Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aspirin Krka 75 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 75 mg acetylsalicylic acid.

Excipients with known effect:
Lactose monohydrate..... 45 mg per tablet.
Sunset yellow (E110)..... 0.0006 mg per tablet.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

Pink, round biconvex film-coated tablets with a diameter of about 7.2 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Secondary prevention of myocardial infarction.
- Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris.
- History of unstable angina pectoris, except during the acute phase.
- Prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG).
- Coronary angioplasty, except during the acute phase.
- Secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out

Aspirin Krka is not recommended in emergency situations. It is restricted to secondary prevention with chronic treatment.

4.2 Posology and method of administration

Posology

Adults
Secondary prevention of myocardial infarction:
The recommended dose is 75-160 mg once daily.

Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris:
The recommended dose is 75-160 mg once daily.

History of unstable angina pectoris, except during the acute phase:
The recommended dose is 75-160 mg once daily.

Prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG):
The recommended dose is 75-160 mg once daily.

Coronary angioplasty, except during the acute phase:
The recommended dose is 75- 160 mg once daily.

Secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out:
The recommended dose is 75-325 mg once daily.

Aspirin Krka should not be used at higher doses unless advised by a doctor, and the dose should not exceed 325 mg a day.
For dosage, national and local treatment guidelines should be taken into account.

Elderly
In general, acetylsalicylic acids should be used with caution in elderly patients who are more prone to adverse events. The usual adult dose is recommended in the absence of severe renal or hepatic insufficiency (see sections 4.3 and 4.4). Treatment should be reviewed at regular intervals.

Paediatric population
Acetylsalicylic acid should not be used in children and adolescents younger than 16 years, except on medical advice where the benefit outweighs the risk (see section 4.4).

Method of administration
For oral use.
The tablets should be swallowed whole with sufficient fluid (1/2 glass of water). Due to the gastro resistant coating the tablets should not be crushed, broken or chewed because coating prevents irritant effects on the gut.

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

4.3 Contraindications

- Hypersensitivity to the active substance or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint) or to any of the excipients listed in section 6.1;
-Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages;
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia;
- Severe hepatic impairment;
- Severe renal impairment;
- Severe cardiac insufficiency;
- Doses >100 mg/day during the third trimester of pregnancy (see section 4.6);
- Methotrexate used at doses >15 mg/week (see section 4.5).

4.4 Special warnings and precautions for use

Aspirin Krka is not suitable for use as an anti-inflammatory/analgesic/antipyretic.

Recommended for use in adults and adolescents from 16 years of age. This medicinal product is not recommended for use in adolescents/children under 16 years unless the expected benefits outweigh the risks. Acetylsalicylic acid may be a contributory factor in the causation of Reye's Syndrome in some children.

There is an increased risk of haemorrhage and prolongation of bleeding time particularly during or after surgery(even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.

Aspirin Krka is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin Krka is to be used with caution in cases of uncontrolled hypertension and when patients have a past history of gastric or duodenal ulcer or haemorrhagic episodes or are undergoing therapy with anticoagulants.

Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

Acetylsalicylic acid should be used with caution in patients with moderately impaired renal or hepatic function (contraindicated if severe), or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Acetylsalicylic acid may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Rare cases of acute myocardial ischemia with or without myocardial infarction as part of a hypersensitivity reaction (Kounis syndrome) have been reported in patients treated with acetylsalicylic acid. In the event of confirmed Kounis syndrome due to acetylsalicylic acid, Aspirin Krka should be discontinued immediately.

Serious skin reactions, including Stevens-Johnson syndrome, have rarely been reported in association with the use of acetylsalicylic acid (see section 4.8). The treatment with Aspirin Krka should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Where prolonged therapy is required, patients should be reviewed regularly.

Concomitant treatment with Aspirin Krka and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage (see section 4.5). If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox (see section 4.5).

Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks (see section 4.5).

Aspirin Krka should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency.

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin Krka taken at overdosage (see section 4.5).

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Aspirin Krka 75 mg contains sunset yellow aluminium lake (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

Methotrexate (used at doses >15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses > 15 mg/week) with Aspirin Krka is contraindicated (see section 4.3).

