Prescribing information
(Summary of Product Characteristics / SPC)

1. Name of drug product

Aspirin Cardio

2. Qualitative and quantitative composition

1 enteric-coated tablet contains: 100 mg acetylsalicylic acid.
For a complete list of excipients, see section 6.1.

3. Pharmaceutical Form

Enteric-coated tablets

4. Clinical Particulars

4.1 Indications

Aspirin® Cardio is indicated for the primary prevention of coronary heart disease in patients at increased risk and the secondary prevention of thrombotic cerebrovascular or cardiovascular disease.

Note:
Aspirin Cardio is not suitable for the treatment of pain due to its amount of active substance.

4.2 Posology and method of administration

Posology:
A daily dose of one Aspirin Cardio enteric-coated tablet (equivalent to 100 mg acetylsalicylic acid per day) is recommended.

Method of administration:
The gastro-resistant tablets should be taken with plenty of water possibly at least 30 minutes before a meal. In order to ensure that the active substance is released in the alkaline environment of the intestine, the gastro-resistant tablets should not be broken, crushed or chewed.

Aspirin cardio is intended for long-term use. The attending doctor must decide on the length of the treatment.

4.3 Contraindications

Aspirin Cardio must not be used:
- in cases of hypersensitivity to the active ingredient acetylsalicylic acid, other salicylates or any of the other ingredients listed in section 6.1.
- by patients with a history of asthma attacks, which were caused by salicylates or substances with a similar action, especially nonsteroidal anti-inflammatory drugs (NSAIDs).
- by patients with acute gastrointestinal ulcers.
- by patients with haemorrhagic diathesis.
- by patients with liver or kidney failure.
- by patients with severe heart failure for which they are not receiving adequate treatment.

- in combination with methotrexate at a weekly dosage of 15 mg or more (see section 4.5).
- in the last trimester of pregnancy at dosages above 150 mg acetylsalicylic acid/day (see section 4.6).

4.4 Special Warnings and precautions for use

Particularly careful medical supervision is required:

- in cases of hypersensitivity to other analgesic/anti-inflammatory/anti-rheumatic drugs or other allergenic substances (see section 4.3).
- in case of concomitant intake of some non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or naproxen. These may weaken the anti-platelet effect of acetylsalicylic acid. Patients should be advised to consult their physician if they are taking acetylsalicylic acid and plan to take any NSAIDs (see section 4.5).
- in patients with other allergies (e.g. with skin reactions, itching, nettle rash).
- in patients with bronchial asthma, hay fever, swelling of the nasal mucosa (nasal polyps), chronic respiratory tract diseases.
- in concomitant therapy with anticoagulant drugs.
- with a history of gastrointestinal ulcers or gastrointestinal bleeding.
- with impaired liver function.
- in patients with impaired renal function or patients with reduced cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major haemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure.
- by patients who are about to undergo surgery (including minor surgery such as dental extractions): the tendency to bleed may be increased.
- in patients suffering from severe glucose-6-phosphate dehydrogenase (G6PD) deficiency: acetylsalicylic acid may induce haemolysis or haemolytic anaemia. Factors that may increase the risk of haemolysis are e.g. high dosage, fever or acute infections.

What other precautions must be taken?

At low doses acetylsalicylic acid reduces the excretion of uric acid. This may cause a gout attack in predisposed patients under certain circumstances.

Paediatric population

Aspirin Cardio should not be taken by children or adolescents with feverish illnesses unless they have been instructed to do so by a doctor and other therapeutic measures have failed. Prolonged vomiting in conjunction with such illnesses could be a sign of Reye's syndrome, a very rare but life-threatening disease which requires immediate medical attention.

Drugs containing acetylsalicylic acid should not be taken for prolonged periods or at high doses without consulting a doctor.

Aspirin Cardio contains less than 1 mmol sodium (23 mg) per enteric-coated tablet, that is to say essentially "sodium-free".

4.5 Interactions with other substances and other forms of interaction

Enhanced effects ranging up to an increased risk of side-effects:

- Anticoagulants / Thrombolytics: Acetylsalicylic acid can increase the risk of bleeding when taken before thrombolytic treatment. Attention should therefore be paid to signs of external or internal bleeding (e.g. bruising) in patients scheduled to undergo thrombolytic treatment.
- Antiplatelet drugs, e.g. ticlopidine, clopidogrel: Bleeding time can be prolonged.

