ASPIRIN® CARDIO

1. NAME OF THE MEDICINAL PRODUCT
Aspirin Cardio

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each enteric-coated tablet contains 100mg acetylsalicylic acid

3. PHARMACEUTICAL FORM
Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Acetylsalicylic acid is indicated in adults for the following cardiovascular uses:

Inhibition of platelet aggregation:
- in unstable angina pectoris
- in acute myocardial infarction
- in reinfarction prophylaxis
- after arterial surgery or interventions (e.g. PTCA)
- for the prevention of transient ischemic attacks (TIA) and cerebral infarction after the onset of precursor stages
- to prevent thrombosis of the coronary blood vessels in patients with multiple risk factors

4.2 Dosage and method of administration

4.2.1 Dosage regimen
In unstable angina pectoris, in reinfarction prophylaxis, after arterial surgery or interventions:
Daily doses of 100-300mg acetylsalicylic acid are recommended.

In acute myocardial infarction:
Daily doses of 100-160 mg acetylsalicylic acid are recommended. The first tablet should be crushed or chewed and swallowed in order to achieve fast absorption.

For the prevention of transient ischemic attacks and cerebral infarction after the onset of precursor stages:
Daily doses to 30-300 mg acetylsalicylic acid are recommended.

For the prevention of thrombosis of the coronary blood vessels in patients with multiple risk factors:
Doses of 100-200 mg daily or 300 mg every other day are recommended.

4.2.2 Method of administration
The tablets should preferably be taken at least 30 minutes before meals, swallowed whole with plenty of water. Tablets should not be crushed, broken or chewed to ensure a release in the alkaline milieu of the intestine (see section “Gastro-resistant tablets (enteric-coated)”).

When using this product in acute myocardial infarction, the first tablet should be crushed or chewed and swallowed in order to achieve fast absorption.

4.2.3 Additional information on special populations

4.2.3.1 Pediatric patients

The safety and efficacy of Aspirin Cardio in children below 18 years of age has not been established. No data are available. Therefore, Aspirin Cardio is not recommended for use in pediatric patients below 18 years

4.2.3.2 Patients with hepatic impairment

Aspirin Cardio is contraindicated in patients with severe hepatic failure (see section "Contraindications"). Aspirin Cardio should be used with particular caution in patients with impaired hepatic function (see section "Special warnings and precautions for use").

4.2.3.3 Patients with renal impairment

Aspirin Cardio is contraindicated in patients with severe renal failure (see section "Contraindications"). Aspirin Cardio should be used with particular caution in patients with impaired renal function since acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure (see section "Special warnings and precautions for use").

4.3 Contraindications

Acetylsalicylic acid must not be used in the following cases:

- hypersensitivity to acetylsalicylic acid or other salicylates, or to any other components of the product (see section "List of excipients")
- a history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory drugs,
- in the presence with gastric or duodenal ulcers,
- hemorrhagic diathesis,
- severe renal failure,
- severe hepatic failure,
- severe cardiac failure,
- combination with methotrexate at doses of 15mg/week or more (see section "Interaction with other medicinal products and other forms of interaction"),
- last trimester of pregnancy (see section "Pregnancy").

4.4 Special warnings and precautions for use

Acetylsalicylic acid should be used with particular caution in the following cases:

- hypersensitivity to analgesics / anti-inflammatory agents / antirheumatic drugs and in the presence of other allergies,
- history of gastrointestinal disorders such as colitis ulcerosa or M. Crohn,
- with concomitant treatment with anticoagulants (see section "Interactions with other medicinal products and other forms of interaction"),
- in patients with impaired renal function or patients with impaired cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major hemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure,
- in patients suffering from severe glucose-6-phosphate dehydrogenase (G6PD) deficiency , acetylsalicylic acid may induce hemolysis or hemolytic anemia. Factors that may increase the risk of hemolysis are e.g. high dosage, fever or acute infections,
- Impaired hepatic function.
- Metamizole and some NSAIDS, such as ibuprofen and naproxen, may attenuate acetylsalicylic acid's inhibitory effect on platelet aggregation. Patients should be advised to talk to their doctor if they are on an acetylsalicylic acid regimen and plan to take

metamizole or NSAIDs (see “Interaction with other medicinal products and other forms of interaction”).
- Acetylsalicylic acid may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are pre-existing asthma, hay fever, nasal polyps, or chronic respiratory disease. This also applies to patients exhibiting allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances.
- Due to its inhibitory effect on platelet aggregation which persists for several days after administration, acetylsalicylic acid may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions).
- At low doses, acetylsalicylic acid reduces the excretion of uric acid. This can possibly trigger gout attacks in predisposed patients.
- Acetylsalicylic acid containing products should not be used in children and adolescents for viral infections with or without fever without consulting a physician. In certain viral illnesses, especially influenza A, influenza B and varicella, there is a risk of Reye´s syndrome, a very rare but possibly life-threatening illness requiring immediate medical action. The risk may be increased when acetylsalicylic acid is given concomitantly; however, no causal relationship has been proven. Should persistent vomiting occur with such diseases, this may be a sign of Reye´s syndrome.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Contraindicated Interactions:

