Core Safety Profile

Active substance: Lysine acetylsalicylate
Pharmaceutical form(s)/strength: 75 mg, 100 mg, 160 mg, 300 mg powder for oral solution; 100mg/mL powder and solvent for solution for injection; 500 mg powder for solution for injection

P-RMS: HU/H/PSUR/0015/002
Date of FAR: 02.10.2013
4.3 Contraindications

- Hypersensitivity to acetylsalicylic acid or to any of the excipients listed in section 6.1, or to other non-steroidal anti-inflammatory drugs (NSAIDs) (cross-reactivity)
- Patients with pre-existing mastocytosis, in whom the use of acetylsalicylic acid may induce severe hypersensitivity reactions (including circulatory shock with flushing, hypotension, tachycardia and vomiting).
- History of asthma induced by the administration of acetylsalicylates or substances with similar activity, particularly non-steroidal anti-inflammatory drugs
- Third trimester of pregnancy (beyond 24 weeks of gestation) (see section 4.6)
- Active peptic ulcer
- Any constitutional or acquired haemorrhagic disease
- Haemorrhagic risk
- Severe hepatic insufficiency
- Severe renal insufficiency
- Severe, uncontrolled cardiac insufficiency
- Co-administration with methotrexate used at doses >15 mg/week at anti-inflammatory doses of acetylsalicylic acid, or at analgesic or antipyretic doses (see section 4.5).
- Co-administration of oral anticoagulants with acetyl salicylic acid used at anti-inflammatory doses, or at analgesic or antipyretic doses and in patients with a history of gastro-duodenal ulcers (see section 4.5).

4.4 Special warnings and precautions for use

- In the event of combination with other medicinal products, to avoid any risk of overdose, check that acetylsalicylic acid is absent from the composition of other medicinal products.
- Reye’s syndrome, a very rare life-threatening disease, has been observed in children and adolescents with signs of viral infection (in particular, varicella and influenza-like episodes) taking acetylsalicylic acid. Consequently, acetylsalicylic acid must only be administered to children and adolescents in this situation following medical advice, when other measures have failed. In the event of persistent vomiting, disturbances of consciousness or abnormal behaviour, treatment with acetylsalicylic acid must be discontinued.
- In children less than 1 month of age, administration of acetylsalicylic acid is only justified in specific situations and on medical prescription.
- In the event of the long-term administration of analgesics at high doses, the onset of headache must not be treated with higher doses.
- The regular use of analgesics, particularly a combination of analgesics, may lead to persistent renal lesions, with a risk of renal insufficiency.
- In some severe forms of G6PD deficiency, high doses of acetylsalicylic acid may cause haemolysis. In the event of G6PD deficiency, acetylsalicylic acid must be administered under medical supervision.
- Monitoring of treatment should be reinforced in the following cases:
  - in patients with a history of gastric or duodenal ulcer, or gastrointestinal bleeding, or gastritis
  - in patients with renal insufficiency
  - in patients with hepatic insufficiency
  - in patients with asthma: the occurrence of an asthma attack, in some patients, may be related to an allergy to non-steroidal anti-inflammatory drugs or to acetylsalicylic acid; in this case, this medicine is contraindicated (see section 4.3)
  - in patients with metrorrhagia or menorrhagia (risk of increasing the volume and duration of periods)
- Gastrointestinal bleeding or ulcers/perforations may occur at any time during treatment, without there being necessarily any prior signs or history in the patient. The relative risk increases in elderly subjects, in subjects with a low body weight, and in patients receiving anticoagulants or platelet aggregation inhibitors (see section 4.5). In the event of gastrointestinal bleeding, treatment must be discontinued immediately.

- In view of the inhibitory effect of acetylsalicylic acid on platelet aggregation, which occurs even at very low doses and persists for several days, the patient should be warned of the risk of haemorrhage in the event of surgery, even of a minor nature (e.g. tooth extraction).

- At analgesic or antipyretic doses, acetylsalicylic acid inhibits the excretion of uric acid; at doses used in rheumatology (anti-inflammatory doses), acetylsalicylic acid has a uricosuric effect.

