SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aspirin C

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One effervescent tablet contains:

Acetylsalicylic acid	400 mg
Ascorbic acid	240 mg

3. PHARMACEUTICAL FORM

Effervescent tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Mild to moderate painful symptoms such as headache, dental pain, period pain, sore throat associated with colds, muscular and joint pain.
- Fever during infectious inflammatory disease.

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

4.2 Posology and Method of Administration

*Adults and children over 15 years**:***

1-2 effervescent tablets as single dose. A maximum daily dose of 6 tablets must not be exceeded.

The single dose can be taken at intervals of 4 to 8 hours if necessary, up to a maximum of 3 doses a day.

Method of administration:

For oral use. The effervescent tablet is to be dissolved in a glass of water before taking. Do not take on an empty stomach.

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

4.3 Contraindications

- Hypersensitivity to salicylates or to any other components of the product,
- History of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory drugs,
- Acute gastrointestinal ulcers,
- Hemorrhagic diathesis,
- Severe liver and kidney failure,
- Severe, non-stabilized heart failure,
- Hemophilia,
- Thrombocytopenia,
- Concomitant treatment with methotrexate at doses of 15 mg/week or more,
- Last trimester of pregnancy,
- Nephrolithiasis or history of nephrolithiasis,

- Hyperoxaluria,
- Hemochromatosis.

4.4 Special Warnings and Precautions for Use

Concerning the use of acetylsalicylic acid

Acetylsalicylic acid should be used with particular caution in the following cases:

- Hypersensitivity to other analgesics / anti-inflammatory or antirheumatic drugs or other allergenic substances,
- Allergies (e.g. cutaneous reactions, itching, urticaria), asthma, hay fever, nasal polyps or chronic respiratory diseases,
- Concomitant treatment with anticoagulants,
- History of gastro-intestinal ulcers or history of gastro-intestinal bleedings,
- Impaired hepatic function,
- 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,
- Before a surgical operation (including minor surgeries, e.g. dental extractions), as it may lead to an increased bleeding tendency,
- 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.

Concerning the use of ascorbic acid

Ascorbic acid should be used with particular caution in the following cases:

- Predisposition for calcium oxalate urolithiasis,
- Iron storage diseases (thalassemia, hemochromatosis).

<u>Other precautions</u>

An effervescent tablet contains 20.3 mmol (466.4 mg) of sodium. This should be taken into consideration by patients on a controlled sodium (low sodium/salt) diet.
Prolonged use of analgesics may lead to the development of a headache, which, when treated with additional analgesics, may cause the headache to persist.
Regular use of analgesics may cause chronic kidney damage with a risk of renal failure (analgesic nephropathy). This risk is especially great when several different analgesics are taken concurrently.
At low doses, acetylsalicylic acid reduces the excretion of uric acid. This can possibly trigger gout attacks in predisposed patients.

Children and adolescents

Children and adolescents should take acetylsalicylic acid containing products for diseases accompanied by fever only when directed by a doctor, and if other therapeutic measures fail. Should persistent vomiting occur with such diseases, this may be a sign of Reye´s syndrome, a very rare but possibly life-threatening illness requiring immediate medical action.

4.5 Interactions with Other Medicinal Products and Other Forms of Interactions

Strengthening of action up to an increased risk of side effects:
Anticoagulants/Thrombolytics:
Acetylsalicylic acid may increase the risk of bleeding, if taken before the beginning of thrombolytic treatment. Therefore, attention should be paid to the signs of external or internal bleeding in patients planning to undergo treatment with thrombolytics.

Inhibitors of platelet aggregation, e.g. ticlopidine, clopidogrel:
Increased risk of bleeding.

Other non-steroidal analgesics/anti-inflammatory drugs (at dosages of 3 g acetylsalicylic acid per day and above):
Increased risk of ulcers and gastrointestinal bleeding.

Systemic glucocorticoids (with the exception of hydrocortisone as replacement therapy for Addison's disease):
Increased risk of gastrointestinal side effects.

Alcohol:
Increased risk of ulcers and gastrointestinal bleeding.

Digoxin:
Increased plasma concentration.

Antidiabetics:
Blood glucose level may lower.

Methotrexate:
Decreased excretion and displacement of methotrexate from its plasma protein binding by salicylates.

Valproic acid:
Displacement from protein binding by salicylate.

Selective Serotonin Re-uptake inhibitors (SSRIs):
Increased risk of gastrointestinal bleeding due to synergistic effects.

Lab Interactions
Because Vitamin C is a reducing agent (i.e. electron donor), it can cause chemical interference in laboratory tests that involve oxidation-reduction reactions, such as the analyses of glucose, creatinine, carbamazepine, uric acid in urine, serum and of occult blood in feaces.
Vitamin C may interfere with tests that measure urinary and blood glucose resulting in false readings, although it has no effect on blood glucose levels.

