SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Acetylsalicylzuur ratiopharm 500 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg acetylsalicylic acid (Ph.Eur.).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White, round, biconvex tablet with cross break score on one side, diameter approx. 12 mm and height approx. 5.5 mm.

The tablet can be divided into equal halves.
The cross break score is only to facilitate breaking for ease of swallowing and not to divide into equal quarters.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment for fever and/or mild to moderate pain.
<Product name> 500 mg tablets is indicated in adults and adolescents from 12 years of age.

4.2 Posology and method of administration

Posology
Adults and adolescents (aged 16 and older):
1 to 2 tablets with each dose to be repeated as needed after a minimum period of 4 hours. The maximum daily dose should not exceed 6 tablets.

Elderly patients (aged 65 and older):
1 tablet with each dose to be repeated as needed after a minimum period of 4 hours. The maximum daily dose should not exceed 4 tablets.

Adolescents aged 12 – 15 years (40 - 50 kg):
1 tablet with each dose to be repeated as needed after a minimum period of 4 hours. The maximum daily dose should not exceed 4 tablets.

Acetylsalicylic acid should not be taken for more than 3 days (for fever) respectively for more than 3 - 4 days (for pain) unless directed by a physician.

Paediatric patients
This medicinal product is not suitable for children under 12 years (under 40 kg).
Other formulations are available which may be more appropriate for this patient group.

Hepatic impairment/ renal impairment
Acetylsalicylic acid should be used with caution in patients with impaired hepatic or renal function or cardiovascular problems (see sections 4.3 and 4.4).

Method of administration
For oral use. The tablets should be taken with plenty of liquid.

4.3 Contraindications

- hypersensitivity to acetylsalicylic acid or other salicylates, or to any of the excipients listed in section 6.1,
- history of asthma or hypersensitivity reactions (e.g. urticaria, angioedema, severe rhinitis, shock) induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory drugs (NSAID),
- active peptic ulcer,
- haemorrhagic diathesis,
- severe renal insufficiency,
- severe hepatic insufficiency,
- severe uncontrolled cardiac insufficiency,
- co-administration with methotrexate used at doses > 15 mg/week (see section 4.5),
- co-administration of oral anticoagulants with acetylsalicylic acid in patients with a history of gastro-duodenal ulcers (see section 4.5),
- third trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

- In the event of combination with other medicinal products, to avoid any risk of overdose, check that acetylsalicylic acid is absent from the composition of other medicinal products.
- Reye's syndrome, a very rare life-threatening disease, has been observed in children with signs of viral infection (in particular, varicella and influenza-like episodes) with or without taking acetylsalicylic acid. Consequently, acetylsalicylic acid must only be administered to children in this situation following medical advice, when other measures have failed. In the event of persistent vomiting, disturbances of consciousness or abnormal behaviour, treatment with acetylsalicylic acid must be discontinued.
- Long-term use of analgesics may cause or worsen headache. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. Where analgesics are used long-term (>3 months) with administration every two days or more frequently, medication overuse headache (MOH) should be suspected. Headache induced by overuse of analgesics (MOH) should not be treated by dose increase. In such cases, the use of analgesics should be discontinued in consultation with the doctor.
- The regular use of analgesics, particularly a combination of analgesics, may lead to persistent renal lesions, with a risk of renal insufficiency.
- In some severe forms of G6PD deficiency, high doses of acetylsalicylic acid may cause haemolysis. In the event of G6PD deficiency, acetylsalicylic acid must be administered under medical supervision.
- Monitoring of treatment should be reinforced in the following cases:
    - in patients with a history of gastric or duodenal ulcer, or gastrointestinal bleeding, or gastritis
    - in patients with renal insufficiency
    - in patients with hepatic insufficiency

  - in patients with asthma: the occurrence of an asthma attack, in some patients, may be related to an allergy to non-steroidal anti-inflammatory drugs or to acetylsalicylic acid; in this case, this medicine is contraindicated (see section 4.3)
  - in patients with metrorrhagia or menorrhagia (risk of increasing the volume and duration of periods)
- Gastrointestinal bleeding or ulcers/perforations may occur at any time during treatment, without there being necessarily any prior signs or history in the patient. The relative risk increases in elderly subjects, in subjects with a low body weight, and in patients receiving anticoagulants or platelet aggregation inhibitors (see section 4.5). In the event of gastrointestinal bleeding, treatment must be discontinued immediately.
- In view of the inhibitory effect of acetylsalicylic acid on platelet aggregation, which occurs even at very low doses and persists for several days, the patient should be warned of the risk of haemorrhage in the event of surgery, even of a minor nature (e.g. tooth extraction).
- Acetylsalicylic acid reduces the excretion of uric acid. This can possibly trigger gout attacks in predisposed patients.
- Use of this medicinal product is not recommended during breast-feeding (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Several substances are involved in interactions, due to their platelet aggregation inhibitory properties: abciximab, acetylsalicylic acid, cilostazol, clopidogrel, epoprostenol, eptifibatide, iloprost, iloprost trometamol, prasugrel, ticlopidine, tirofiban, ticagrelor.
The use of multiple platelet aggregation inhibitors increases the risk of bleeding, as does their combination with heparin or related molecules, oral anticoagulants or other thrombolytics, and must be taken into consideration by maintaining regular clinical monitoring.