- At high doses used in rheumatology (anti-inflammatory doses), patients should be monitored for possible onset of signs of overdose. In case of buzzing in the ears, impaired hearing or dizziness, treatment modalities should be reassessed. In children, it is recommended to monitor for salicylism, especially at the beginning of treatment.

- Use of this medicinal product is not recommended during breast-feeding (see section 4.6)

Formulation-specific safety information:
- Intravenous formulations are reserved for use in adults and not suitable for use in children.
- 1000-mg sachets are not suitable for use in children weighing less than 50 kg.
- 500-mg-sachets are not suitable for children weighing less than 30 kg in analgesic and antipyretic indications, and for children weighing less than 20 kg in anti-inflammatory (rheumatic) indications.
- 250-mg-sachets are not suitable for children weighing less than 15 kg.
- 100 mg sachets are not suitable for use in children weighing less than 6 kg.

For non-prescription formulations of acetylsalicylic acid > 500 mg/d:
- There is some evidence that drugs which inhibit cyclo-oxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Applies to products containing lactose:
- Patients with congenital galactosaemia, glucose/galactose malabsorption or lactase deficiency should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Several substances are involved in interactions, due to their platelet aggregation inhibitory properties:
Abciximab, acetylsalicylic acid, clopidogrel, epoprostenol, eptifibatide, iloprost and iloprost trometamol, ticlopidine and tirofiban.
The use of multiple platelet aggregation inhibitors increases the risk of bleeding, as does their combination with heparin or related molecules, oral anticoagulants or other thrombolytics, and must be taken into consideration by maintaining regular clinical monitoring.

Contraindicated combinations (see section 4.3):
- Methotrexate at doses >15 mg/week at anti-inflammatory doses of acetylsalicylic acid, or at analgesic or antipyretic doses of acetylsalicylic acid: Increased toxicity of
methotrexate, in particular haematological toxicity (due to reduction in renal clearance of methotrexate by acetylsalicylic acid).

- Oral anticoagulants at anti-inflammatory doses of acetylsalicylic acid, or at analgesic or antipyretic doses of acetylsalicylic acid and in patients with a history of gastro-duodenal ulcers: Increased risk of haemorrhage.

Combinations not recommended:
- Oral anticoagulants at analgesic or antipyretic doses of acetylsalicylic acid and in patients with no history of gastro-duodenal ulcers: Increased risk of haemorrhage.
- Oral anticoagulants at doses of acetylsalicylic acid used for inhibition of platelet aggregation and in patients with a history of gastro-duodenal ulcers: Increased risk of haemorrhage. Other non-steroidal anti-inflammatory drugs (NSAIDs) at anti-inflammatory doses of acetylsalicylic acid, or at analgesic or antipyretic doses of acetylsalicylic acid: Increased risk of gastrointestinal ulcers and haemorrhage.
- Low molecular weight heparins (and related molecules) and unfractionated heparins at curative doses, or in elderly patients (≥65 years) regardless of the dose of heparin, and for anti-inflammatory doses of acetylsalicylic acid or analgesic or antipyretic doses of acetylsalicylic acid: Increased risk of haemorrhage (inhibition of platelet aggregation and aggression of the gastroduodenal mucosa by acetylsalicylic acid). Another anti-inflammatory drug, or another analgesic or antipyretic should be used.
- Clopidogrel (beyond the approved indications for this combination in patients with acute coronary syndrome): Increased risk of haemorrhage. If co-administration cannot be avoided, clinical monitoring is recommended.
- Uricosurics (benzbromarone, probenecid): Reduction in the uricosuric effect due to competition for elimination of uric acid in renal tubules.
- Ticlopidine: Increased risk of haemorrhage. If co-administration cannot be avoided, clinical monitoring is recommended.
- Glucocorticoids (except hydrocortisone replacement therapy) for anti-inflammatory doses of acetylsalicylic acid: Increased risk of haemorrhage.
- Pemetrexed in patients with mild to moderate renal impairment (creatinine clearance between 45 ml/min and 80 ml/min): Increased risk of pemetrexed toxicity (due to decreased renal clearance of pemetrexet by acetylsalicylic acid) at anti-inflammatory doses of acetylsalicylic acid.

