contraindications

- peptic ulcer and/or gastrointestinal haemorrhages
- gastric patients, and patients who have experienced gastric pain when previously using the 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
- methotrexate used at doses > 15 mg / week (see section 4.5).
- Doses > 128 mg carbasalate calcium/day which is equivalent to 100 mg acetylsalicylic acid/day (1 tablet {productname}/day) during the third trimester of pregnancy.

### 4.4 Special warnings and precautions for use

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 (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, sulphapyrazone is not recommended (see section 4.5).

Acetyl salicylic acid must be used with care in cases of very severe menstrual bleeding. It is preferable to stop use of acetyl salicylic 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 acetyl salicylic 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 acetyl salicylic 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.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose

malabsorption should not take this medicinal product.

Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

## 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 and thrombolytics. Clinical and biological parameters of haemostasis should be regularly monitored.

### Contra-indicated combinations

- Methotrexate (used at doses > 15mg / 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 Ascal is contra-indicated (see section 4.3).

### Not recommended associations

- Uricosurics agents (benzbromarone, probenecid, and sulphinpyrazone) : reduced effect of uric acid excretion by competition of renal tubular uric acid elimination. Therefore, the concomitant use of Ascal with uricosurics 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 combinations 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 15mg / 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, Ascal 100 mg and heparin.

### Combinations to be taken into account

- Other anticoagulants (coumarin derivatives, heparin at preventive dosage), other platelet anti-aggregants and other thrombolytics : increased risk of bleeding.

- NSAIDs : increased risk of bleeding and of damage on gastro-intestinal mucosa and enhancement of prolonging bleeding time

- 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).

- Antacids : Antacids can increase the renal excretion of ASA by alkalinising the urine.

- Alcohol : addition of their own damage on gastro-intestinal mucosa and enhancement of prolonging bleeding time

## 4.6 Fertility, pregnancy and lactation

### **Pregnancy**

Low doses, up to 128 mg carbasalate calcium/day which is equivalent to 100 mg acetylsalicylic acid/day (1 tablet (productname)/day):

Clinical studies indicate that doses up to 100 mg acetylsalicylic acid/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of more than 128 mg up to 640 mg carbasalate calcium/day which is equivalent to 100- 500 mg acetylsalicylic acid/day (more than 1 tablet {productname}/day):

There is insufficient clinical experience regarding the use of doses above 100 mg acetylsalicylic acid/day up to 500 mg acetylsalicylic acid/day. Therefore, the following recommendations for doses of 500 mg acetylsalicylic acid/day and above apply also for this dose range:

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, acetyl salicylic 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, 128 mg carbasalate calcium/day which is equivalent to 100 mg acetylsalicylic acid/day and higher (more than 1 tablet {productname}/day) is contraindicated during the third trimester of pregnancy.

### **Lactation**

Acetyl salicylic acid is excreted into the maternal milk in small amounts. Since after incidental use no adverse effects were observed in the infant, 100 mg acetyl salicylic acid can be taken once during breastfeeding as indicated in the posology (not more than 1 tablet per day). With chronic use or intake of high doses, breast feeding should be stopped.

## **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 carbasalate calcium 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 acetyl salicylic 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 ( $(\geq 1/100, < 1/10)$ ), Uncommon ( $(\geq 1/1,000, < 1/100)$ ), Rare ( $(\geq 1/10,000, < 1/1,000)$ ), 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 blood loss 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: hypoglycemia.

### *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, nephrotic 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)

## 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 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 acetyl salicylic acid is 25-30 gram. Plasma salicylate concentrations above 300 mg/l (1,67 mmol/l) 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. Alkalisating of the urine (250 mmol NaHCO<sub>3</sub> for 3 hours) while monitoring the urine pH is indicated. Haemodialysis is the preferred treatment for severe intoxication. Treat other signs of intoxication symptomatically.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, Platelet aggregation inhibitors excl. Heparin

ATC code: B01AC08

Ascal 100 mg contains carbasalate calcium, a complex of calcium acetyl salicylic acid and urea that is fully soluble in a small amount of water. Each effervescent tablet contains the equivalent of 78 mg of acetyl salicylic acid which, after solution, is fully available as an ion for absorption.