Methotrexate used at doses of 15 mg/week or more:
Increased hematological 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”).

4.5.2 Combinations requiring precautions for use:

Lithium:
The plasma concentration of Lithium will be increased.

Methotrexate, used at doses of less than 15 mg/week:
Increased hematological 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).

Metamizole and NSAIDs:
The concurrent (same day) administration of metamizole and some NSAIDs, such as ibuprofen and naproxen, may attenuate the irreversible platelet inhibition induced by acetylsalicylic acid. The clinical relevance of these interactions is not known. Treatment with metamizole or some NSAIDs, such as ibuprofen or naproxen, in patients with increased cardiovascular risk may limit the cardiovascular protection of acetylsalicylic acid (see section “Special warnings and precautions for use”)

Anticoagulants, thrombolytics/other inhibitors of platelet aggregation/hemostasis:
Increased risk of bleeding.

Other non steroidal anti inflammatory drugs with salicylates:
Increased risk of ulcers and gastrointestinal bleeding due to synergistic effect.

Selective Serotonin Re-uptake Inhibitors (SSRIs):
Increased risk of upper gastrointestinal bleeding due to possibly synergistic effect

Digoxin:
Plasma concentrations of digoxin are increased due to a decrease in renal excretion.

Antidiabetics, e.g. insulin, sulphonylureas:
Increased hypoglycemic effect at higher doses of acetylsalicylic acid via hypoglycemic action of acetylsalicylic acid and displacement of sulfonylurea from its plasma protein binding.

Diuretics in combination with acetylsalicylic acid:
Decreased glomerular filtration via decreased renal prostaglandin synthesis.

Systemic glucocorticoids
The risk of gastrointestinal haemorrhage and ulcers may be increased during concomitant treatment with corticosteroids.

Angiotensin converting enzyme inhibitors (ACE) in combination with acetylsalicylic acid at higher doses:
Decreased glomerular filtration via inhibition of vasodilatory prostaglandins. Further-more, decreased antihypertensive effect.

Valproic acid:
Increased toxicity of valproic acid due to displacement from protein binding sites.

Alcohol:
Increased damage to gastro-intestinal mucosa and prolonged bleeding time due to additive effects of acetylsalicylic acid and alcohol.

Uricosurics such as benzbromarone, probenecid:
Decreased uricosuric effect (competition of renal tubular uric acid elimination).

Antihypertensives
Antihypertensive effect may be decreased.

4.6 Pregnancy and lactation

4.6.1 Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of malformations 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 have shown reproductive toxicity (see section “Preclinical safety data”).
There have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolve after treatment cessation.

During the first and second trimester of pregnancy, acetyl salicylic acid containing drugs should not be given unless clearly necessary. Antenatal monitoring for ductus arteriosus constriction should be considered after exposure to acetylsalicylic acid from gestational week 20 onward. Treatment with acetylsalicylic acid should be discontinued if ductus arteriosus constriction is found.

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 child, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even after very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, acetylsalicylic acid is contraindicated during the third trimester of pregnancy.

4.6.2 Lactation

Do not use this product if you are breastfeeding unless advised to do so by a doctor.

4.6.3 Fertility
Based on the limited published data available, the studies in humans showed no consistent effect of acetylsalicylic acid on impairment of fertility and there is no conclusive evidence from animal studies.

4.7 Effects on ability to drive and use machines
None

4.8 Undesirable effects

The listed adverse drug reactions (ADRs) are based on spontaneous postmarketing reports with all Aspirin formulations, including oral short- and long-term treatment, thus an organization according to CIOMS III categories of frequency is not pertinent.

Upper and lower gastrointestinal tract disorders such as common signs and symptoms of nausea, vomiting, diarrhoea, dyspepsia, gastrointestinal and abdominal pain, rarely gastrointestinal inflammation, gastrointestinal ulcer, potentially but rarely leading to gastrointestinal ulcer hemorrhage and perforation, with the respective laboratory and clinical signs and symptoms and intestinal diaphragm disease.