Not recommended combinations

Uricosuric agents, e.g. probenecid, sulfinpyrazone
Salicylates reverse the effect of probenecid and sulfinpyrazone. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

Anticoagulants and thrombolytics e.g. coumarin, heparin, warfarin, alteplase
Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored (see section 4.4).
Particularly, treatment with acetylsalicylic acid should not be initiated within the first 24 hours after treatment with alteplase in acute stroke patients. Concomitant use is therefore not recommended.

Anti-platelet agents (e.g clopidogrel, ticlopidine, cilostazol and dipyridamole) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine)
Increased risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics, e.g. sulphonylureas and insulin
Salicylates may increase the hypoglycaemic effect of antidiabetics. Thus, some downward re-adjustment of the dosage of the antidiabetic may be appropriate if large doses of salicylates are used. Increased blood glucose controls are recommended.

Digoxin and lithium
Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary

Diuretics and antihypertensives
NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. Blood pressure should be well monitored.Concomitant administration with ACE-inhibitors, angiotensin II receptor antagonists and calcium-channel blocker increases the risk of acute renal insufficiency in combination with high-dose ASA.
Loop diuretics: Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended. In case of association with verapamil the bleeding time should be monitored.

Carbonic anhydrase inhibitors (acetazolamide)
May result in severe acidosis and increased central nervous system toxicity
Systemic corticosteroids
The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered (see section 4.4).

Methotrexate (used at doses < 15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Other NSAIDs
Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

Ibuprofen
Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid 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).

Metamizole

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 acetylsalicylic acid for cardioprotection.

Ciclosporin, tacrolimus
Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Valproate
Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin
Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Alcohol
Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy

Low doses (up to 100 mg/day):
Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100- 500 mg/day:
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

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 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, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

Breastfeeding
Low quantities of salicylates and of their metabolites are excreted into the breast milk. Since adverse effects for the infant have not been reported up to now, short-term use of the recommended dose does not require suspending lactation. In cases of long-term use and/or administration of higher doses, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with Aspirin Krka.
Based on the pharmacodynamic properties and the side effects of acetylsalicylic acid, no influence on the reactivity and the ability to drive or use machines is expected.

4.8 Undesirable 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 (< 1/10,000)
- Not known (cannot be estimated from the available data)

	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders	Increased bleeding tendencies		Thrombocytopenia, granulocytosis, aplastic anaemia	Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).
Immune system disorders			Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock.	
Metabolism and nutrition disorders				Hyperuricemia, hypoglycaemia
Nervous system disorders			Intracranial haemorrhage	Headache, vertigo
Ear and labyrinth disorders				Reduced hearing ability; tinnitus
Cardiac disorders				Kounis syndrome (acute myocardial ischemia with or without myocardial infarction as part of a hypersensitivity reaction) (see section 4.4).
Vascular disorders			Haemorrhagic vasculitis	
Respiratory, thoracic and mediastinal disorders		Rhinitis, dyspnoea	Bronchospasm, asthma attacks	
Gastrointestinal disorders	Dyspepsia; nausea, vomiting, diarrhoea		Severe gastrointestinal haemorrhage,	Gastric or duodenal ulcers and perforation
Hepatobiliary disorders			Reye´s syndrome	Hepatic insufficiency, hepatic enzyme increased
Skin and subcutaneous tissue disorders		Urticaria	Stevens-Johnson syndrome, Lyells syndrome, purpura,	

			erythema nodosum, erythema multiforme	
Renal and urinary disorders				Impaired renal function, acute renal failure
Reproductive system and breast disorders			Menorrhagia	

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Although considerable inter-individual variations are involved, it can be considered that the toxic dose is about 200 mg/kg in adults and 100 mg/kg in children. The lethal dose of acetylsalicylic acid is 25-30 grams. Plasma salicylate concentrations above 300 mg/l indicate intoxication. Plasma concentrations above 500 mg/l in adults and 300 mg/l in children generally cause severe toxicity.
Overdose may be harmful for elderly patients and particularly for small children (therapeutic overdose or frequent accidental intoxications may be fatal).

