SUMMARY OF PRODUCT CHARACTERISTICS

Aspirin® Cardio 100,

Composition

Active substances: Acetylsalicylic acid

Excipients

Cellulose powder, maize starch, methacrylic acid-ethyl acrylate copolymer 1:1, polysorbate 80, sodium laurilsulfate (E 487) equiv. sodium max. 0.01 mg, talc (E 553b), triethyl citrate.

Pharmaceutical form and active substance quantity per unit

1 Aspirin Cardio 100 gastro-resistant tablet contains 100 mg acetylsalicylic acid (ASA).

Indications/Uses

- Prevention of thrombosis (reocclusion prophylaxis) after aortocoronary bypass, percutaneous transluminal coronary angioplasty (PTCA) and arteriovenous shunt in dialysis patients.
- Prophylaxis of cerebrovascular insults after precursor stages have occurred (transient ischaemic attacks,TIA).
- Reduction of the risk for further coronary thromboses after myocardial infarction (reinfarction prophylaxis).
- Myocardial infarction prophylaxis in connection with other therapy measures in patients with a very high cardiovascular risk in accordance with the risk/benefit assessment of the treating physician.
- Unstable angina pectoris.
- Prophylaxis of arterial thromboses after vascular surgeries.
- As part of the standard therapy of acute myocardial infarction
- Prevention of vascular occlusions in the event of arterial occlusive disease.

Dosage/Administration

Unless prescribed otherwise by the physician, the following dosages are recommended:

Cardiovascular indications without aortocoronary bypass and without PTCA:

1 x 100 mg/day.

Prevention of thrombosis after aortocoronary bypass and percutaneous transluminal coronary angioplasty (PTCA):

100 – 300 mg/day.

Prophylaxis of cerebrovascular insults after precursor stages (TIA) have occurred:
3 x 100 mg/day or 1 x 300 mg/day.

It is recommended to take the tablets with a small amount of fluid at least half an hour before a meal. Drink approximately ½ –1 glass of liquid afterwards. In order for the active ingredient not to be released until it reaches the alkaline environment of the intestine, the tablets may not be crushed, broken or chewed owing to their enteric coating.

Acute myocardial infarction:
In the event of acute myocardial infarction, 200–300 mg acetylsalicylic acid intravenously or orally with a quickly reabsorbing acetylsalicylic acid preparation (non enterically-coated form). The tablets should be crushed or chewed before being swallowed in order for them to be absorbed more quickly. 100 mg Aspirin Cardio daily from the second day on.

Aspirin Cardio should not be used in children and adolescents under the age of 18 as there is no data on its efficacy and safety in this patient population.

Contraindications

- Hypersensitivity against salicylates and/or other anti-inflammatories or one of the excipients in accordance with the composition (see section “Composition”).
- History of bronchospasm, urticaria or allergy-like symptoms following intake of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Haemorrhagic diathesis.
- Active gastric and/or duodenal ulcers or gastrointestinal haemorrhage. Inflammatory gastrointestinal diseases (such as Crohn’s disease, ulcerative colitis).
- Severe liver dysfunction (liver cirrhosis and ascites).
- Severe renal dysfunction (creatinine clearance <30 mL/min).
- Severe heart failure (NYHA III-IV).
- Combination with methotrexate at doses of 15 mg/week or more (see section “Interactions”).
- Third trimester of pregnancy (see section “Pregnancy, lactation”).
- Treatment of post-operative pain following a coronary bypass procedure (with use of a heart-lung machine).

Warnings and precautions

Gastrointestinal ulcers, haemorrhage or perforation can occur at any time, including without warning symptoms or historical signs, during treatment with COX-2-selective or non-selective non-steroidal anti-inflammatory drugs (NSAIDs). To reduce this risk, the lowest effective dose should be administered for the shortest possible duration of therapy.

For some selective COX-2 inhibitors, placebo-controlled studies revealed an increased risk of thrombotic cardio- and cerebrovascular complications. It is not yet known whether this risk is directly correlated with the COX-1/COX-2 selectivity of the relevant NSAID. As no comparable clinical study data are currently available for acetylsalicylic acid with maximum doses and long-term therapy, a similarly increased risk cannot be ruled out. Until corresponding data are available, acetylsalicylic acid may be used only after a careful benefit/risk assessment in clinically confirmed coronary heart disease, cerebrovascular diseases, peripheral arterial occlusive disease or in patients with significant risk factors (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking). In this case also, because of this risk, the lowest effective dose should be administered for the shortest possible duration of therapy.