Due to its inhibitory effect on platelets, acetylsalicylic acid may be associated with an increased risk of bleeding. Bleedings, such as perioperative hemorrhage, hematomas, epistaxis, urogenital bleedings, gingival bleedings, have been observed. Rare to very rare serious bleedings, such as gastrointestinal tract hemorrhage, cerebral hemorrhage (especially in patients with uncontrolled hypertension and/or on concomitant antihemostatic agents), which in single cases may be potentially life-threatening, have been reported.

Hemorrhage may result in acute and chronic posthemorrhagic anemia/iron-deficiency anemia (due to e.g. occult microbleeding) with respective laboratory and clinical signs and symptoms, such as asthenia, pallor, hypoperfusion.
Hemolysis and hemolytic anemia in patients with severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency have been reported.

Renal impairment and acute renal failure have been reported.

Hypersensitivity reactions with respective laboratory and clinical manifestations include asthma syndrome, mild to moderate reactions potentially affecting skin, respiratory tract, gastrointestinal tract, and cardiovascular system, including symptoms such as rash, urticaria,

edema, pruritus, rhinitis, nasal congestion, cardio-respiratory distress, and very rarely, severe reactions, including anaphylactic shock.

Transient hepatic impairment with increase in liver transaminases has very rarely been reported. Isolated cases of liver and kidney function disturbances, and severe skin reactions have been reported.

Dizziness and tinnitus have been reported, which may be indicative of an overdose.

4.9 Overdose

Salicylate toxicity (> 100 mg/kg/day over 2 days may produce toxicity) may result from chronic, therapeutically acquired, intoxication, and from, potentially life-threatening, acute intoxications (overdose), ranging from accidental ingestions in children to incidental intoxications.

Chronic salicylate poisoning can be insidious as signs and symptoms are non-specific. Chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses. Symptoms include dizziness, vertigo, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage. Tinnitus can occur at plasma concentrations of 150 to 300 micrograms/mL. More serious adverse events occur at concentrations above 300 micrograms/mL.

The principle feature of acute intoxication is severe disturbance of the acid-base balance, which may vary with age and severity of intoxication. The most common presentation for a child is metabolic acidosis. The severity of poisoning cannot be estimated from plasma concentration alone. Absorption of acetylsalicylic acid can be delayed due to reduced gastric emptying, formation of concretions in the stomach, or as a result of ingestion of gastro-resistant preparations. Management of acetylsalicylic acid intoxication is determined by its extent, stage and clinical symptoms and according to standard poisoning management techniques. Predominant measures should be the accelerated excretion of the drug as well as the restoration of the electrolyte and acid-base metabolism.

Due to the complex pathophysiologic effects of salicylate poisoning, signs and symptoms/investigational findings may include: Refer to table 1

Table 1

Signs and Symptoms	**Investigational findings**	**Therapeutic measures**
Mild to moderate intoxication		Gastric lavage, repeated administration of activated charcoal, forced alkaline diuresis
Tachypnoea, hyperventilation, respi-ratory alkalosis	Alkalemia, alkaluria	Fluid and electrolyte management
Diaphoresis		
Nausea, vomiting		
Moderate to-severe intoxication		Gastric lavage, repeated administration of activated charcoal, forced alkaline diuresis, hemodialysis in severe cases

Signs and Symptoms	Investigational findings	Therapeutic measures
Respiratory alkalosis with compensatory metabolic acidosis,	Acidemia, aciduria	Fluid and electrolyte management
Hyperpyrexia		Fluid and electrolyte management
Respiratory: ranging from hyperventilation, non-cardiogenic pulmonary edema to respiratory arrest, asphyxiation		
Cardiovascular: ranging from dysarrhythmias, hypotension to cardio-vascular arrest	e.g. Blood pressure, ECG alteration	
Fluid and electrolyte loss: dehydration, oliguria to renal failure	e.g. Hypokalemia, hypernatremia, hyponatremia, altered renal function	Fluid and electrolyte management
Impaired glucose metabolism, ketosis	Hyperglycemia, hypoglycemia (especially in children) Increased ketone levels	
Tinnitus, deafness		
Gastrointestinal: GI bleeding		
Hematologic: ranging from platelet inhibition to coagulopathy	e.g. PT prolongation, hypoprothrombinemia	
Neurologic: Toxic encephalopathy and CNS depression with manifes-tations ranging from lethargy, confusion to coma and seizures		

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Acetylsalicylic acid inhibits platelet aggregation by blocking thromboxane A2 synthesis in platelets. Its mechanism of action is based on irreversible inhibition of cyclo-oxygenase (COX-1). This inhibitory effect is especially pronounced in platelets, because platelets are unable to resynthesize this enzyme. Thus, it is used for various vascular indications.

