Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
Aspirin® 500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains: 500 mg acetylsalicylic acid.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
- Pain relief
- Fever reduction

Please note the instructions for children and adolescents (see section 4.4).

4.2 Posology, method and duration of administration
Unless otherwise prescribed, the usual dose is:

Age	Single dose	Total daily dose
Children from 12 years	**1** tablet (equivalent to 500 mg acetylsalicylic acid)	**Up to 3** tablets (equivalent to 1,500 mg acetylsalicylic acid)
Adolescents and adults	**1–2** tablets (equivalent to 500–1.000 mg acetylsalicylic acid)	**8** tablets (equivalent to 4000 mg acetylsalicylic acid)

A single dose can be taken at intervals of 4 to 6 hours if necessary.

Patients with hepatic impairment
Acetylsalicylic acid should be used with caution in patients with hepatic impairment (see section 4.4).

Patients with renal impairment
Acetylsalicylic acid should be used with caution in patients with renal impairment (see section 4.4).

Method of administration
Take the tablets with plenty of liquid (e.g. a glass of water). Patients with swallowing difficulties can allow the tablets to disintegrate in a spoonful of water.

Do not take on an empty stomach.

Aspirin should not be used for more than 4 days without consulting a doctor.

4.3 Contraindications
- Hypersensitivity to acetylsalicylic acid or other salicylates or to any other ingredient listed in section 6.1.
- A history of asthma attacks induced by the administration of salicylates or substances with a similar action, in particular non-steroidal anti-inflammatory drugs.

- Acute gastrointestinal ulcers.
- Haemorrhagic diathesis.
- Hepatic and renal failure.
- Severe, uncontrolled heart failure.
- In combination with methotrexate at doses of 15 mg or more per week (see section 4.5).
- The last trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

- Hypersensitivity to other analgesics / anti-inflammatory drugs / anti-rheumatics or other allergenic substances (see section 4.3).
- Allergies (e.g. skin reactions, itching, urticaria), asthma, hay fever, swelling of the mucosal membrane of the nose (nasal polyps) or chronic respiratory diseases.
- Concomitant treatment with anticoagulants (see section 4.5).
- History of gastrointestinal ulcers or bleeding.
- Impaired hepatic function.
- Patients with impaired renal function or patients with impaired cardiovascular blood flow (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major haemorrhagic events): Acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure.
- Before surgery (including minor surgery such as dental extractions). Bleeding tendency may be increased.
- In patients with severe glucose-6-phosphate dehydrogenase deficiency: acetylsalicylic acid may induce haemolysis or haemolytic anaemia. Factors that can increase the risk of haemolysis include high dosage, fever or acute infection.

What other precautions must be taken?

Prolonged use of analgesics can cause headaches which, if treated with more analgesics, can in turn result in persistence of the headaches.

Habitual use of analgesics can lead to permanent kidney damage with the risk of renal failure (analgesic nephropathy). The risk is particularly high when several different analgesics are taken concomitantly.

At low doses, acetylsalicylic acid reduces uric acid excretion. This can possibly trigger a gout attack in predisposed patients who already tend to have decreased urine excretion.

Children or adolescents

Acetylsalicylic acid should not be taken by children or adolescents with febrile illness unless they have been instructed to do so by a doctor and other therapeutic measures have failed. Prolonged vomiting in conjunction with such illnesses could be a sign of Reye's syndrome, a very rare but life-threatening disease requiring immediate medical attention.

4.5 Interaction with other medicinal products and other forms of interaction

Potentiation of effects including increased risk of adverse effects:

- Anticoagulants / thrombolytics: When taken before thrombolytic treatment, acetylsalicylic acid can increase the risk of bleeding. It is therefore important to be alert to signs of external or internal bleeding in patients who are scheduled to undergo thrombolytic treatment.
- Platelet aggregation inhibitors, e.g. ticlopidine, clopidogrel: Increased risk of bleeding.
- Other non-steroidal analgesic/anti-inflammatory drugs (at doses of 3 g acetylsalicylic acid per day and above): Increased risk of gastrointestinal ulcers and bleeding.
- Systemic glucocorticoids (except hydrocortisone as replacement therapy in Addison's disease): Increased risk of gastrointestinal side effects.
- Alcohol: Increased risk of gastrointestinal ulcers and bleeding.
- Digoxin: Increased plasma concentration.
- Antidiabetics: blood sugar levels may fall.
- Methotrexate: Reduced excretion and displacement from plasma protein binding sites by salicylates (see section 4.3).

- Valproic acid: Displacement from plasma protein binding sites by salicylates can occur.
- Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding due to synergistic effects.