The renal effects of NSAIDs include fluid retention with oedema and/or hypertension. In patients with cardiac dysfunction and other conditions that predispose them to fluid retention, acetylsalicylic acid must be used with caution.

Caution is also required in patients receiving concomitant diuretics or ACE inhibitors and those at increased risk of hypovolaemia.

Caution is indicated in:

- patients with limited renal function or limited cardiovascular function (such as renal vessel disease, congestive heart failure, volume depletion, major surgeries, sepsis, or major bleeding), because acetylsalicylic acid may further increase the risk of renal dysfunction or acute renal failure.
- hepatic insufficiency.
- concomitant administration of NSAIDs such as ibuprofen or naproxen; NSAIDs can weaken the thrombocyte aggregation inhibitory effect of acetylsalicylic acid. Patients should contact their doctor if they are taking Aspirin Cardio and wish to take a pain medication containing a NSAID at the same time (see section “Interactions”).
- chronic or relapsed gastric or duodenal symptoms.

- bronchial asthma or general tendency to hypersensitivity; acetylsalicylic acid can promote bronchospasms and induce asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory disease. This applies also for patients showing allergic reactions also to other agents (e.g. with rashes, pruritus or urticaria).
- nasal polyps.
- in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as acetylsalicylic acid might induce haemolysis or haemolytic anaemia. Factors that increase this risk include e.g. high dosages, fever or acute infections.
- concomitant treatment with anticoagulants.
- Due to the inhibitory effect on platelet aggregation and the prolongation of the bleeding time lasting several days after intake of acetylsalicylic acid, increased bleeding tendency may occur, particularly during and after surgical operations (including minor surgeries, e.g., dental extractions).

At low dosages, acetylsalicylic acid reduces excretion of uric acid. In patients who tend to have low uric acid excretion, this may trigger gout.

Aspirin Cardio must be used in children and adolescents under 18 years of age with fever and/or viral diseases only as prescribed and only as a second-line therapy (due to the possibility of Reye's syndrome, a life-threatening encephalopathy associated with the leading symptoms of severe vomiting, impaired consciousness, liver dysfunction).
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

Interactions

Contraindicated combinations

- Methotrexate used at doses of 15 mg/week or more: Increased haematological toxicity of methotrexate (decreased renal clearance of methotrexate by anti-inflammatory agents in general and displacement of methotrexate from its plasma protein binding by salicylates), see section “Contraindications”.

Combinations requiring precautions for use

- Methotrexate used at doses of less than 15 mg/week: increased toxicity of methotrexate (decreased renal clearance of methotrexate by anti-inflammatory agents in general and displacement of methotrexate from its plasma protein binding by salicylates).
- Anti-diabetics (e.g., insulin, sulphonylureas): the blood sugar level may decrease.

- Increased effects of anticoagulants/thrombolytics, barbiturates, lithium, sulfonamides and triiodothyronine.
- Pharmacodynamic interactions between selective serotonin re-uptake inhibitors (SSRIs) and acetylsalicylic acid may occur: Increased risk of bleeding due to synergistic effects.
- Increased digoxin plasma levels due to reduced renal excretion.
- Increased plasma levels of phenytoin and valproate. Acetylsalicylic acid causes displacement of the bound valproic acid from the serum protein binding sites and reduction of its metabolism. Thus the plasma levels of valproate become increased, leading to a higher rate of undesirable effects up to signs of intoxication, such as tremor, nystagmus, ataxia and personality changes.
- Increase of effects and side effects of all non-steroidal anti-rheumatics.
- The administration of NSAIDs such as ibuprofen or naproxen on the same day can weaken the irreversible thrombocyte aggregation inhibitory effect of acetylsalicylic acid. The clinical relevance of this interaction is not known. The treatment of patients with a high cardiovascular risk with some NSAIDs, such as ibuprofen or naproxen, can limit the cardioprotective effect of acetylsalicylic acid (see section “Warnings and precautionary measures”).
- Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly.Therefore, metamizole should be used with caution in patients taking low dose acetylsalicylic acid for cardioprotection.
- Antihypertensive agents (ACE inhibitors and β-blockers): The blood pressures of hypertonic patients who are treated with these drugs and Aspirin Cardio must be closely monitored and their dosages adjusted, if applicable.
- Diuretics in combination with acetylsalicylic acid at higher doses: Decreased diuretic effect.
- Decreased uricosurics effect (e.g. probenecid, sulfinpyrazone).
- Systemic glucocorticoids: Increased risk of gastrointestinal ulcers and bleeding: Decreased blood salicylate levels during corticosteroid treatment, risk of salicylate overdose after treatment with glucocorticoids is stopped.
- Alcohol: Increased risk of gastrointestinal ulcers and bleeding; prolonged bleeding time.
- Extension of penicillin plasma half-lives.