Symptoms of moderate intoxications
Tinnitus, hearing disorders, headache, vertigo, confusion and gastrointestinal symptoms (nausea, vomiting and abdominal pain).

Symptoms of severe intoxications
Symptoms are related to severe disruption of the acid-base balance. In the first instance hyperventilation occurs, which results in respiratory alkalosis. Respiratory acidosis ensues due to suppression of the respiratory centre. In addition, metabolic acidosis occurs as a result of the presence of salicylate.
Since younger children are often not seen until they have reached a late stage of intoxication, they are usually in the stage of acidosis.
Furthermore, the following symptoms may occur: hyperthermia and perspiration, resulting in dehydration: feelings of restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system may lead to coma, cardiovascular collapse or respiratory arrest.

Management
If a toxic dose has been ingested, hospital admission is required. In the event of moderate intoxication, inducing the patient to vomit should be attempted.
If this fails, gastric lavage may be attempted during the first hour after ingestion of a substantial amount of the medicine.
Afterwards, administer activated carbon (adsorbent) and sodium sulphate (laxative).
Activated charcoal may be given as a single dose (50 g for an adult, 1 g/kg body weight for a child up to 12 years).
Alkalisation of the urine (250 mmol $NaHCO^3$, for three hours) whilst checking urine pH levels.
In the event of severe intoxication, haemodialysis is to be preferred.
Other symptoms to be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors excl. Heparin, ATC code: B01AC06

Mechanism of action

Acetylsalicylic acid inhibits the platelet activation: blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A^2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatous lesions.
Inhibition of TXA^2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid.

Pharmacodynamic effects
The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%.
Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption.
Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.
Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly.
In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid 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 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.

5.2 Pharmacokinetic properties

Absorption
After oral administration, acetylsalicylic acid is rapidly and completely absorbed from the gastrointestinal tract. The principal site of absorption is the proximal small intestine. However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process. The degree of hydrolysis is dependent on the rate of absorption.
After intake of Aspirin Krka gastro-resistant tablets the maximum plasma levels of acetylsalicylic acid and salicylic acid are reached after about – 3.5 and 4.5 hours, respectively, following administration in the fasted state. If the tablets are taken with food, maximum plasma levels are reached approximately 3 hours later than in the fasted state.

Distribution
Acetylsalicylic acid as well as the main metabolite salicylic acid, are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. The degree of protein binding of salicylic acid is strongly dependant of both the salicylic acid and albumin concentration. The volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight.
Salicylic acid slowly diffuses into the synovial fluid, crosses the placental barrier and passes into breast milk.

Biotransformation
Acetylsalicylic acid is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. Salicylic acid is subsequently predominantly converted into glycine and glucuronic acid conjugates, and traces of gentisic acid.
Elimination kinetics of salicylic acid is dose-dependent, because the metabolism is limited by liver enzyme capacity. Thus, elimination half-time varies and is 2-3 hours after low doses, 12 hours after usual analgetic doses and 15-30 hours after high therapeutic doses or intoxication.

Elimination
Salicylic acid and its metabolites are predominantly excreted via the kidneys.

5.3 Preclinical safety data

The preclinical safety profile of acetylsalicylic acid is well documented.
In experimental animal studies, salicylates have shown no other organ injury than renal damage.
In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications.
Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
lactose monohydrate
cellulose, microcrystalline
silica, colloidal anhydrous
potato starch
Film-coating
talc
triacetin
methacrylic acid-ethylacrylate copolymer (1:1) dispersion 30%
sodium laurilsulfate*
polysorbate 80*
polyvinyl alcohol (E1203)
titanium dioxide (E171)
macrogol 3350 (E1521)
carmine (E120)
sunset yellow aluminium lake (E110)

* It may contain sodium laurilsulfate and polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister (PVC/Aluminium).

Pack sizes:
Blisters: 28, 30, 50, 56, 60, 84, 90 and 100 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/070/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th March 2017
Date of last renewal: 19th December 2021

10 DATE OF REVISION OF THE TEXT

October 2026