Attenuation of effects:
- Diuretics (at doses of 3 g acetylsalicylic acid per day and above).
- ACE inhibitors (at doses of 3 g acetylsalicylic acid per day and above).
- Uricosuric agents (e.g. probenecid, benzbromarone).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or embryo-foetal development. Data from epidemiological studies have raised concern about an increased risk of miscarriage and malformations after the use of a prostaglandin synthesis inhibitors in early pregnancy. The risk is believed to increase with dose and duration of therapy. Available epidemiological data for acetylsalicylic acid indicate an increased risk of gastroschisis.
Animal studies have shown reproductive toxicity (see section 5.3).
From the 20th week of pregnancy onward, use of Aspirin may cause oligohydramnios resulting from foetal renal dysfunction. This can occur shortly after the start of treatment and is generally reversible after discontinuation of treatment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. There have also been reports of constriction of the ductus arteriosus after treatment in the second trimester of pregnancy, although this regressed after discontinuation of treatment in most cases. Aspirin should therefore not be administered during the first and second trimester of pregnancy unless this is absolutely necessary. If Aspirin is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible. After Aspirin has been taken for several days from the 20th week of pregnancy, antenatal monitoring for oligohydramnios and constriction of the ductus arteriosus should be considered. Aspirin should be discontinued if oligohydramnios or constriction of the ductus arteriosus is found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may:
expose the fetus to:
- cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension)
- impaired kidney function (see above)

expose the mother and neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, a platelet aggregation-inhibiting effect that can occur even at very low doses;
- inhibition of uterine contractions, which can lead to delayed labor or prolonged parturition.

Consequently, acetylsalicylic acid is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Fertility:

There is evidence that drugs that inhibit cyclooxygenase/prostaglandin synthesis may impair female fertility through an effect on ovulation. This effect is reversible on discontinuation of treatment.

Lactation:

Acetylsalicylic acid and its metabolites pass into breast milk in small quantities. Adverse effects on infants have not been reported to date. It is therefore not necessary to interrupt breast-feeding due to occasional use at the recommended dosage. Nonetheless, in the case of use for extended periods or consumption of high doses, breastfeeding should be stopped.

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

The following undesirable effects include all reported side effects following treatment with acetylsalicylic acid, including those following long-term high-dose therapy in rheumatoid arthritis patients. Apart from isolated cases, the incidence figures are based on short-term use of daily doses of not more than 3 g acetylsalicylic acid.

The evaluation of adverse effects is based on the following frequency rates:

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: Frequency cannot be estimated from the available data.	

Blood and lymphatic system disorders:
In rare to very rare cases serious bleeding has been reported, e.g. cerebral bleeding, especially in patients with uncontrolled hypertension and/or simultaneous treatment with anticoagulants, which in isolated cases may be life-threatening.
Haemolysis and haemolytic anaemia have been reported in patients with severe glucose-6-phosphate dehydrogenase deficiency.
Bleeding, e.g. epistaxis, bleeding of gums, bruising or genitourinary bleeding with possible prolongation of bleeding time (see section 4.4). This effect can persist for 4 to 8 days after use.

Gastrointestinal disorders:
Common:
Gastrointestinal disorders such as heartburn, nausea, vomiting, abdominal pain.
Rare:
Gastrointestinal ulcers, which in very rare cases can lead to perforation.
Gastrointestinal bleeding, which in very rare cases can lead to iron-deficiency anaemia.
Gastrointestinal inflammation.
Not known:
In the event of prior damage to the intestinal mucosa, multiple membranes can form in the intestinal lumen, which may result in subsequent stenosis (particularly with long-term treatment).

Nervous system disorders
Headache, dizziness, impaired hearing, tinnitus and mental confusion can be signs of overdose (see section 4.9).

Skin and subcutaneous tissue disorders:
Uncommon:
Hypersensitivity reactions such as skin reactions.
Rare:
Hypersensitivity reactions such as severe skin reactions (including erythema multiforme exudativum).

Immune system disorders:
Rare:
Hypersensitivity reactions of the respiratory tract, gastrointestinal tract and cardiovascular system, especially in asthmatic patients.
Possible symptoms are: Drop in blood pressure, dyspnoea attacks, rhinitis, nasal congestion, anaphylactic shock or angio-oedema.

Hepatobiliary disorders:
Very rare:
Elevated hepatic enzyme values.

Renal and urinary disorders:
Renal impairment and acute renal failure have been reported.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il/

4.9 Overdose

Salicylate toxicity can result from chronic, therapeutic overdose or potentially life-threatening acute poisoning (overdose due to inadvertent intake by children including accidental intoxication).

Chronic salicylate poisoning
Chronic salicylate poisoning can be problematic, as the signs and symptoms are non-specific. **Mild** salicylate poisoning generally occurs following repeated intake of high doses (> 100/mg/kg/day over 2 days can be toxic). Symptoms include drowsiness, dizziness, tinnitus, hearing impairment, sweating, nausea and vomiting, headache and confusion and can be controlled by reducing the dose.