Pregnancy, lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformations and gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy.

Animal studies showed that administration of a prostaglandin inhibitor leads to increased pre- and post-implantation loss and to embryo/foetal lethality. Furthermore, increased incidences of several deformities, including cardiovascular deformities, were reported in animals receiving a prostaglandin inhibitor during organogenesis. Narrowing of the ductus arteriosus has been reported after treatment in the second trimester, which resolved in most cases after treatment was discontinued.

First and second trimester

During the first and second trimester of pregnancy, acetylsalicylic acid should not be administered unless clearly necessary.

If acetylsalicylic acid is used by a woman who is trying for a baby, or if it is used during the first or second trimester of pregnancy, the dose should be kept as low and the duration of treatment as short as possible. Consider prenatal monitoring for stenosis of the ductus arteriosus after taking acetylsalicylic acid from 20 weeks of pregnancy. Discontinue acetylsalicylic acid treatment if stenosis of the ductus arteriosus occurs.

Third trimester

During the third trimester of pregnancy, acetylsalicylic acid is contraindicated. All prostaglandin inhibitors may:

- expose the foetus to the following risks:
    - cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension);
    - Renal dysfunction that may progress to renal failure with oligo-hydramniosis.
- expose mother and child to the following risks:
    - possible prolongation of bleeding time, an anti-platelet aggregation effect which may occur even at very low doses;
    - inhibition of uterine contractions resulting in delayed or prolonged labour.

Fertility: The use of acetylsalicylic acid can impair female fertility and is therefore not recommended in women who wish to become pregnant. In women struggling to become pregnant or undergoing infertility testing, discontinuation of acetylsalicylic acid should be considered.

Lactation

Salicylates pass into the breast milk. The concentration in the breast milk is equal or even

higher than the concentration in the plasma of the mother.
During lactation only with compelling indication, whereby the infant must be weaned in the event of a regular administration of high doses (> 300 mg/day).

Effects on ability to drive and use machines
Aspirin Cardio has no influence on the ability to drive and use machines.

Undesirable effects
The incidence rates are defined as follows:
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: < 1/10,000
Not known (cannot be estimated from the available data)
In addition, further adverse drug reactions were reported in spontaneous reports about all acetylsalicylic acid formulations, including oral short- and long-term treatments. Indication of incidence rates is not possible in these cases.
Blood and lymphatic system disorders:
Prolonged bleeding time.
Rare: Thrombocytopenia, agranulocytosis, pancytopenia, leukopenia, aplastic anaemia, iron deficiency anaemia.
Not known: Haemolysis and haemolytic anaemia were reported in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
Due to its anti-platelet effect, acetylsalicylic acid may increase the bleeding risk. Bleeding, such as perioperative bleeding, haematomas, epistaxis, urogenital bleeding, gum bleeding has been observed.
In rare to very rare cases serious bleeding, such as gastrointestinal haemorrhage, cerebral haemorrhage, especially in patients with uncontrolled hypertension and/or on concomitant anticoagulants, which in single cases may be potentially life-threatening, has been reported.

Immune system disorders:
Uncommon: Asthma.
Rare: Hypersensitivity reactions such as erythematous/eczematous skin symptoms, urticaria, rhinitis, nasal congestion, bronchospasm, angioneurotic oedema, decrease of blood pressure up to shock.
Very rare: Severe skin reactions, including exudative erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).

Metabolism and nutrition disorders:
Very rare: Hypoglycaemia, acid-base imbalance.

Nervous system disorders:
Rare: Headache, vertigo, tinnitus, impaired vision, impaired hearing, confusion.

Gastrointestinal disorders:
Very common: Occult bleeding (70%).
Common: Stomach complaints.
Uncommon: Dyspepsia, nausea, vomiting, diarrhoea.
Rare: Gastrointestinal bleeding, gastrointestinal ulceration, which, in very rare cases, may lead to perforation.
Formation of intestinal diaphragm-like structures, particularly with long-term use (intestinal diaphragm disease).