5.2 Pharmacokinetic properties

5.2.1 Absorption

Following oral administration, acetylsalicylic acid is absorbed rapidly and completely from the gastro-intestinal tract. During and after absorption acetylsalicylic acid is converted into its main metabolite, salicylic acid.

5.2.1.1 Gastro-resistant tablets (enteric-coated)

Due to the principle of the acid-resistant formulation of Aspirin 100mg gastro-resistant tablets, acetylsalicylic acid is not released in the stomach but in the alkaline milieu of the intestine. Therefore, C_{max} of acetylsalicylic acid is reached 2-7 hours after administration of the gastro-resistant tablets, i.e., delayed in comparison to immediate-release tablets.

Simultaneous ingestion of food leads to a delayed but complete absorption of acetylsalicylic acid, implying that its rate of absorption, but not the extent of absorption, is altered by food. Due to the mechanistic relationship between the total plasma exposure of acetylsalicylic acid and its inhibitory effect on platelet aggregation, the delay of absorption for Aspirin gastro-resistant tablets is not considered relevant for the chronic therapy with low dose Aspirin in order to accomplish adequate inhibition of platelet aggregation. Nevertheless, in order to assure the beneficial gastro-resistance of the formulation, Aspirin gastro-resistant tablets should be taken preferably (30 minutes or more) before meals, with plenty of liquid (see section “Dosage and method of administration”).

5.2.2 Distribution

Both acetylsalicylic acid and salicylic acid are extensively bound to plasma proteins and are rapidly distributed throughout the body. Salicylic acid passes into breast milk and crosses the placenta (see section “Pregnancy and lactation”).

5.2.3 Metabolism / Biotransformation

The parent drug acetylsalicylic acid is converted into its main metabolite salicylic acid. The acetyl group of acetylsalicylic acid begins to split off hydrolytically even during passage through the intestinal mucosa but mainly this process takes place in the liver. The main metabolite salicylic acid is eliminated predominantly by hepatic metabolism. Its metabolites are salicyluric acid, salicylic phenolic glucuronide, salicylacyl glucuronide, gentisic acid, and gentisuric acid.

5.2.4 Elimination / Excretion / Linearity

The elimination kinetics of salicylic acid is dose-dependent, as metabolism is limited by liver enzyme capacity. The elimination half-life therefore varies from 2 to 3 hours after low doses to up to about 15 hours at high doses. Salicylic acid and its metabolites are excreted mainly via the kidneys. Available pharmacokinetic data of acetylsalicylic acid do not indicate a

clinical meaningful deviation from dose-proportionality in the dose range of 100 mg to 500 mg.

5.3 Preclinical safety data

In experimental animal studies, salicylates have shown no other organ injury than renal damage.

Acetylsalicylic acid has been extensively studied in vitro and in vivo for mutagenicity; no relevant evidence of a mutagenic potential was found. The same applies to carcinogenicity studies.

Salicylates have exhibited teratogenic effects in animal studies and a number of different species.

Implantation disorders, embryotoxic and fetotoxic effects and impairment of learning ability in the offspring after prenatal exposure have been described.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Cellulose powdered
Maize starch
Methacrylic acid-ethylacrylate copolymer
Polysorbate 80
Sodium laurilsulfate
Talc
Triethyl citrate
Purified water*
*purified water is used as solvent and will be removed during the coating process

6.2 Incompatibilities
Not applicable.

6.3 Storage Conditions
Keep ASPIRIN Cardio in a cool dry place. Do not store it above 30°C. Medication should be kept out of reach of children.

For further information, please consult doctor or pharmacist.

6.4 Nature and contents of container
Alu/Alu PVC blisters in carton of 3x10 tablets/ blister
Alu/Alu PVC blisters in carton of 10 x 10 tablets/ blister
Not all presentations are available.

7. MANUFACTURER
Bayer AG
Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

8. DATE OF REVISION OF THE TEXT
December 2022

If you would like to report a side effect for any Bayer Pharmaceutical or Consumer Health product, you can do it easily using our online reporting portal: https://safetrack-public.bayer.com/ or scan the QR code available below. Please also remember to seek medical advice directly from your doctor or pharmacist.

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