Contraindicated combinations (see section 4.3):
- Methotrexate at doses > 15 mg/week: Increased toxicity of methotrexate, in particular haematological toxicity (due to reduction in renal clearance of methotrexate by acetylsalicylic acid).
- Oral anticoagulants in patients with a history of gastro-duodenal ulcers: Increased risk of haemorrhage.

Combinations not recommended:
- Oral anticoagulants in patients with no history of gastro-duodenal ulcers: Increased risk of haemorrhage.
- Other non-steroidal anti-inflammatory drugs (NSAIDs): Increased risk of gastrointestinal ulcers and haemorrhage.
- Low molecular weight heparins (and related molecules) and unfractionated heparins at curative doses, or in elderly patients (≥ 65 years) regardless of the dose of heparin: Increased risk of haemorrhage (inhibition of platelet aggregation and aggression of the gastroduodenal mucosa by acetylsalicylic acid). Another anti-inflammatory drug, or another analgesic or antipyretic should be used.
- Clopidogrel (beyond the approved indications for this combination in patients with acute coronary syndrome): Increased risk of haemorrhage. If co-administration cannot be avoided, clinical monitoring is recommended.
- Ticlopidine: Increased risk of haemorrhage. If co-administration cannot be avoided, clinical monitoring is recommended.
- Uricosurics (benzbromarone, probenecid): Reduction in the uricosuric effect due to competition for elimination of uric acid in renal tubules.
- Glucocorticoids (except hydrocortisone replacement therapy) for anti-inflammatory doses of acetylsalicylic acid: Increased risk of haemorrhage.
- Alcohol: Increased risk of gastrointestinal ulcers and bleeding.

- Pemetrexed in patients with mild to moderate renal impairment (creatinine clearance between 45 ml/min and 80 ml/min): Increased risk of pemetrexed toxicity (due to decreased renal clearance of pemetrexed by acetylsalicylic acid).
- Anagrelide: Increased risk of haemorrhage and decrease of the antithrombotic effect. If co-administration cannot be avoided, clinical monitoring is recommended.

Combinations requiring precautions for use:
- Diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists: Acute renal failure may occur in dehydrated patients due to decreased glomerular filtration rate secondary to decreased synthesis of renal prostaglandins. In addition, reduction of antihypertensive effect may occur. Ensure that the patient is hydrated and renal function is monitored at the beginning of treatment.
- Methotrexate at doses ≤ 15 mg/week: Increased toxicity of methotrexate, in particular haematological toxicity (due to reduction in renal clearance of methotrexate by acetylsalicylic acid). Blood counts should be monitored weekly during the first weeks of co-administration. Close monitoring is required in patients with renal impairment (even mild) as well as in elderly patients.
- Clopidogrel (in the approved indications for this combination in patients with acute coronary syndrome): Increased risk of haemorrhage. Clinical monitoring is recommended.
- Gastrointestinal topicals, antacids: Increased renal excretion of acetylsalicylic acid due to alkalinisation of urine. Charcoal: Reduced absorption of acetylsalicylic acid due to adsorption. It is recommended to administer gastrointestinal topicals, antacids and charcoal at least 2 hours apart from acetylsalicylic acid.
- Pemetrexed in patients with normal renal function: Increased risk of pemetrexed toxicity (due to decreased renal clearance of pemetrexed by acetylsalicylic acid). Renal function should be monitored.

Combinations to be taken into account:
- Glucocorticoids (except hydrocortisone replacement therapy): Increased risk of haemorrhage.
- Deferasirox: Increased risk of gastrointestinal ulcers and haemorrhage.
- Low molecular weight heparins (and related molecules) and unfractionated heparins at preventive doses in patients under 65 years of age: Co-administration acting at different levels of haemostasis increases the risk of haemorrhage. Therefore, in patients less than 65 years of age, co-administration of heparins at preventive doses (or related molecules), and acetylsalicylic acid, should be taken into account by maintaining clinical monitoring, and laboratory monitoring as needed.
- Thrombolytics: Increased risk of haemorrhage.
- Selective Serotonin Re-uptake Inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline): Increased risk of haemorrhage.

4.6 Fertility, pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the course of pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage, cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy.

The absolute risk of cardiovascular malformations was increased from less than 1% to approximately 1.5%. The risk seems to increase with dose and duration of treatment.

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, an increased incidence of various malformations, including cardiovascular malformations, has been reported in animals given a prostaglandin synthesis inhibitor during the period of organogenesis.