Hepatobiliary disorders:
Rare: Liver dysfunction.
Very rare: Increased transaminases.

Renal and urinary disorders:
Rare: Renal dysfunction.
Not known: Acute renal failure.

Other:
Very rare: Reye's syndrome (see section “Warnings/precautions”).
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

Overdose
A massive overdose can be life-threatening. Infants are more sensitive than adults.
Severe poisoning symptoms may develop acutely or also slowly (i.e., within 12–24 hours after intake). After oral intake of doses up to 150 mg ASA/kg body weight, mild intoxication, and of doses > 300 mg/kg body weight, severe intoxication can be expected.
Absorption of acetylsalicylic acid may be delayed by slower gastric emptying, concretion formation in the stomach or by enteric coatings.

Poisoning severity cannot be estimated by plasma levels alone. Close controls by arterial blood gas analysis (ABGA) are required, because therapy is not based on salicylic acid levels but on clinical symptoms and the ABGA.

Warning
Local signs of irritation that are usually paramount in the event of acetylsalicylic acid overdose, such as nausea, vomiting, and stomach pains can be absent as this ASA preparation has an enteric coating and is resorbed only in the small intestine.

Signs and symptoms
Headache, nausea, vomiting, hypoglycaemia or hyperglycaemia, skin rashes, vertigo, tinnitus, impaired vision and hearing, tremor, confusion, hyperthermia, perspiration, hyperventilation, respiratory alkalosis with metabolic compensation leading to metabolic acidosis, electrolyte imbalance, exsiccosis, seizures, coma, respiratory distress syndrome, cardiac dysrhythmia.
The symptoms of chronic salicylate poisoning are unspecific (e.g., tinnitus, headache, excitation, perspiration, hyperventilation) and therefore might be ignored.

Treatment
Due to the life-threatening situation after severe poisoning, all required measures must be immediately taken: immediate hospitalization, prevention or reduction of resorption by administration of separated doses of activated charcoal within the first 4 hours (10-fold of charcoal weight relative to acetylsalicylic acid); in case of massive intoxication: gastric lavage or gastroscopic removal of the tablets.
Control and correct electrolytes. Glucose administration, early use of sodium bicarbonate for correcting acidosis and for promoting elimination (urine pH > 8), improved diuresis, cooling in association with hyperthermia, benzodiazepines with convulsions.
Potential haemodialysis in case of severe poisoning.
Decompensation leading to death after successful intubation has been described. Therefore, if possible, intubate only after initiation of alkalinisation, minimise apnoea time, as well as watch maintenance of hyperventilation.
Ask for detailed information about the therapy at *Tox Info* Suisse.

Properties/Effects
ATC code
B01AC06

Mechanism of action

As even small doses of acetylsalicylic acid are absorbed, all circulating blood platelets on their way from the gastrointestinal tract to the liver are irreversibly inhibited in the pre-hepatic mesenteric blood vessels. Acetylsalicylic acid has an antithrombotic effect by inhibiting thromboxane A_2 synthesis in the thrombocytes. The cyclooxygenase of the endothelium (prostacyclin synthesis), which is regenerated more quickly, is confronted by ASA concentrations with only a very minor activity during the entire post-hepatic circulation. The platelet function responsible for haemostasis is not affected significantly.

Pharmacodynamics

See *Mechanism of action.*

Clinical efficacy

Primary prevention: In a meta-analysis of the US Preventive Task Force (Ann Int Med 2002;136:161-172), it has been demonstrated based on 5 prospective clinical studies that the risk for myocardial infarction (odds ratio 0.72 (CI 95% 0.60–0.87) is reduced in patients without prior cardiac event but with various risk factors (age > 50 years, hypertension, diabetes mellitus, smoker, hypercholesterolemia, family history) through prophylactic treatment with acetylsalicylic acid 75–125 mg over a period of 5 to 7 years. This was documented only for non-lethal coronary events; a benefit in the event of stroke and regarding the overall mortality was not observed. The risk for severe gastrointestinal bleeding was in comparison to the control 0.8% versus 0.48%, the risk for cranial bleeding 0.22% versus 0.17%. The bleeding risk was increased in patients above the age of 70 years.

Prophylaxis should be carried out only after satisfactory control of the blood pressure and in combination with other therapeutic measures (diet, treatment of diabetes and lipid metabolism, stopping smoking). The risk can be estimated based on tables of the European Society of Cardiology (European Heart Journal, 1998,19:1434-1503).

