SUMMARY OF PRODUCT CHARACTERISTICS

Cardiopirin® 100 mg, gastro-resistant tablets,
Packaging: blister 3 x 10 tablets

Manufacturer: G.L. Pharma GmbH
Address: Schlossplatz 1 A-8502 Lannach, Austria

Applicant: PharmaSwiss d.o.o.
Address: Vojvode Stepe 18, 11 000 Belgrade, Serbia
1. **NAME OF THE MEDICINAL PRODUCT**
Cardiopirin® 100 mg, gastro-resistant tablets
INN: acetylsalicylic acid

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
1 gastro-resistant tablet contains 100 mg acetylsalicylic acid.

Excipients:
Lactose monohydrate ......................... 60 mg

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**
Gastro-resistant tablet.
White, round, biconvex film-coated tablet without break-score.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic Indications**
It is necessary to consult a doctor prior to the first administration of the medicine.

- For decreasing the risk of myocardial infarction in patients with angina pectoris.
- For relapse prophylaxis after myocardial infarction.
- For the prophylaxis of thrombosis after vascular surgery e.g. coronary bypass surgery.
- For the secondary prevention of transient ischaemic attacks (TIA) and apoplexy.
- For the treatment of acute myocardial infarction.
- For the prophylaxis of cardiovascular events in patients with diabetes mellitus and high cardiovascular risk.

4.2. **Posology and method of administration**

**Adults**

For decreasing the risk of myocardial infarction in patients with angina pectoris:
100 to 300 mg acetylsalicylic acid daily.
For relapse prophylaxis after myocardial infarction:
100 to 300 mg acetylsalicylic acid daily.
For the prophylaxis of thrombosis after vascular surgery e.g. coronary bypass surgery:
100 to 300 mg acetylsalicylic acid daily.
For the secondary prevention of transient ischaemic attacks (TIA) and apoplexy:
100 to 300 mg acetylsalicylic acid daily.
For the treatment of acute myocardial infarction:
150 to 300 mg acetylsalicylic acid daily.
For the prophylaxis of cardiovascular events in patients with diabetes mellitus and high cardiovascular risk:
100 to 300 mg acetylsalicylic acid daily, 100 mg in special cases.

**Children**
Cardiopirin is not indicated in children.
Medicines containing acetylsalicylic acid may be given to children below 16 years of age only if prescribed by a doctor (see section 4.4 Special warnings and precautions for use).

**Mode of administration:**
The film-coated tablets should be swallowed as a whole with some liquid with or without meals at the same time of the day.

**Duration of application:**
Long-term treatment with the lowest possible dose.

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Known hypersensitivity (allergy, asthma attacks) to other salicylates or other nonsteroidal analgesics / antirheumatics (NSAIDs).
- Gastric and intestinal ulcers.
- Haemorrhagic diathesis, thrombocytopenia, haemophilia.
- Renal insufficiency and oxaluria.
- Severe hepatic insufficiency.
- Severe, not sufficiently controlled cardiac insufficiency.
- Concomitant treatment with methotrexate in doses of 15 mg per week or higher.
- During the last 3 months of pregnancy (see section 4.6 Pregnancy and lactation).
- Acetylsalicylic acid should not be used in children younger than 16 years, except with prevention of trombosis in cardial surgery.

### 4.4. Special Warnings and Precautions for Use

Caution is required in cases of:

- known hypersensitivity to other analgesics / antiphlogistics / antirheumatics,
- other allergies (e.g. accompanied by skin reactions, pruritus, urticaria),
- asthma bronchiale, hay fever, swelling of the mucosa in the nose (nasal polyps), chronic airway diseases,
- concomitant therapy with antithrombotic medicines (e.g. coumarin derivatives, heparin - except for low-dose heparin treatment),
- genetically determined glucose-6-phosphate dehydrogenase deficiency (haemolytic anaemia),
- gastrointestinal complaints (e.g. gastritis),
- history of gastric or duodenal ulcers or gastrointestinal bleeding,
- disorders of the renal and/or hepatic function.

Prior to surgical procedures (even to smaller procedures such as dental surgery), the doctor has to be informed about the intake of this medicine, and the antithrombotic effect of acetylsalicylic acid needs to be considered. Prolongation of bleeding time may occur.