Acetylsalicylic acid should be used only when absolutely necessary in the first and second trimester of pregnancy. If acetylsalicylic acid is administered to a woman who wants to become pregnant or to a pregnant woman during the first and second trimester of pregnancy, the dose should be as low as possible and treatment duration as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension);
- renal impairment, which may progress to renal failure with oligo-hydroamniosis.

In late pregnancy, the mother and the newborn may present:
- prolongation of bleeding time due to inhibition of platelet aggregation which may occur even after administration of very low doses of acetylsalicylic acid.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, acetylsalicylic acid is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding
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, incidental use of the recommended dose does not require suspending lactation. In cases of regular use and/or administration of higher doses breastfeeding should be discontinued. (see section 4.4).

Fertility
There is some evidence that medicines which inhibit cyclo-oxygenase / prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Frequencies: not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Bleeding and haemorrhagic tendency (epistaxis, bleeding gums, purpura, etc.) with an increase in bleeding time. The bleeding risk may persist for 4 to 8 days after discontinuation of acetylsalicylic acid. It may cause an increased risk of haemorrhage in the event of surgery. Intracranial and gastrointestinal haemorrhage may also occur.

Immune system disorders
Hypersensitivity reactions, anaphylactic reactions, asthma, angioedema

Nervous system disorders
Headache, dizziness, sensation of hearing loss, tinnitus, which are usually indicative of an overdose.
Intracranial haemorrhage

Respiratory, thoracic and mediastinal disorders
Rhinitis, dyspnoea, bronchospasm

Gastrointestinal disorders

Abdominal pain, dyspepsia, nausea, vomiting
Occult or patent gastrointestinal haemorrhage (hematemesis, melaena, etc.) resulting in iron-deficiency anaemia. The bleeding risk is dose-dependent.
Gastric ulcers and perforations

Hepatobiliary disorders
Elevation of hepatic enzymes mainly reversible when the treatment is stopped, liver injury, mainly hepatocellular

Skin and subcutaneous tissue disorders
Urticaria, severe skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme

Renal and urinary tract disorders
Impaired renal function

General disorders
Reye's syndrome (see section 4.4)

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 the national reporting system listed in Appendix V.

4.9 Overdose

The risk of overdose is of concern in elderly subjects and particularly in young children (therapeutic overdose or, more frequently, accidental poisoning) where it can be fatal.

Symptoms
Moderate poisoning:
Symptoms such as buzzing in the ears, sensation of impaired hearing, headache, and dizziness are indicative of an overdose and may be controlled by a reduction in the dosage.

Severe poisoning:
Symptoms include: Fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular collapse, respiratory insufficiency, severe hypoglycaemia.
In children, an overdose may be fatal at a dose as low as 100 mg/kg in a single intake.

Emergency management
- Immediate transfer to a specialized hospital unit
- Gastrointestinal lavage and administration of activated charcoal
- Control of acid-base balance
- Alkalinisation of the urine with monitoring of urine pH.
- Haemodialysis in cases of severe poisoning
- Symptomatic treatment

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system, other analgesics and antipyretics.

ATC-Code: N02BA01

Acetylsalicylic acid belongs to the group of acidic non-steroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on irreversible inhibition of cyclo-oxygenase enzymes involved in prostaglandin synthesis.

Clinical studies of acetylsalicylic acid in oral doses of in general 0.3 to 1.0 g have shown efficacy for the relief of pain, such as tension-type headache, migraine headache, dental pain, sore throat, primary dysmenorrhoea, muscular and joint pain, and in febrile conditions, such as colds or influenza, for the reduction of temperature.
Acetylsalicylic acid also inhibits platelet aggregation by blocking thromboxane A2 synthesis in platelets. Thus, it is used for various vascular indications at doses of in general 75 to 300 mg daily.

5.2 Pharmacokinetic properties

Absorption:
After oral administration, acetylsalicylic acid is rapidly and completely absorbed from the gastrointestinal tract. During and after absorption, acetylsalicylic acid is converted into its main active metabolite salicylic acid. The maximum plasma levels of acetylsalicylic acid and salicylic acid are reached after 10-20 minutes and 0.3-2 hours, respectively.

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.

Biotransformation
Acetylsalicylic acid is rapidly converted to salicylic acid by hydrolysis. This hydrolysis is due to nonspecific esterases found in many body tissues

Elimination:
Salicylic acid is eliminated predominantly by hepatic metabolism. Its metabolites are salicyluric acid, salicylic phenolic glucuronide, salicylacyl glucuronide, gentisic acid, and gentisuric acid.
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.

5.3 Preclinical safety data

The preclinical safety profile of acetylsalicylic acid is well documented.
In animal studies, salicylates have caused kidney damage and gastrointestinal ulcers. 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 in a number of different species (e.g. cardiac and skeletal malformations, midline defects). 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

Maize starch,
Powdered cellulose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

30, 50 and 100 tablets in blisters (White opaque PVC foil/Aluminum foil).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Ratiopharm GmbH
Graf-Arco-Strasse 3
89079 Ulm
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 126642

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 15 februari 2022

10. DATE OF REVISION OF THE TEXT