Combinations requiring precautions for use:
- Diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists at anti-inflammatory doses of acetylsalicylic acid or analgesic or antipyretic doses of acetylsalicylic acid: Acute renal failure may occur in dehydrated patients due to decreased glomerular filtration rate secondary to decreased synthesis of renal prostaglandins. In addition, reduction of antihypertensive effect may occur. Ensure that the patient is hydrated and renal function is monitored at the beginning of treatment.
- Methotrexate at doses ≤15 mg/week at anti-inflammatory doses of acetylsalicylic acid, or at analgesic or antipyretic doses of acetylsalicylic acid: Increased toxicity of methotrexate, in particular haematological toxicity (due to reduction in renal clearance of methotrexate by acetylsalicylic acid). Blood counts should be monitored weekly during the first weeks of co-administration. Close monitoring is required in patients with renal impairment (even mild) as well as in elderly patients.
- Methotrexate at doses >15 mg at doses of acetylsalicylic acid used for inhibition of platelet aggregation: Increased toxicity of methotrexate, in particular haematological toxicity (due to reduction in renal clearance of methotrexate by acetylsalicylic acid). Blood counts should be monitored weekly during the first weeks of co-administration. Close monitoring is required in patients with renal impairment (even mild) as well as in elderly patients.
• Clopidogrel (in the approved indications for this combination in patients with acute coronary syndrome): Increased risk of haemorrhage. Clinical monitoring is recommended.
• Gastrointestinal topicals, antacids and charcoal: Increased renal excretion of acetylsalicylic acid due to alkalinisation of urine. It is recommended to administer gastrointestinal topicals and antacids at least 2 hours apart from acetylsalicylic acid.
• Pemetrexed in patients with normal renal function: Increased risk of pemetrexed toxicity (due to decreased renal clearance of pemetrexed by acetylsalicylic acid) at anti-inflammatory doses of acetylsalicylic acid. Renal function should be monitored.
• Low molecular weight heparins (and related molecules) and unfractionated heparins at preventive doses in patients under 65 years of age: Co-administration acting at different levels of haemostasis increases the risk of haemorrhage. Therefore, in patients less than 65 years of age, co-administration of heparins at preventive doses (or related molecules), and acetylsalicylic acid, whatever the dose, should be taken into account by maintaining clinical monitoring, and laboratory monitoring as needed.
• Low molecular weight heparins (and related molecules) and unfractionated heparins at curative doses or in elderly patients (≥65 years) regardless of the dose of heparin, and for doses of a cetylsalicylic acid used for inhibition of platelet aggregation: Increased risk of haemorrhage (inhibition of platelet aggregation and aggression of the gastroduodenal mucosa by acetylsalicylic acid).
• Thrombolytics: Increased risk of haemorrhage.
• Oral anticoagulants at doses of acetylsalicylic acid used for inhibition of platelet aggregation: Increased risk of haemorrhage.
• Other non-steroidal anti-inflammatory drugs (NSAIDs) at doses of acetylsalicylic acid used for inhibition of platelet aggregation: Increased risk of gastrointestinal ulcers and haemorrhage.
• Glucocorticoids (except hydrocortisone replacement therapy) for analgesic and antipyretic doses of acetylsalicylic acid: Increased risk of haemorrhage.
• Selective Serotonin Re-uptake Inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline): Increased risk of haemorrhage.
• Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly (see section 5.1). 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.

4.6 Pregnancy and lactation

Pregnancy

Low doses, < 100 mg per day:
Clinical studies indicate that acetylsalicylic acid at doses below 100 mg/day appear to be safe in case of extremely limited obstetric uses, requiring specialized monitoring.

Doses between 100 mg and 500 mg per day:
Clinical experience with administration of acetylsalicylic acid at doses between 100 mg and 500 mg is insufficient. Therefore, the same recommendations apply as for doses above 500 mg per day (see paragraph below).

Doses ≥ 500 mg per day:
Inhibition of prostaglandin synthesis may adversely affect the course of pregnancy and/or the embryofetal development. Data from epidemiological studies suggest an increased risk of
miscarriage, cardiac malformations and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of cardiovascular malformations was increased from less than 1% to approximately 1.5%. The risk seems to increase with dose and duration of treatment. 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, an increased incidence of various malformations, including cardiovascular malformations, has been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic phase of gestation. Unless absolutely necessary, acetylsalicylic acid should not be administered during the first 24 weeks of pregnancy. If acetylsalicylic acid is administered to a woman who wants to become pregnant or to pregnant woman during the first 24 weeks of pregnancy, the dose should be as low as possible and treatment duration as short as possible.