Additional intake of other salicylates or other nonsteroidal antiphlogistics/antirheumatics should be avoided.

In taking acetylsalicylic acid in higher doses for many years, kidney damage may not be excluded. The renal function should be monitored regularly.

Symptoms of outer or inner bleeding (e.g. bruises) need to be monitored in patients that are about to receive thrombolytic treatment.
In low doses, acetylsalicylic acid reduces uric acid excretion. This may precipitate gout attacks in predisposed patients.

For the treatment of fever, acetylsalicylic acid should be used in children and adolescents only if prescribed by a doctor and only in cases where other measures are not appropriate. Life-threatening complications (Reye’s syndrome) have been observed in isolated cases in children and adolescents. If continued vomiting, dehydration, impaired consciousness, and convulsions occur, immediate intensive-care treatment is required. However, a causal connection to the intake of special medicines has not been proved.

This medicine contains lactose monohydrate. Patients with a rare congenital galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction with other medicinal products and other forms of interaction
The concomitant intake of acetylsalicylic acid with other medicines may increase or decrease their effects.

Increase of:
- the effect of anticoagulant and antithrombotic drugs (e.g. coumarin derivates, heparin, dipyridamole, sulfinpyrazone),
- the effects of other antithrombotic drugs, e.g. ticlopidine, clopidogrel: prolongation of bleeding time may occur,
- antidiabetic effects - the hypoglycaemic effect of sulfonylurea derivatives,
- the desirable and undesirable effects of nonsteroidal antiphlogistics and antirheumatics,
- the desirable and undesirable effects of methotrexate,
- the risk of gastrointestinal bleeding during concomitant use of glucocorticoids or alcohol,
- the plasma levels of digoxin, barbiturates, and lithium,
- the effect of sulfonamide and sulfonamide combinations including cotrimoxazole,
- the effect of triiodothyronine,
- the effect of valproic acid.

Decrease of:
- the effect of aldosteron antoagonists (spironolactone and canrenone),
- the effect of loop diuretics (e.g. furosemide),
- the effect of uricosuric agents (probenecid, sulfinpyrazone),
- the effect of ACE inhibitors.

Non-absorbable complexes may be produced by concomitant intake tetracyclines. Therefore an interval of at least 1-3 hours should be observed between the intakes.

Caution is required during concomitant treatment with ciclosporine or tacrolimus.

Experimental data suggest that ibuprofen may inhibit the effect of low dose ASA 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
**Pregnancy**

Inconsistent data is available from epidemiological studies concerning a relationship between the intake of acetylsalicylic acid during early pregnancy and an increased risk for malformations (cleft palates, malformations of the heart), however, this risk appears to be low within the therapeutic dose range (daily doses of 50 and 150 mg).

Due to inhibition of prostaglandin synthesis, analgesic doses of acetylsalicylic acid may cause a prolongation of gestation, if taken during the last trimester, and a premature closure of the ductus arteriosus Botalli, if taken from the 28th to 30th week of pregnancy onwards. Such doses may furthermore cause increased tendency to bleed in mother and child as well as intracranial bleeding in preterm infants, if taken shortly before labour.

Present experience from the use of ASA in pregnant women in daily doses between 50 and 150 mg during the second and third trimester does not indicate evidence for tocolysis, increased tendency to bleed, or a premature closure of the ductus arteriosus Botalli. There are not data for daily doses between 150 and 300 mg.

1. and 2. trimester
During the first and second trimester, Cardiopirin should be prescribed only if clearly indicated.

3. trimester
The administration of Cardiopirin during the last trimester is contraindicated (see section 4.3 Contraindications).

**Lactation**

The active substance acetylsalicylic acid and its metabolites are excreted into breast milk in small amounts. As harmful effects on the child have not been established so far, cessation of breast feeding is not required during the short-term administration of daily doses of up to 150 mg. During long-term administration.

**4.7. Effects on ability to drive and use machines**

Special studies on this have not been conducted. Based on the pharmacodynamic properties and undesirable effects, an influence on reactivity and the ability to drive is not expected.