The volume of urea is very small (13.1%) therefore even at high doses it forms only a fraction of the volume that is found as a metabolite in normal protein metabolism.

Carbasalate calcium is a thrombocyte aggregation inhibitor. The antithrombotic effect is due to the irreversible acetylating of the enzyme cyclo-oxygenase in the thrombocyte, through which the formation of the prostaglandin thromboxane A<sub>2</sub> is inhibited. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days) and the effect is cumulative after repeated dosing. As a result it is possible to achieve maximum thromboxane A<sub>2</sub> inhibition after initially higher starting dose followed by lower maintenance doses to compensate for the creation of new thrombocytes.

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

### ABSORPTION

After oral administration, acetyl salicylic acid is rapidly absorbed in the proximal part of the small bowel. The maximum plasma concentration is reached after 0.5-2 hours. However, a considerable part of the dose is hydrolysed in the gastric wall during absorption. Simultaneous ingestion of food delays the uptake of acetyl salicylic acid (lower peak plasma concentrations).

### DISTRIBUTION

The volume of distribution of acetyl salicylic acid is approx. 0.20 l/kg bodyweight. The first conversion product formed from acetyl salicylic acid, anti-inflammatorily effective salicylic acid, is bound to plasma proteins, primarily albumin, to the 90% level.

Salicylic acid diffuses slowly to the synovia and the synovial fluid. It penetrates the placenta and passes over into the maternal milk.

### BIOTRANSFORMATION

Acetyl salicylic acid is primarily converted into salicylic acid by hydrolysis. The half-life of acetyl salicylic acid is short, approx. 15-20 minutes.

Salicylic acid is then converted into glycine acid and glucuronic acid conjugates and traces of gentisinic acid. At higher therapeutic doses the conversion capacity of salicylic acid is already exceeded and the pharmacokinetics is non-linear. This leads to a prolongation of the apparent elimination half-life of salicylic acid from a few hours to approximately 24 hours.

### EXCRETION

Excretion is primarily via the kidneys.

The tubular resorption of salicylic acid is pH-dependent. By alkalising the urine the proportion of unchanged salicylic acid in the excretion increases from approx. 10% to approx. 80%.

## 5.3 Preclinical safety data

Mutagenic and carcinogenic potential.

The acetylsalicylic acid has been assessed in many in vitro and in vivo pre-clinical studies. Taken together the results didn't reveal any mutagenic effect.

Long term studies on rat and mouse didn't reveal any carcinogenic effect.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

lactose monohydrate  
adipic acid (E 355)  
sodium hydrogen carbonate (E 500a)  
magnesium stearate (E 470b)  
crospovidone (E 1202)  
povidone K90 (E 1201)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

Shelf life of the medicinal product as packaged for sale (30 effervescent tablets): 3 years;

Shelf life after first opening the container: 1 month.

Shelf life of the medicinal product as packaged for sale (90 effervescent tablets): 3 years;

Shelf life after first opening the container: 3 months.

Shelf life of the medicinal product as packaged for sale (100 effervescent tablets): 3 years;  
Shelf life after first opening the container: 100 days.

#### **6.4 Special precautions for storage**

Do not refrigerate or freeze.

Store in the original packaging, in order to protect from moisture.

Keep the container tightly closed.

Do not store above 30°C.

#### **6.5 Nature and contents of container**

30, 90 or 100 effervescent tablets in a polypropylene tablet container with polyethylene cap (containing a desiccant cartridge), packed in a cardboard outer box.

Not all pack sizes may be marketed

#### **6.6 Special precautions for disposal and other handling**

No special requirements

### **7 MARKETING AUTHORISATION HOLDER**

Meda Health Sales Ireland Limited  
Unit 35/35, Block A  
Dunboyne Business Park  
Dunboyne  
Co. Meath  
Ireland

### **8 MARKETING AUTHORISATION NUMBER**

PA 1332/11/1

### **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 25 February 2005

Date of last renewal: 9 February 2009

### **10 DATE OF REVISION OF THE TEXT**

April 2015