Acute salicylate poisoning
The main manifestation of **acute poisoning** is a severe disturbance in the acid-base balance, which can vary with age and the degree of poisoning. The most common sign of acute poisoning in children is metabolic acidosis. The severity of poisoning cannot be estimated from the plasma concentrations alone. The absorption of acetylsalicylic acid may be delayed by slowing of gastric emptying, concrement formation in the stomach or as a result of taking gastro-resistant medicinal products. Tinnitus can occur at plasma levels of 150 to 300 µg/mL. Further severe adverse effects can occur at concentrations over 300 µg/mL.

The pathophysiological effects of salicylate poisoning are complex.

Mild to moderate poisoning manifests as nausea, vomiting, tachypnoea, hyperventilation, respiratory alkalosis and diaphoresis.

Signs of **moderate to severe poisoning** include respiratory alkalosis with compensatory metabolic acidosis, hyperpyrexia, impaired glucose metabolism and ketosis, tinnitus, deafness, gastrointestinal bleeding, respiratory disorders (from hyperventilation up to respiratory arrest), cardiovascular disorders (from arrhythmia up to cardiovascular shock), water and electrolyte disturbances (from dehydration up to kidney failure), haematological disorders (from inhibition of platelet function up to coagulopathy), toxic encephalopathy and CNS depression (from lethargy up to coma and seizures).

Treatment of acetylsalicylic acid poisoning is guided by the extent, severity and clinical symptoms corresponding to standard measures to manage poisoning. The first emergency measures must be to accelerate the excretion of the drug and to restore the electrolyte and acid-base balance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system, other analgesics and antipyretics, salicylic acid and derivatives.
ATC code: N02BA01

Acetylsalicylic acid is a member of the class of acid-forming non-steroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on irreversible inhibition of cyclooxygenase enzymes involved in prostaglandin synthesis.

Acetylsalicylic acid is used at oral doses of between 0.3 and 1.0 g to treat mild to moderate pain and fever, e.g. associated with colds or flu, to lower fever and to treat joint and muscle pain.

It is also used to treat acute and chronic inflammatory diseases such as rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.
Acetylsalicylic acid also inhibits platelet aggregation by blocking the synthesis of thromboxane A2 in platelets. For this reason, doses of 75 to 300 mg daily are used in various cardiovascular indications.

5.2 Pharmacokinetic properties

Acetylsalicylic acid is absorbed rapidly and completely from the gastrointestinal tract following oral administration. During and after absorption acetylsalicylic acid is converted into its main active metabolite, salicylic acid. Peak plasma levels of acetylsalicylic acid and salicylic acid are reached after 18 - 30 minutes and 0.72–2 hours, respectively. The given durations depend on the pharmaceutical form.
For Aspirin (500 mg tablets), the active substance acetylsalicylic acid has mean peak plasma concentrations (C_{max}) of 5.4 µg/mL; mean time to peak plasma concentrations (T_{max}) is 30 min; mean total exposure to acetylsalicylic acid (area under the curve/AUC) is 6.2 µg x h/mL.
For salicylic acid, mean peak plasma concentrations (C_{max}) are 25.4 µg/mL; mean time to peak plasma concentrations (T_{max}) is 2 h; mean total exposure (area under the curve/AUC) is 145 µg x h/mL.
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.
Acetylsalicylic acid is converted into its main metabolite, salicylic acid. The acetyl group of the acetylsalicylic acid starts being cleaved by hydrolysis as it passes through the intestinal mucosa. This process takes place primarily in the liver. The metabolites of salicylic acid are salicyluric acid, salicyl phenolic glucuronide, salicyl acyl glucuronide, gentisic acid and gentisuric acid.
The elimination kinetics of salicylic acid are dose-dependent, as metabolism is limited by hepatic enzyme capacity. The elimination half-life therefore varies from 2 to 3 hours after low doses to about 15 hours after high doses. Salicylic acid and its metabolites are excreted primarily via the kidneys.

5.3 Preclinical safety data

The preclinical safety profile of acetylsalicylic acid is well documented. In animal studies, salicylates caused kidney damage but no other organic lesions. Acetylsalicylic acid has been extensively studied for mutagenicity and carcinogenicity. No relevant evidence of a mutagenic or carcinogenic potential has been found.
Salicylates have exhibited teratogenic effects in a number of different animal species (e.g. cardiac and skeletal malformations, gastroschisis). Implantation disorders, embryotoxic and foetotoxic effects and impairment of learning ability in offspring after prenatal salicylate exposure have been described.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Powdered cellulose

6.2 Incompatibilities

None

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C, protect from moisture.

6.5 Nature and contents of container

Blister packs containing 20 tablets.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURER

Bayer Bitterfeld, Germany

8. MARKETING AUTHORISATION HOLDER

Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240

9. MARKETING AUTHORISATION NUMBER

025 43 21130 00

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