Secondary prevention: In a meta-analysis carried out by the Antithrombotic Trialists Collaboration (BMJ 2002;324:71-85), the effect of acetylsalicylic acid vs. placebo was compared in 287 studies with 135,000 high-risk patients and a comparison of different platelet aggregation inhibitors was carried out in 77,000 patients. High-risk patients were patients with an acute vascular event or a vascular event reported in the medical history (myocardial infarction, transient ischemic attack (TIA), with unstable angina pectoris, arterial occlusive disease, after vascular surgeries such as aortocoronary bypass, percutaneous transluminal coronary angioplasty (PTCA), peripheral angioplasty, and in dialysis patients

with arteriovenous shunt. A reduction of severe vascular events (odds reduction 25%; p < 0.0001) and the vascular mortality was observed. The absolute benefit outweighed the risk of extracranial bleeding in all highrisk categories stated.

Pharmacokinetics

Absorption

After oral administration, acetylsalicylic acid is absorbed rapidly and completely from the gastrointestinal tract. During and after absorption acetylsalicylic acid is converted into the metabolite salicylic acid. The enteric coating of the tablets leads to a delayed release, not in the stomach but only in the alkaline environment of the small intestine, which also leads to a delayed resorption of the substance. Due to the protection of the gastric mucosa, this formulation is superior over the common ASA tablet especially in the long-term treatment.
In comparison with aspirin, maximum salicylate concentrations are delayed and are not reached in the blood until after 2 to 7 hours.

Distribution

Salicylic acid is bound to 60–90% to plasma proteins.
The bioavailability of the salicylate lies between 80 and 100%.

Salicylic acid passes into breast milk and crosses the placenta (see section “Pregnancy, lactation”).

Metabolism

The systemically available acetylsalicylic acid is degraded with a half-life of about 15 minutes. Salicylic acid formed during hydrolysis has a plasma half-life of about 2-3 hours, this is significantly increased after the administration of high doses (> 3 g) due to the saturation of the conjugating enzyme system.
The biotransformation of salicylic acid occurs mainly in the liver. Salicylic acid is formed by the binding of salicylic acid to glycine and is further converted by conjugation with glucuronic acid or sulphuric acid. A small part is oxidised to gentisic acid and converted to gentisinuric acid.

Elimination

Elimination occurs almost completely via the kidney, in the form of salicylic acid (approx. 10%), salicyluric acid (approx. 75%) and salicyluric acid conjugates (approx. 10%).
The elimination half-life varies between 2–3 hours after smaller doses and up to 12 hours after the usual analgesic doses.

Kinetics in special patient groups
Elimination in patients with hepatic impairment: Since metabolisation of acetylsalicylic acid occurs mainly in the liver, a slower breakdown of the acetylsalicylic acid to salicylic acid has to be expected (cumulation).

Elimination in patients with renal impairment: In patients with renal failure, the rate of breakdown of salicylic acid in blood plasma is not affected; in contrast, the concentration of inactive salicylic acid metabolites, mainly of conjugated salicyluric acid, increases.
Salicylates pass the placental barrier, however they only appear in small amounts in breast milk.

Preclinical data
The preclinical safety profile of acetylsalicylic acid is well documented. In animal tests salicylates caused kidney damage but no other organic lesions. Acetylsalicylic acid has been adequately tested for mutagenicity and carcinogenicity; no relevant evidence of a mutagenic or carcinogenic potential was found.
Salicylates have been found to have embryotoxic as well as teratogenic effects in a variety of animal species (e.g. cardiac and skeletal malformations, gastroschisis).
There have been reports of interference in implantation, foetotoxic effects, and disturbance of learning capacity in the offspring after prenatal exposure of salicylates.

Pharmaceutical particulars

List of excipients
Cellulose powder
Maize starch
Methacrylic acid-ethylacrylate copolymer (1:1)
Polysorbate 80
Sodium laurilsulfate
Talc
Triethyl citrate

Incompatibilities
None

Shelf life

36 months

Special precautions for storage

Do not store above 30°C

Keep out of reach of children.

Only on prescription.

Nature and contents of container

Alu/Alu Blister packs: 3 x 10 Tablets

Special precautions for disposal and other handling

No special requirements.

Manufactured by:

Bayer AG

51368 Leverkusen,

Germany

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