Summary of Product Characteristics

1. Name of medicinal product
Aspirin® C

2. Qualitative and quantitative composition
One effervescent tablet contains: 400 mg acetylsalicylic acid (Ph-Eur.) and 240 mg ascorbic acid

Complete list of excipients see section 6.1.

3. Pharmaceutical Form
Effervescent tablet

4. Clinical particulars

4.1 Therapeutic Indications
- Pain relief
- Fever reduction
- Antirheumatic treatment

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

4.2 Posology, and method of administration

Posology

The usual dose is:

Age	Single dose	Total daily dose
Children 9-12	**1 effervescent tablet** (equivalent to 400 mg acetylsalicylic acid and 240 mg ascorbic acid)	**3 effervescent tablets** (equivalent to 1,200 mg acetylsalicylic acid and 720 mg ascorbic acid)
Adolescents and adults	**1-2 effervescent tablets** (equivalent to 400-800 mg acetylsalicylic acid and 240-480 mg ascorbic acid)	**8 effervescent tablets** (equivalent to 3,200 mg acetylsalicylic acid and 1 mg ascorbic acid)

The single dose can be taken at intervals of 4 to 6 hours if necessary. The total daily dose must not be exceeded.

Method of administration

The tablets are taken dissolved in water.
Do not take on an empty stomach.

Aspirin C must not be taken for more than 4 days without consulting a physician.

Paediatric population
Acetylsalicylic acid may be used in children and adolescents under 12 years only if prescribed by a doctor.

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).

4.3 Contraindications

- Hypersensitivity to acetylsalicylic acid, other salicylates, ascorbic acid or to any of the excipients listed in section 6.1,
- History of asthma attacks caused by salicylates or substances with similar effects, especially nonsteroidal anti-inflammatory drugs.
- Acute gastrointestinal ulcers.
- Haemorrhagic diathesis.
- Liver and kidney failure.
- Severe, uncontrolled heart failure.
- Concomitant treatment with methotrexate at doses of 15 mg/week or more (see section 4.5).
- Last trimester of pregnancy (see section 4.6).
- Nephrolithiasis or history of nephrolithiasis
- Hyperoxaluria
- Haemochromatosis

4.4 Special warnings and precautions for use

Related to Acetylsalicylic acid

- Hypersensitivity to other analgesics / anti-inflammatory or antirheumatic drugs or other allergenic substances (see section 4.3).
- Existing allergies (e.g. skin reactions, pruritus, urticaria), asthma, hay fever, swelling of the nasal mucous membranes (nasal polyps) or chronic respiratory disease;
- Concomitant treatment with anticoagulants (see section 4.5).
- History of gastrointestinal ulcers or bleeding.
- Impaired liver function.
- Patients with impaired renal function or patients with reduced cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major haemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure.
- Before surgery (including minor procedures such as dental extractions); bleeding tendency could be increased.
- Patients suffering from severe glucose-6-phosphate dehydrogenase (G6PD) deficiency: acetylsalicylic acid may induce haemolysis or haemolytic anaemia. Factors that may increase the risk of haemolysis are e.g. high dosage, fever or acute infections.

Rare cases of acute myocardial ischaemia with or without myocardial infarction in the context of a hypersensitivity reaction (Kounis syndrome) have been reported in patients who have been treated with acetylsalicylic acid. If occurrence of Kounis syndrome caused by acetylsalicylic acid is confirmed, treatment with Aspirin Plus C must be discontinued immediately.

What other precautions must be taken?

One effervescent tablet contains 20.3 mmol (466.4 mg) sodium, which is equivalent to 23% of the maximum daily intake of 2 g of sodium per day recommended by the WHO for adults. Aspirin C is

rich in sodium. This must be taken into account by patients on a sodium-controlled (low-sodium/low-salt) diet.

Long-term consumption of analgesics can cause headaches resulting in further intake of pain medications that may in turn result in the persistence of headaches.

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

At low doses acetylsalicylic acid reduces the excretion of uric acid. This may cause a gout attack in patients which already have a tendency to low urine excretion.

Children or adolescents
Acetylsalicylic acid should not be taken by children or adolescents with feverish illnesses 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 which requires immediate medical treatment.