- Nonsteroidal anti-inflammatory drugs and antirheumatics with salicylates: risk of gastrointestinal ulcers and haemorrhages is increased.
- Systemic glucocorticoids (with the exception of hydrocortisone as hormone replacement therapy for Addison's disease): increased risk of gastrointestinal haemorrhages and ulcers.
- Alcohol: elevated risk of gastrointestinal ulcers and bleeding.
- Digoxin: elevated plasma level.
- Antidiabetics such as insulin, sulfonylureas in combination with acetylsalicylic acid at higher doses: the blood glucose level can be reduced.
- Methotrexate: decrease in elimination and displacement from plasma protein binding sites by salicylates.
- Valproic acid: displacement from plasma protein binding sites by salicylates.
- Selective-Serotonin-Reuptake Inhibitors (SSRIs): elevated risk of gastrointestinal bleeding due to synergistic effects.

Weakening of effects:
- Aldosterone antagonists (spironolactone and canrenoate).
- Loop diuretics (e.g. furosemide).
- Antihypertensives (especially ACE inhibitors).
- Uricosuric agents (e.g. probenecid, benzbromarone).
- NSAIDs: Concomitant use (on the same day) of certain NSAIDs (acetylsalicylic acid excluded), such as ibuprofen or naproxen, can weaken the irreversible anti-platelet effect of acetylsalicylic acid. The clinical relevance of this interaction is not known. Treatment of patients with an increased cardiovascular risk with some NSAIDs, such as ibuprofen or naproxen, may reduce the cardioprotective effect of acetylsalicylic acid (see section 4.4).
- 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.

Patients should not take Aspirin Cardio in conjunction with any of the above-mentioned substances unless expressly instructed to do so by a doctor.

4.6 Pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryonic/foetal development. Data from epidemiological studies indicate an increased risk of miscarriages, cardiac malformations and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with the dose and duration of therapy.
If taken in the last trimester of pregnancy, analgesic acetylsalicylic acid dosages can, as a result of inhibition of prostaglandin synthesis, lead to prolongation of gestation. At these dosages, an increased bleeding tendency in the mother and child is also to be expected, as well as an increased incidence of intracranial bleeding in preterm infants if taken shortly before birth.

From the 20th week of pregnancy onward, use of Aspirin Cardio may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. There have also been reports of constriction of the ductus arteriosus after treatment in the second trimester of pregnancy, although this regressed after discontinuation of treatment in most cases. During the first and second trimester of pregnancy, therefore, Aspirin Cardio should not be given unless clearly necessary. If Aspirin Cardio is used by a woman attempting to conceive, or

during the first and second trimester of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and constriction of the ductus arteriosus should be considered after exposure to Aspirin Cardio for several days from gestational week 20 onward. Aspirin Cardio should be discontinued if oligohydramnios or constriction of the ductus arteriosus is found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction (see above)

the mother and 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, Aspirin Cardio is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breastfeeding
Small quantities of the active ingredient acetylsalicylic acid and its metabolites pass into breast milk. Detrimental effects on the infant have not been reported to date, it is therefore not generally necessary to interrupt breast-feeding if the daily dose does not exceed 150 mg. The infant should be weaned if higher doses are taken (more than 150 mg daily).

4.7 Effects on the ability to drive and use machines

Acetylsalicylic acid has no influence on the ability to drive and to use machines.

4.8. Undesirable effects

The following incidence rating is used to evaluate the frequency of side effects:

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:	< 10,000
Not known:	frequency cannot be estimated from the available data

Blood and lymphatic system disorders:
Rare to very rare serious bleedings, such as cerebral bleeding, especially in patients with uncontrolled hypertension and/or concomitant treatment with anticoagulants, which in isolated cases may be potentially life-threatening, have been reported.
Haemolysis and haemolytic anaemia in patients with severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency have been reported.
Bleeding, e.g. nosebleeds, bleeding gums, cutaneous bleeding or urogenital bleeding, possibly with prolongation of the bleeding time. This effect can persist for 4 to 8 days after use.

Immune system disorders:

Rare:

- Hypersensitivity reactions of the skin, respiratory tract, gastrointestinal tract and cardiovascular system, especially in asthmatics. Symptoms may include hypotension, attacks of dyspnoea, rhinitis, nasal congestion, anaphylactic shock and angioneurotic oedema.