Beyond 24 weeks of pregnancy, all prostaglandin synthesis inhibitors may expose the fetus to:
- Cardio-pulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension).
- Renal impairment, which may progress to renal failure with oligo-hydramnios.

In late pregnancy, the mother and the newborn may present with:
- Prolongation of bleeding time due to inhibition of platelet aggregation which may occur even after administration of very low doses of acetylsalicylic acid.
- Inhibition of uterine contractions resulting in delayed or prolonged labor.
Consequently, acetylsalicylic acid is contraindicated in the third trimester of pregnancy (beyond 24 weeks of gestation) (see section 4.3).

**Lactation**
Acetylsalicylic acid passes into breast milk: Acetylsalicylic acid is therefore not recommended during breast-feeding (see section 4.4).

**4.7 Effects on ability to drive and use machines**
No effects on ability to drive and use machines have been observed.

**4.8 Undesirable effects**
Frequencies cannot reliably be estimated based on the available data. Therefore frequencies are listed as “not known”.

**Blood and lymphatic system disorders**
Haemorrhagic syndromes (epistaxis, bleeding gums, purpura, etc.) with an increase in bleeding time. The bleeding risk may persist for 4 to 8 days after discontinuation of acetylsalicylic acid. It may cause an increased risk of haemorrhage in the event of surgery. Intracranial and gastrointestinal haemorrhage may also occur. Intracranial haemorrhage may be fatal, especially when administered in the elderly.

**Thrombocytopenia**

**Gastrointestinal disorders**
Abdominal pain
Occult or patent gastrointestinal haemorrhage (haematemesis, melena, etc.) resulting in iron-deficiency anaemia. The bleeding risk is dose-dependent. Gastric ulcers and perforations
Upper gastrointestinal disorders: oesophagitis, erosive duodenitis, erosive gastritis, esophageal ulceration, perforation
Lower gastrointestinal disorders: small (jejunum and ileum) and large (colon and rectum) intestinal ulcers, colitis and intestinal perforation
These reactions may or may not be associated with hemorrhage, and may occur at any dose of acetylsalicylic acid and in patients with or without warning symptoms or a previous history of serious GI events.

**General disorders and administration site conditions**
Reye’s syndrome (see section 4.4)

*Affects to IV formulations only:*
Pain and local skin reactions at the injection site

**Hepatobiliary disorders**
Elevation of hepatic enzymes, liver injury, mainly hepatocellular

**Immune system disorders**
Hypersensitivity reactions, anaphylactic reactions, asthma, angioedema

**Nervous system disorders**
Headache, dizziness, sensation of hearing loss, tinnitus, which are usually indicative of an overdose.
Intracranial haemorrhage

**Respiratory, thoracic and mediastinal disorders:**
Non-cardiogenic pulmonary edema with chronic use and in the context of a hypersensitivity reaction due to acetylsalicylic acid.

**Skin and subcutaneous tissue disorders**
Urticaria, skin reactions

### 4.9 Overdose

The risk of overdose is of concern in elderly subjects and particularly in young children (therapeutic overdose or, more frequently, accidental poisoning) where it can be fatal. Non-cardiogenic pulmonary edema can occur with acute and chronic acetylsalicylic acid overdose (see section 4.8).

**Symptoms**
Moderate poisoning:
Symptoms such as buzzing in the ears, sensation of impaired hearing, headache, and dizziness are indicative of an overdose and may be controlled by a reduction in the dosage.
Severe poisoning:
Symptoms include: Fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse, respiratory insufficiency, severe hypoglycaemia.
In children, an overdose may be fatal at a dose as low as 100 mg/kg in a single intake.

**Emergency management**
- Immediate transfer to a specialized hospital unit
- Gastrointestinal lavage and administration of activated charcoal
- Control of acid-base balance
- Alkalisation of the urine with monitoring of urine pH
- Haemodialysis in cases of severe poisoning
- Symptomatic treatment