4.5 Interactions with other medicinal products and other forms of interaction

Enhanced effects ranging up to an increased risk of side effects:
- Anticoagulants / thrombolytics: Acetylsalicylic acid can increase the risk of bleeding when taken before thrombolytic treatment. Attention should therefore be paid 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 nonsteroidal analgesics / anti-inflammatory drugs (at doses of 3 g acetylsalicylic acid per day or more): increased risk of gastrointestinal ulcers and bleeding;
- Systemic glucocorticoids (with the exception of hydrocortisone as replacement therapy in Addison's disease): increased risk of gastrointestinal side effects;
- Alcohol: increased risk of gastrointestinal ulcers and bleeding;
- Digoxin: increase in plasma levels;
- Antidiabetics: the blood glucose level can be reduced;
- Methotrexate: decrease in excretion and displacement from plasma protein binding sites by salicylates (see section 4.3);
- Valproic acid: displacement from plasma protein binding sites by salicylate;
- Selective Serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding due to synergistic effects.

Weakening of effects:
- Diuretics (at doses of 3 g acetylsalicylic acid per day or more).
- ACE inhibitors (at doses of 3 g acetylsalicylic acid per day or more).
- Uricosuric agents (e.g. probenecid, benzbromarone).
- Deferoxamine: Concurrent use with ascorbic acid may enhance tissue iron toxicity, especially in the heart, causing cardiac decompensation.

Interactions of ascorbic acid in laboratory tests
Vitamin C is a reducing agent (i.e., an electron donor) and can cause chemical interference in laboratory tests involving oxidation-reduction reactions, e.g., analysis of glucose, creatinine, carbamazepine, uric acid in urine, serum and haemoccult test. Vitamin C can interfere in tests in which urine and blood glucose are measured and lead to false

measurement results, although vitamin C does not have any influence on blood glucose levels.

4.6 Fertility, pregnancy and lactation

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 as well as cardiac malformations and of gastroschisis after the use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of cardiac malformations increases from less than 1% to up to 1.5%. The risk is believed to increase with dose and duration of therapy.
In animals, administration of a prostaglandin synthesis inhibitor has been found to result in increased pre- and post-implantation disorders and embryo-foetal mortality. In addition, increased incidences of various deformities, including cardiovascular deformities, have been reported in animals administered prostaglandin synthesis inhibitors during the organ development phase.

From the 20th week of pregnancy, use of acetylsalicylic acid may cause foetal renal impairment leading to oligohydramnios. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. 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. Acetylsalicylic acid should therefore not be administered during the first and second trimester of pregnancy unless this is absolutely necessary. If acetylsalicylic acid is used in a woman who is attempting to conceive or who is in the first or second trimester of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible. After acetylsalicylic acid has been taken for 5 days or more from the 20th week of pregnancy, prenatal monitoring for oligohydramnios and constriction of the ductus arteriosus should be considered. Acetylsalicylic acid should be discontinued if oligohydramnios or constriction of the ductus arteriosus is identified.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors can:
expose the foetus to the following risks:

- cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension)
- renal impairment (see above)

The mother and the neonate are exposed to the following risks at the end of pregnancy:

- possible prolongation of bleeding time due to a platelet aggregation inhibiting effect which may occur even at very low doses.
- inhibition of labour that may lead to delayed or prolonged delivery.

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

Lactation

Salicylates and its metabolites pass into breast milk in small quantities. Since no adverse effects on the infant have been observed so far after occasional use, interruption of breast-feeding is usually unnecessary when the recommended dose is occasionally used.

However, when used for extended periods or at higher doses, breast feeding should be discontinued.

Fertility
There is some evidence suggesting that drugs which inhibit cyclooxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on the ability to drive and use machines

Acetyl salicylic acid and ascorbic acid do not influence the ability to drive and to use machines

4.8. Adverse effects

Acetylsalicylic acid

The following adverse effects comprise all reported side effects following treatment with acetylsalicylic acid, including those following long-term, high-dose therapy in rheumatism patients. The incidence figures for events that go beyond isolated cases are based on short-term use of daily doses of not more than 3 g acetylsalicylic acid.