**4.8. Undesirable effects**

Undesirable effects are classified according to their severity and frequency:

- **Very common:** ≥ 1 out of 10
- **Common:** ≥ 1/100, < 1/10
- **Uncommon:** ≥ 1/1 000, < 1/100
- **Rare:** ≥ 1/10 000, < 1/1 000
- **Very rare:** <1/10 000, not known (frequency cannot be estimated from the available data)

**Blood and lymphatic system disorders**

Rare: prolongation of bleeding time, thrombocytopenia.

Bleeding such as nose bleed, gingival bleeding, and skin bleeding with probable prolongation of bleeding time. This effect may last for 4 to 8 days after the beginning of treatment. Rarely to very rarely, severe bleeding has been reported, such as cerebral bleeding, especially in patients with uncontrolled hypertension and/or concomitant anticoagulant treatment, which, in
isolated cases, may be life-threatening.

**Nervous system disorders**
Headache, vertigo, confusion, hearing disturbances or tinnitus may be symptoms of overdosage, especially in children and the elderly (see also section 4.9 Overdose).

**Immune system disorders**
Uncommon: hypersensitivity reactions such as bronchospasm and skin reactions.
Rare: hypersensitivity reactions (Erythema exsudativum multiforme in isolated cases), possibly accompanied by decrease in blood pressure, dyspnoea, anaphylactic reactions and angioneurotic oedema, especially in asthmatics.

**Respiratory, thoracic and mediastinal disorders**
Rare: triggering of asthma attacks.

**Gastrointestinal disorders**
Common: gastrointestinal disorders such as heart burn, nausea, vomiting, abdominal pain, and diarrhea as well as minimal gastrointestinal blood loss (microbleeding).
Uncommon: gastrointestinal bleeding as well as gastrointestinal ulcers.
Symptoms of severe gastric bleeding may be black stools or vomiting of blood.

After long-term administration of Cardiopirin, iron deficiency anaemia may occur due to occult gastrointestinal blood loss.

**Metabolism and nutrition disorders**
Very rare: hypoglycaemia.
Acetylsalicylic acid reduces excretion of uric acid. This may precipitate gout attacks in predisposed patients.

**Hepatobiliary disorders**
Very rare: increase of hepatic enzyme values.

**Renal and urinary disorders**
Rare: the intake of higher doses for long periods may lead to kidney damage.

### 4.9. Overdose

In general, it has to be distinguished between chronic overdose with acetylsalicylic acid accompanied by mostly disorders of the central nervous system such as drowsiness, vertigo, confusion, and nausea (“salicylism”), and acute intoxications. The main aspect of acute intoxications with acetylsalicylic acid is a sever disturbance of the acidbase balance. Even in therapeutic doses, respiratory alkalosis occurs due to increased respiration. It is compensated by increased renal excretion of hydrogen carbonate, thus the blood pH is at a normal value. In toxic doses, this compensation is not sufficient and the blood pH as well as the concentration of hydrogen carbonate decrease. Blood PCO2 values may be normal. Apparently, there is the clinical picture of metabolic acidosis. Actually, it is a combination of respiratory and metabolic acidosis. The reasons are: impaired respiration due to toxic doses, accumulation of acid, partly due to reduced renal excretion (sulfuric and phosphoric acid as well as salicylic acid, lactic acid, acetoacetic acid etc.) resulting from a disturbance of carbohydrate metabolism. Additionally, there is a disorder of the electrolyte balance. Severe potassium loss occurs.
Symptoms of acute intoxication
Symptoms of slight acute intoxication (200 - 400 μg/ml):
Besides disturbances of the acid-base balance, the electrolyte balance (e.g. potassium loss), hypoglycaemia, skin rash as well as gastrointestinal bleeding hyperventilation, tinnitus, nausea, vomiting, visual and hearing impairment, headache, vertigo, and confusion were observed.

In severe intoxications (more than 400 μg/ml), delirium, tremor, dyspnoea, heavy sweating, exsiccosis, hyperthermia, and coma may occur.
In lethal intoxications, death usually occurs as a result of respiratory failure.

