CARDIO ASPIRIN®

Acetylsalicylic Acid 100mg

ENTERIC COATED TABLET

Composition
Each enteric-coated tablet Cardio Aspirin contains acetyl salicylic acid 100 mg.

Pharmaceutical Form
Gastro-resistant (enteric-coated) tablet

Pharmacodynamic Properties
The biochemical mode of action of acetylsalicylic acid on the inhibition of platelet aggregation is therefore based on:
1. An irreversible inhibition of cyclo-oxygenase in the platelets, and
2. A reversible inhibition of cyclo-oxygenase in the vessel wall.

Pharmacokinetic properties
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.
Due to the principle of the acid-resistant formulation of Cardio Aspirin® 100/300 mg enteric – coated 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 enteric – coated 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 Cardio Aspirin® enteric – coated 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, Cardio Aspirin® enteric – coated tablets should be taken preferably (30 minutes or more) before meals, with plenty of liquid *(see section "Administration")*.
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
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.

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.

Indications

- To reduce the risk of further coronary thrombosis during recovery phase from myocardial infarction (re-infarction prophylaxis)
- To lower the risk of morbidity and/or MI attack (myocardial infarct) in patients with history of MI or unstable angina pectoris
- To prevent thrombosis (re-occlusion prophylaxis) after aorto-coronary bypass
- To reduce the risk of recurrent transient ischaemic attack (TIA) and stroke in patients with TIA.
  Note :
  Due to possibility of Reye's syndrome, the use of enteric-coated tablet Cardio Aspirin 100 in children and adults with fever should only be on physician's recommendation or if other measures have been proven ineffective.

Dosage
Unless specific instruction from the doctor, the recommended dosages are as follows:

- Usually 100 mg daily
- Reducing the risk of morbidity and mortality in patients with previous myocardial infarction:
  A daily dose of 100 mg to 300 mg is currently recommended
- Reducing the risk of transient ischaemic attacks (TIA) and stroke in patients with TIA:
  A daily dose of 100 mg to 300 mg is currently recommended.

Additional information on special populations

Patients with renal impairment

Cardio Aspirin 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 "warnings and precautions").*

Administration
Enteric - coated tablets should preferably be taken at least 30 minutes before meals, with plenty of water. Enteric - coated tablets should not be crushed, broken or chewed to ensure a release in the alkaline milieu of the intestine.

Contraindications
Enteric-coated tablet Cardio Aspirin 100 must not be given to patients with gastric or duodenal ulcers and in patients with tendency of pathologic haemorrhagic disorders, patients with other bleeding disorders, and hypersensitivity to Acetosal.

Warnings and Precautions

- Medicinal products containing acetylsalicylic acid should be used in children and adolescents with febrile diseases only after careful risk-benefit-evaluation because of the possibility of Reye's syndrome, a rare but serious illness.
- Do not use in pregnant women and nursing mothers unless on a doctor's advice.
- Cardio Aspirin should not be used in patients with severe hepatic damage, hypo-prothrombinemia, or vitamin K deficiency.
- Discontinue its use in case of tinnitus, impaired hearing, or dizziness.
- Consult a doctor immediately in case of persisting gastric irritation.
- Cardio Aspirin should not be used in long-term treatment or in high doses without prior consultation with a doctor.
- Consultation with a doctor is required when enteric-coated tablet Aspirin 100 is to be given to patients also receiving anticoagulant (e.g. coumarin derivatives and heparin); patients with glucose-6-phosphate-dehydrogynase deficiency; asthmatic patients; patients hypersensitive to salicylates, other anti-inflammatory/anti-rheumatic agents, or other allergenic agents; patients with chronic or recurrent gastric or duodenal symptoms; patients with kidney dysfunction; and pregnant women, particularly in the last trimester.
- Cardio Aspirin should be used with particular caution 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.
- 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

Note:
Patients with asthma, hay fever, swelling of nasal mucosa (nasal polyp), or patients with chronic respiratory infection (especially when accompanied with signs of hay fever), and patients hypersensitive to all kind of analgesic and anti-rheumatic agents are at risk of asthmatic attack when using enteric-coated tablet Aspirin 100 (same analgesic/analgesic intolerance). Therefore, they must be consulted with a doctor before using this drug. This also apply for patients allergic to other agents, e.g. which are causing skin reaction, itchy, or urticaria.

Undesirable effects

Summary of the safety profile
The listed adverse drug reactions (ADRs) are based on spontaneous post-marketing reports with all aspirin formulations and clinical trials (CTs) with aspirin as a study drug. Frequency calculation is based on data from the aspirin arm of the ARRIVE study only.