Metabolism:

Very rare:

- Hypoglycaemia.
- At low dosages, acetylsalicylic acid reduces the excretion of uric acid. This may cause a gout attack in predisposed patients.

Nervous system disorders:

Headache, dizziness, impaired hearing ability, tinnitus and mental confusion can be signs of an overdose (see also section 4.9).

Gastrointestinal disorders:

Common:

- Gastrointestinal disorders such as heartburn, nausea, vomiting, abdominal pain and diarrhoea.
- Minor gastrointestinal bleeding (microhaemorrhaging).

Uncommon:

- Gastrointestinal ulcers which in very rare cases can lead to perforation.
- Gastrointestinal bleeding.
  Prolonged use of Aspirin Cardio may cause iron deficiency anaemia due to occult blood loss from the gastrointestinal tract.
- Gastrointestinal inflammation.

Not known:

- If there is pre-existing damage to the intestinal mucosa, formation of multiple membranes may occur in the intestinal cavity, possibly with subsequent stenosis.

If you pass black stools (tarry stools) or vomit blood, both of which are a sign of serious bleeding in the stomach, inform a doctor immediately.

Hepatobiliary disorders:

Very rare:

- Increase of liver enzyme values.

Skin and subcutaneous tissue disorders:

Uncommon:

- Skin reactions (very rare cases ranging up to erythema exsudativum multiforme).

Renal and urinary disorders:

Very rare:

- Renal impairment and acute renal failure.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

A distinction is made between chronic acetylsalicylic acid over-dosage with predominantly central nervous manifestations such as light-headedness, dizziness, confusion or nausea ("salicylism") and acute intoxication.
The cardinal feature of acute intoxication with acetylsalicylic acid is severe disruption of the acid-base balance. Even in the therapeutic dose range, respiratory alkalosis occurs as a consequence of increased respiration. This is compensated for by increased renal excretion of bicarbonate, which normalises the blood's pH value. At toxic doses, the level of compensation is no longer sufficient and both the pH value and the bicarbonate concentration in the blood drop. The plasma PCO_2 value may be temporarily normal. The apparent clinical picture is that of metabolic acidosis. However, the actual condition is a combination of respiratory and metabolic acidosis. The causes are: Respiratory restriction caused by toxic doses, acid accumulation, partially due to decreased renal excretion (sulphuric acid, phosphoric acid, salicylic acid, lactic acid, acetoacetic acid etc.) caused by impairment of carbohydrate metabolism. This is compounded by impairment of electrolyte balance. Major potassium loss occurs.

Symptoms of acute intoxication
Symptoms of milder acute intoxication (200 - 400 µg/ml):
In addition to disruption of the acid-base balance and electrolyte balance (e.g. potassium loss), hypoglycaemia, skin rashes and gastrointestinal haemorrhaging, hyperventilation, tinnitus, nausea, vomiting, impaired vision and hearing, headache, dizziness and confusion have been observed.
With severe intoxication (above 400 µg/ml), delirium, tremor, difficulty breathing, sweating, dehydration, hyperthermia and coma may occur.
In the event of intoxication with a fatal outcome, death usually occurs as a result of respiratory failure.

Treatment of intoxication
The therapeutic measures for treatment of intoxication with acetylsalicylic acid depend upon the extent, stage and clinical symptoms of the intoxication. They comprise the standard measures for decreasing absorption of the active ingredient, monitoring of the water and electrolyte balances, impaired temperature regulation and respiration.
Treatment is focused on measures to accelerate excretion and normalise the acid-base balance and the electrolyte balance. Infusion solutions of sodium hydrogen carbonate and potassium chloride and diuretics are administered. The urine reaction should be alkaline to increase the degree of salicylate ionisation and decrease the rate of back-diffusion to the tubules.
Monitoring of the blood values (pH, PCO_2, hydrogen bicarbonate, potassium, etc.) is strongly recommended. In severe cases, haemodialysis may be necessary.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, Platelet aggregation inhibitors, acetylsalicylic acid.
ATC code: B01AC06