Treatment of intoxication
Treatment options in case of intoxication with acetylsalicylic acid are based upon the severity, stadium, and the clinical symptoms of intoxication. They comply with the usual measures for reduced resorption of the active substance, monitoring of water and electrolyte balance as well for disturbed temperature regulation and respiration. Priority should be given to measures that promote excretion and normalization of acid-base and electrolyte balance. Aside from i.v. sodium hydrogen carbonate and potassium chloride, diuretics may be given. Urine should be alkaline as to increase ionisation of salicylates and to decrease tubular reabsorption. Monitoring of blood levels (pH, PCO2, hydrogen carbonate, potassium etc.) is highly advisable. In severe cases, intensive medical treatment (alkalised forced diuresis, haemodialysis) may be required; administration of diazepam in cases of convulsions.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic Group: platelet aggregation inhibitors, acetylsalicylic acid
ATC code: B01AC06

The antithrombotic effect of acetylsalicylic acid is based on the inhibition of thromboxane A2-synthesis in thrombocytes. This is achieved by acetylation of cyclooxygenase, resulting in inhibition of thromboxane-A2 synthesis (a platelet aggregation-supporting and vasoconstricting prostaglandin) in thrombocytes. This is a permanent effect and is usually maintained throughout the whole 8-day lifetime of thrombocytes.

New clinical findings prove antithrombotic effects of ASA even in low doses. ASA is also used for the treatment of the rarely occurring Kawasaki syndrome. The corresponding dosage should be derived from the current scientific literature.

Because of the inhibition of prostaglandin synthesis, acetylsalicylic acid also belongs to the group of acid-forming nonsteroidal antiinflammatory drugs (NSAIDs) with analgesic, antipyretic, and antiphlogistic properties.

5.2. Pharmacokinetic Properties

Absorption
After the application as gastro-resistant formulation, ASA is absorbed in the duodenum. Maximum plasma levels are achieved 3 hours after administration.
**Distribution**
Binding to plasma proteins is concentration-dependent: values of 49% up to more than 70% (acetylsalicylic acid) and 66% to 98% (salicylic acid), respectively, have been obtained. Cardiopirin gastro-resistant tablets are bioequivalent with a hydrous solution of acetylsalicylic acid; due to the particular pharmaceutical form, the half-life is prolonged from 2 to 4 hours.

Salicylic acid passes the placenta and is excreted into breast milk.

**Metabolism**
Acetylsalicylic acid is hydrolised enzymatically to salicylic acid in the intestinal mucosa, but predominantly in the liver. Furthermore, salicylic acid is glucuronised in the liver.

**Elimination**
Excretion of salicylic acid (85 % in alkaline and 10 % in acid urine) as well as its conjugates and derivates happens mainly renal.

**5.3. Preclinical Safety Data**
Preclinical results of experiments were achieved after oral, nasal, subcutaneous and intravenous application in mice, rats, guinea pigs, rabbits, and dogs. In chronic toxicity experiments using human therapeutic doses of ASA, no significant differences compared with the control group were noticed. In vitro investigations showed no mutagenic potential of ASA. Studies in mice and rats proved no cancerogenic potential of ASA.

Reproduction toxicology:
In animal experiments (rat, dog) using higher doses of ASA, teratogenic effects occurred. Implantation disorders, embryo- and fetotoxic effects as well as disorders of the ability to learn have been described in the offspring after prenatal exposure.

### 6. PHARMACEUTICAL PARTICULARS

#### 6.1. List of Excipients

**Core of the tablet:**
Lactose monohydrate,
celulose, microcrystal,
colloidal anhydrous silica,
potato starch,
**Film tablets:**
talc,
glycerol triacetat,
methacrylic acidethylacrylate copolymer (1:1) dispersion 30%

#### 6.2. Incompatibilities

Not applicable.

#### 6.3. Shelf Life
3 years.

6.4. Special precautions for storage

Do not store above 25° C.
Keep the product in the outer carton in order to protect from light and moisture.

6.5. Nature and Contents of Container

PVC/aluminium blister, 3 blisters containing 10 tablets

6.6. Special precautions for disposal

In accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

PharmaSwiss d.o.o.,
Vojvode Stepe 18,
11000 Belgrade

8. MARKETING AUTHORISATION NUMBERS

446/2005/12 . . . . . . . . . . . . . 127/2011/12

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04.10.2005. . . . . . . . . . . . . . . . . . . . . . . .05.01.2007.

10. DATE OF REVISION OF THE TEXT

December 2010.