The following incidence rating is used to evaluate the frequency of side effects:

Very common:	≥ 1/10
Common:	≥ 1/100, < 1/10
Uncommon:	≥ 1/1.000, < 1/100
Rare:	≥ 1/10.000, < 1/1.000
Very rare:	< 1/10.000
Unknown:	Frequency could not be estimated by given data

Blood and lymphatic system disorders:
Rare to very rare serious bleedings, such as cerebral haemorrhage (especially in patients with uncontrolled hypertension and/or on concomitant treatment with anticoagulants), which in isolated cases may be potentially life-threatening, have been reported.
Haemolysis and haemolytic anaemia in patients with severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency have been reported.
Bleeding, e.g. nosebleeds, bleeding gums or skin bleeding, or bleeding of the genitourinary system with possible prolongation of the bleeding time (see section 4.4). This effect may persist for 4 to 8 days after use.

Gastrointestinal system disorders:
Common:
Gastrointestinal disorders such as heartburn, diarrhoea, 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, potentially resulting in subsequent stenosis (particularly in cases of long-term treatment).

Nervous system disorders:
Headache, dizziness, impaired hearing, ringing in the ears (tinnitus) and mental confusion may be signs of an overdose (see section 4.9).

Skin and subcutaneous tissue disorders:
Uncommon:
Hypersensitivity reactions like skin reactions.
Rare:
Hypersensitivity reactions like severe skin reactions (up to erythema exsudativum multiforme).

Immune system disorders:
Rare:
Hypersensitivity reactions of the respiratory tract, the gastrointestinal tract and the cardiovascular system, especially in asthmatic patients.
Symptoms may include: drop in blood pressure, attacks of dyspnoea, rhinitis, nasal congestion, anaphylactic shock or angioedema.

Cardiac disorders
Not known:
Kounis syndrome (acute myocardial ischaemia with or without myocardial infarction, resulting from a hypersensitivity reaction), of unknown frequency (see section 4.4).

Hepatobiliary disorders:
Very rare:
Elevated liver enzyme values.

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

Ascorbic acid (Vitamin C)
The adverse effects listed below are based on "spontaneous reports", so grading according to frequency is therefore not possible (frequency not known).

Immune system disorders
Hypersensitivity reactions, allergic reactions and anaphylactic shock.

Gastrointestinal disorders
Diarrhoea, nausea, vomiting, gastrointestinal pain, abdominal pain.

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 and from potentially life-threatening acute poisoning (overdose due to inadvertent intake in children, including accidental intoxication).

Chronic salicylate poisoning can be insidious, 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.

The main feature of acute poisoning is a severe acid-base imbalance, 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 assessed on the basis of the plasma concentration alone. The absorption of acetylsalicylic acid can be delayed by reduced gastric emptying, concrement formation in the stomach or as a result of ingestion of gastro-resistant medicinal products. Tinnitus can occur at plasma concentrations of 150 to 300 mcg/mL. Further severe adverse effects can occur at concentrations over 300 mcg/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 are: respiratory alkalosis with compensatory metabolic acidosis, hyperpyrexia, impaired glucose metabolism and ketosis, tinnitus, deafness, gastrointestinal bleeding, respiratory disorders (ranging from hyperventilation to respiratory arrest), cardiovascular disorders (ranging from arrhythmia to cardiovascular shock), fluid and electrolyte disturbances (ranging from dehydration to kidney failure), haematological conditions (ranging from antiplatelet effects to coagulopathy), toxic encephalopathy and CNS depression (ranging from lethargy to coma and seizures).

Treatment of acetylsalicylic acid poisoning is guided by the extent, severity, and clinical symptoms and is based on standardised procedures for poisoning. In severe cases, haemodialysis may be necessary. The first emergency measures should be to accelerate the excretion of the drug and to restore the electrolyte and acid-base balance.

The literature includes isolated reports of acute and chronic ascorbic acid overdose. In patients with glucose-6-phosphate dehydrogenase deficiency, this may lead to oxidative haemolysis, disseminated intravascular coagulation and significantly elevated oxalate levels in serum and urine.
Elevated oxalate levels may lead to calcium oxalate deposits in dialysis patients.
In addition, some reports show that high doses of ascorbic acid (oral or IV) can cause calcium oxalate deposits, calcium oxalate crystalluria (in patients predisposed to increased crystal aggregation), tubulointerstitial nephropathy and acute renal failure (result of calcium oxalate crystals).