Acetylsalicylic acid has an irreversible platelet aggregation-inhibiting action. This antiplatelet effect is achieved by acetylation of cyclooxygenase, irreversibly inhibiting the formation of thromboxane A_2 (a prostaglandin with a platelet aggregation-promoting and vasoconstrictive action) in the platelets. The effect is long-term and usually persists for the entire eight-day lifespan of a platelet.
Paradoxically, acetylsalicylic acid also inhibits the formation of prostacyclin (a prostaglandin with platelet aggregation-inhibiting but vasodilating effects) in the endothelial cells of the vascular walls. This effect is transient.
Once the acetylsalicylic acid has been washed out of the blood, the nucleated endothelial cells resume their production of prostacyclin. As a consequence, once daily administration of low-dosage (< 300 mg / day) acetylsalicylic acid causes inhibition of thromboxane A_2 in the platelets without markedly impairing prostacyclin formation.
Acetylsalicylic acid also belongs to the class of acid-forming nonsteroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on irreversible inhibition of cyclooxygenase enzymes involved in prostaglandin synthesis.
Acetylsalicylic acid is used at higher oral doses to treat mild to moderate pain, elevated temperature and acute and chronic inflammatory diseases (e.g. rheumatoid arthritis).

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are administered concomitantly. In one study, when a single dose of ibuprofen 400 mg was taken 8 h before or 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 a clinical setting imply that no firm conclusion 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

Acetylsalicylic acid is converted before, during and after absorption into its main metabolite salicylic acid. The metabolites are excreted primarily via the renal route.
In addition to salicylic acid, the main metabolites of acetylsalicylic acid include the glycine conjugate of salicylic acid (salicyluric acid), the ether and ester glucuronides of salicylic acid (salicyl phenolic glucuronide and salicyl acetyl glucuronide) and gentisic acid produced by oxidation of salicylic acid and its glycine conjugate.
Depending on the formulation, absorption of acetylsalicylic acid following oral administration is rapid and complete. The residual acetyl portion of acetylsalicylic acid undergoes partial hydrolytic cleavage during its passage through the mucous membranes of the gastrointestinal tract.
Peak plasma concentrations are attained after 10 -20 minutes (acetylsalicylic acid) and 0.3 -2 hours (total salicylate).
The elimination kinetics of salicylic acid are dependent to a great extent on the dose, as the capacity for metabolism of salicylic acid is limited (elimination half-life fluctuates between 2 and 30 h).
The elimination half-life of acetylsalicylic acid is only a few minutes; the elimination half-life of salicylic acid is 2 h after consumption of a dose of 0.5 g acetylsalicylic acid and 4 h after administration of 1 g; following consumption of a single dose of 5 g, the elimination half-life is extended to 20 h.
Protein binding in human plasma is dependent on the concentration; values ranging from 49 % to over 70 % (acetylsalicylic acid) and 66 % to 98 % (salicylic acid) have been reported.
Salicylic acid has been detected in cerebrospinal fluid and synovial fluid after consumption of acetylsalicylic acid.

Salicylic acid crosses the placental barrier and passes into breast milk.

5.3 Preclinical safety data

The preclinical safety profile of acetylsalicylic acid is well documented. In animal tests salicylates caused kidney damage and gastrointestinal ulcers.
Acetylsalicylic acid has been appropriately tested for mutagenicity and carcinogenicity; no relevant evidence of a mutagenic or carcinogenic potential was found.
Salicylates have been found to have teratogenic effects in a number of animal species.
There have been implantation disorders, embryotoxic and foetotoxic effects, and learning disorders in young animals after prenatal exposure.

6. Pharmaceutical data

6.1 Other ingredients

Maize starch
Powdered Cellulose
Talc
Methacrylic acid – ethylacrylate copolymer 1:1 dispersion 30%
Triethyl citrate
Polysorbate 80
Sodium lauryl sulphate

6.2 Incompatibilities

None

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

6.4 Special storage instructions

Store below 25°C.

6.5 Type and contents of container

PP aluminium blisters:
Packs of 28, 30, 84, 90 and 98 enteric-coated tablets
Not all pack sizes may be marketed.

6.6 Special requirements for disposal

No special requirements.

7. Manufacturer:

Bayer Bitterfeld GmbH,
06803 Greppin, Germany

8. Registration holder

Bayer Israel Ltd
36 Hacharash St., Hod Hasharon 45240

Revised in March 2024.