Weakening of effects:
- Diuretics (at dosages of 3 g acetylsalicylic acid per day and above);

- Angiotensin converting enzyme inhibitors (at dosages of 3 g acetylsalicylic acid per day and above);
- Uricosuric agents (e.g. probenecid, benzbromarone);
- Deferoxamine: Concurrent use with ascorbic acid may enhance tissue iron toxicity; especially in the heart, causing cardiac decompensation.

4.6 Pregnancy and Lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal 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-fetal 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. 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.

During the first and second trimester of pregnancy, acetyl salicylic acid should not be given unless clearly necessary. If acetyl salicylic 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. 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 entail the following risks:

for the fetus:

- cardiopulmonary toxicity (constriction/ premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydramnios.

for the mother and the neonate 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, acetyl salicylic 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 breastfeeding 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 Ability to Drive and Use Machinery

No effects on the ability to drive and use machinery have been observed.

4.8 Undesirable Effects

Blood and lymphatic system disorders:

Rare to very rare serious bleedings, such as cerebral hemorrhage (especially in patients with uncontrolled hypertension and/or on concomitant antihemostatic agents), which in single cases may be potentially life-threatening, have been reported.

Hemolysis and hemolytic anemia in patients with severe glucose-6-phosphate dehydrogenase deficiency.

Bleeding, e.g. nosebleeds, bleeding gums or skin bleeding, or bleeding of the genitourinary system with possibly prolongation of the bleeding time (see section 4.4). This effect can persist for 4 to 8 days after use.

Gastrointestinal system disorders:

Common:

Gastrointestinal disorders such as heartburn, diarrhea, 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 anemia.

Gastrointestinal inflammations.

Intestinal diaphragm disease with frequency not known (especially in long-term treatment).

Liver- and biliary disorders:

Very rare:

Increase of liver values.

Nervous system disorders:

Headache, dizziness, impaired hearing ability; tinnitus and mental confusion can 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 respiration tract, the gastrointestinal tract and the cardiovascular system, especially in asthmatics.

Possibly with: drop in blood pressure, attacks of dyspnea, rhinitis, nasal congestion, anaphylactic shock or angioneurotic edema.

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

Reporting of suspected adverse reactions after authorization of the medicinal product is important. lt allows continued monitoring of the benefit/risk balance of the medicinal product.

Adverse effects related to ascorbic acid.

The adverse effects listed below are based on "spontaneous reports", so that sorting according to frequency is not possible (frequency is not known).

Immune system disorders: hypersensitivity reactions, allergic reactions and anaphylactic shock.

Gastrointestinal disorders: diarrhea, nausea, vomiting, gastrointestinal pain, abdominal pain.

4.9 Overdose

Intoxication is more likely in elderly patients and, in particular, infants (therapeutic overdosage or accidental intoxication can be fatal in them).

Symptomatology:
Moderate intoxication:
Tinnitus, hearing disorders, diaphoresis, nausea, vomiting, headache and vertigo are reported in all cases of overdosage and can be eliminated by reducing the dose.

Severe intoxication:
Fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular shock, respiratory failure, severe hypoglycemia.

Therapeutic measures: hospitalization, gastric lavage, administration of activated carbon and evacuant.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Salicylic acid and derivatives. Acetylsalicylic acid, combinations excluding psycholeptics. ATC-Code: N02BA51.

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 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 the platelets. To this end, doses of 75 to 300 mg daily are used for various cardiovascular indications.

The water-soluble vitamin ascorbic acid is part of a protective system of the organism against oxygen radicals and other oxidants of endogenous and exogenous origin which also play a particular 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 the intracellular basic substance (muco-polysaccharides) which, together with the collagen fibers, is 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 stomach 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 10-20 minutes and 0.3-2 hours respectively.
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 metabolization 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 hours at low doses and up to about 15 hours 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/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 studies, salicylates have been shown to cause no further damage to organs except for kidney damage at high doses.
Acetylsalicylic acid has been investigated in detail regarding its mutagenic and

cancerogenic potential. The overall findings provided no relevant evidence of a mutagenic effect. The same applies to carcinogenicity studies.
Salicylates have shown teratogenic effects (such as cardiac or skeletal malformation, gastroschisis) in several animal species in animal studies.
Impaired implantation, embryotoxic and fetotoxic effects and impaired learning ability of offspring have been described after prenatal exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium dihydrogen citrate
Sodium hydrogen carbonate
Citric acid
Sodium carbonate (H_2O-free).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special Precautions for Storage

Do not store above 25 °C. Keep out of reach of children.

6.5 Nature and Contents of Container

2 effervescent tablets are sealed in strip made of foil 40 g/m² paper with 14 g/m² PE on 25 µm Al with 18 g/m² ionomere.
5 strips with package insert are placed in a carton.

6.6 Special Precautions for Disposal

OTC product.

7. MAH NAME AND ADDRESS

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