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Acetylsalicylic acid

Acetylsalicylic acid belongs to the class of acid-forming nonsteroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on the 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. with colds or flu, to lower temperatures 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. To this end, doses of 75 to 300 mg daily are used for various cardiovascular indications.

Ascorbic acid

The water-soluble vitamin ascorbic acid is part of a protective system of the body against oxygen radicals and other oxidants of endogenous and exogenous origin which also play an important role in the inflammatory process and in leukocyte function. Both *in vitro* and *ex vivo* experiments indicate that ascorbic acid has a positive effect on the leukocytic immune response in humans.
Ascorbic acid is essential for the synthesis of intracellular substances (muco-polysaccharides) which, together with the collagen fibres, are responsible for sealing the capillary walls.

Clinical studies have yielded evidence that using acetylsalicylic acid and ascorbic acid in combination provides protection against acetylsalicylic acid-induced gastric lesions and oxidative stress.

5.2 Pharmacokinetic properties

Acetylsalicylic acid is absorbed rapidly and completely from the gastrointestinal tract after oral administration. Acetylsalicylic acid is converted into its main metabolite salicylic acid during and after absorption. Peak plasma levels of acetylsalicylic acid and salicylic acid are achieved after 15-30 min. and 0.72-2 h respectively. The given durations depend on the pharmaceutical form. The addition of ascorbic acid leads to little or no variability in the PK parameters of acetylsalicylic acid.
Both acetylsalicylic acid and salicylic acid are bound largely to plasma proteins and rapidly distributed to all parts of the body. Salicylic acid passes into breast milk and crosses the placental barrier.
Salicylic acid is eliminated predominantly by metabolism in the liver; the metabolites are salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid.
The elimination kinetics of salicylic acid are dose-dependent, as metabolism is limited by the liver enzymes' capacity. The elimination half-life therefore varies and lies between 2 and 3 h at low doses and up to about 15 h at high doses. Salicylic acid and its metabolites are excreted primarily via the renal route.

Absorption of ascorbic acid (concentration-dependent in the proximal section of the small intestine) is limited. As the single dose increases, bioavailability decreases (60-75% after 1 g, 16% after 12 g). The unabsorbed fraction is broken down by the flora in the large bowel, mainly into CO_2 and organic acids. In healthy adults, the maximum metabolic turnover of 40-50 mg/day is reached at plasma concentrations of 0.8-1.0 mg/dL. Total turnover is in the range of 1 mg/day. At extremely high oral doses, plasma concentrations of up to 4.2 mg/dL are achievable in the short-term after three hours. Under these conditions, ascorbic acid is excreted predominantly (>80%) unchanged in the urine (half-life 2.9 hours). The pool in the body following regular administration of approximately 180 mg/day is at least 1.5 g. Significant accumulation occurs in the pituitary gland, adrenal glands, eye lenses and white blood cells.

5.3 Preclinical safety data

The preclinical safety profile of acetylsalicylic acid is well documented. In animal tests salicylates have caused kidney damage and gastrointestinal ulcers. Acetylsalicylic acid has been adequately tested for mutagenicity and carcinogenicity; no relevant evidence of a mutagenic or carcinogenic potential was found.

Salicylates have been found to have teratogenic effects in a number of animal species. There have been reports of implantation disturbances, embryotoxic and foetotoxic effects, and disturbances of learning capacity in the young offspring after prenatal exposure.
Non-clinical studies of acute toxicity, repeated dose toxicity and toxicity to reproduction and development revealed no special hazard for humans.
Isolated positive findings in *in vitro* genotoxicity studies have not been confirmed in *in vivo* studies and are not considered to be clinically relevant. 2-year carcinogenicity studies with F344/N rats and B6C3F1 mice yielded no evidence of carcinogenic potential for ascorbic acid.

6 Pharmaceutical data

6.1 List of excipients

Sodium hydrogen citrate, sodium hydrogen carbonate, citric acid, sodium carbonate.

6.2 Incompatibilities

None.

6.3 Shelf-life

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

6.4 Special storage instructions

Store below 25°C.

6.5 Type and contents of container

Blister.
Original pack contains 10, 20 effervescent tablets.
Not all pack sizes may be marketed.

6.6 Special precaution for disposal and other handling

No special requirements.

7. Product license holder

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

8. Registration number

057 86 24955 00

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