Tabulated list of adverse reactions
The frequencies of ADRs reported with aspirin are summarized in the table below.
Frequency groupings are defined according to the following convention :
common (≥ 1/100 to < 1/10),

uncommon (≥ 1/1,000 to < 1/100),
rare (≥ 1/10,000 to < 1/1,000)
The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

Table 1: Adverse drug reactions (ADRs) reported in ARRIVE* or during post-marketing surveillance in patients treated with Aspirin Cardio

System organ class	Common	Uncommon	Rare	Not known
Blood and the lymphatic system disorders		Iron deficiency anaemia [a]	Haemorrhagic anaemia	Haemolysis [b] Haemolytic anaemia [b]
Immune system disorders		Hypersensitivity Drug hypersensitivity Allergic edema and angioedema	Anaphylactic reaction	Anaphylactic shock
Nervous system disorders	Dizziness	Cerebral and intracranial hemorrhage[c]		
Ear and labyrinth disorders	Tinnitus			
Cardiac disorders				Cardio-respiratory distress [d]
Vascular disorders		Haematoma	Haemorrhage Muscle haemorrhage	Procedural haemorrhage
Respiratory, thoracic and mediastinal disorders	Epistaxis Rhinitis	Nasal congestion		Aspirin-exacerbated respiratory disease
Gastrointestinal disorders	Dyspepsia Gastrointestinal and abdominal pains Gastrointestinal inflammation Gastrointestinal tract hemorrhage[c]	Gingival bleeding Gastrointestinal erosion and ulcer	Gastrointestinal ulcer perforation	Intestinal diaphragm disease
Hepatobiliary disorders		Hepatic impairment	Transaminases increased	

Skin and subcutaneous tissue disorders	Rash Pruritus	Urticaria		
Renal and urinary disorders	Urogenital tract hemorrhage		Renal impairment [e] Renal failure acute [e]	
Injury, poisoning and procedural complications	See overdose section			

*ARRIVE is a Bayer sponsored clinical trial with 6270 subjects in aspirin 100 mg arm and 6276 subjects in placebo arm. The median duration of aspirin exposure was 5.0 years with a range of 0 to 7 years.
[a] In the context of bleeding
[b] In the context of severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency
[c] LT/Fatal cases were reported in ASA and placebo with the same frequency, <0.1%
[d] In the context of severe allergic reactions
[e] In patients with pre-existing impaired renal function or impaired cardiovascular circulation

Drug interactions
The following may be aggravated:
- Effects of anticoagulant (e.g. coumarin derivatives and heparin)
- Risk of gastrointestinal bleeding in concomitant use with corticosteroids and alcohol
- Favourable and unfavourable effects of all analgesic and non-steroidal anti-rheumatic agents
- Effects of hypoglycemic agents (sulphonylurea)
- Adverse reactions of methotrexates.
- Effects of spironolactone, furosemide, and uricosuric antipodagnic may be reduced and, therefore, concomitant use with these drugs should be avoided except on doctor's recommendation.
- 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 "Warnings and precautions"*).
- **Non-steroidal anti-inflammatory drugs with salicylates**
  Increased risk of ulcers and gastrointestinal bleeding due to synergistic effect.
- **Systemic glucocorticoids, except hydrocortisone used as replacement therapy in Addison's disease**
  Concurrent use may increase the incidence of gastrointestinal bleeding and ulceration.

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. Available data do not support any association between intake of acetylsalicylic acid and an increased risk for miscarriage.
Animal studies have shown reproductive toxicity. There have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation.
Antenatal monitoring for ductus arteriosus constriction should be considered after exposure to acetyl salicylic acid from gestational week 20 onward. Treatment with acetyl salicylic 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 (constriction / premature closure of the ductus arteriosus and pulmonary hypertension)

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.

List of Excipients
Cellulose powdered, Maize starch, Methacrylic acid-ethyl acrylate copolymer (1:1)[a], Polysorbate 80[a], Sodium laurilsulfate[a], Talc, Triethyl citrate

Storage
Store below 30°C.

Presentation
Box of 3 blisters @ 10 tablets.

Made by Bayer AG, Leverkusen, Germany for Bayer Consumer Care AG, Switzerland

Imported by PT Bayer Indonesia, Depok-Indonesia.

Reg. No.: XXXXXXXXXXXXXX

Harus Dengan Resep Dokter