Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alka-Seltzer Effervescent Tablets Acetylsalicylic Acid (Aspirin) 324mg Sodium Hydrogen Carbonate 1744mg Citric Acid 965mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 324 mg acetylsalicylic acid (Aspirin), 965 mg citric acid and 1744 mg sodium hydrogen carbonate. The active ingredients in water become sodium citrate 1296 mg, sodium acetylsalicylate 364 mg and sodium bicarbonate 328 mg.

Excipient(s) with known effect:
Sodium 477 mg
Sodium benzoate (E 211) 0.013 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablets (Tablet)
White circular tablet – one face flat with bevelled edge; reverse embossed with the name Alka-Seltzer, and a rim.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For fast and effective symptomatic relief of mild to moderate pain including headache, migraine, neuralgia, toothache, sore throat, period pains, aches and pains.

Symptomatic relief of sprains, strains, rheumatic pain, sciatica, lumbago, fibrositis, muscular aches and pains, joint swelling and stiffness.

Symptomatic relief of influenza, feverishness, feverish colds.

4.2 Posology and method of administration

Posology
The dose in adults, elderly and children aged 16 years and over, is one or two tablets in water. The dose may be repeated every four hours, as required, with a maximum of eight tablets in 24 hours. Aspirin must not be taken for longer than 3-5 days without consulting a doctor.

Paediatric population
Do not give to children and adolescents aged under 16 years, except on medical advice, where the benefit outweighs the risk.

In case of accidental administration or use in children, see section "Special warnings and special precautions for use".

Method of administration
Alka-Seltzer tablets must always be dissolved in a glass of water prior to oral administration. The tablets dissolve more quickly in warm water. The tablets should preferably be taken after meals.

4.3 Contraindications

Alka-Seltzer must not be used in the following cases:

- hypersensitivity to acetylsalicylic acid or other salicylates, or to any of the excipients listed in section 6.1,

- a history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory drugs,
- acute gastrointestinal ulcers,
- haemorrhagic diathesis,
- severe renal failure,
- severe hepatic failure,
- severe cardiac failure,
- combination with methotrexate at doses of 15 mg/week or more (see interactions with other medicinal products and other forms of interaction),
- last trimester of pregnancy.

4.4 Special warnings and precautions for use

Alka-Seltzer should be used with particular caution in the following cases:

- hypersensitivity to analgesics / anti inflammatory agents / anti-rheumatics and in the presence of other allergies,
- history of gastro-intestinal ulcers including chronic or recurrent ulcer disease or history of gastro-intestinal bleedings,
- with concomitant treatment with anticoagulants (see interactions with other medicinal products and other forms of interaction),
- 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,
- impaired hepatic function.

Acetylsalicylic acid may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are pre-existing asthma, hay fever, nasal polyps, or chronic respiratory disease. This also applies to patients exhibiting allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances.

Due to its inhibitory effect on platelet aggregation which persists for several days after administration, acetylsalicylic acid may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental extractions).

At low doses, acetylsalicylic acid reduces the excretion of uric acid. This can possibly trigger gout attacks in predisposed patients.

In patients suffering from severe glucose-6-phosphate dehydrogenase (G6PD) deficiency, acetylsalicylic acid may induce hemolysis or hemolytic anaemia. Factors that may increase the risk of hemolysis are high dosage, fever, or acute infections, for example.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs. Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver and can be fatal. For this reason aspirin should not be given to children and adolescents aged under 16 years unless specifically indicated.

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

Prolonged use, except under medical supervision, can be harmful.

If symptoms persist, the physician should be consulted.

This medicinal product contains 477 mg sodium per tablet, equivalent to 23.85% of the WHO recommended maximum daily intake of 2 g of sodium for an adult. The maximum daily dose of this product is equivalent to 190.80% of the WHO recommended maximum daily intake for sodium. Alka-Seltzer Effervescent Tablets are considered high in sodium. This should be particularly taken into account for those on a low salt diet.
This medicine contains 0.013 mg Sodium benzoate (E 211) in each effervescent tablet.

4.5 Interaction with other medicinal products and other forms of interaction

Contra-indicated Interactions:

Methotrexate used at doses of 15 mg/week or more:
Increased hematological toxicity of methotrexate (decreased renal clearance of methotrexate by anti-inflammatory agents in general and displacement of methotrexate from its plasma protein binding by salicylates) (see Section 4.3 Contraindications).

Combinations requiring precautions for use:

Methotrexate, used at doses of less than 15 mg/week:
Increased haematological toxicity of methotrexate (decreased renal clearance of methotrexate by anti-inflammatory agents in general and displacement of methotrexate from its plasma protein binding by salicylates).

Anticoagulants, thrombolytics/other inhibitors of platelet aggregation/hemostasis:
Increased risk of bleeding.

Other non-steroidal anti-inflammatory drugs with salicylates at higher doses:
Increased risk of ulcers and gastrointestinal bleeding due to synergistic effect.

Ibuprofen:
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin 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 from regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Selective Serotonin Re-uptake Inhibitors (SSRIs):
Increased risk of upper gastrointestinal bleeding due to possibly synergistic effect.

Digoxin:
Plasma concentrations of digoxin are increased due to a decrease in renal excretion.

Antidiabetics, e.g. insulin, sulphonylureas:
Increased hypoglycemic effect by high doses of acetylsalicylic acid via hypoglycemic action of acetylsalicylic acid and displacement of sulfonylurea from its plasma protein binding.

Diuretics in combination with acetylsalicylic acid:
Decreased glomerular filtration via decreased renal prostaglandin synthesis.

Systemic glucocorticoids, except hydrocortisone used as replacement therapy in Addison's disease:
Decreased blood salicylate levels during corticosteroid treatment and risk of salicylate overdose after this treatment is stopped via increased elimination of salicylates by corticosteroids.

Angiotensin converting enzyme inhibitors (ACE) in combination with acetylsalicylic acid:
Decreased glomerular filtration via inhibition of vasodilatory prostaglandins. Further-more, decreased antihypertensive effect.

Valproic acid:
Increased toxicity of valproic acid due to displacement from protein binding sites.

Alcohol:
Increased damage to gastro-intestinal mucosa and prolonged bleeding time due to additive effects of acetylsalicylic acid and alcohol.

Uricosurics such as benzbromarone, probenecid:
Decreased uricosuric effect (competition of renal tubular uric acid elimination).

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fœtal development. Data from epidemiological studies raise concern about an increased risk of miscarriage and of malformations after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. Available data do not support any association between intake of acetylsalicylic acid and an increased risk for miscarriage. For acetylsalicylic acid the available epidemiological data regarding malformation are not consistent, but an increased risk of gastroschisis could not be excluded. A prospective study with exposure in early pregnancy (1st-4th month) of about 14,800 mother-child pairs has not yielded any association with an elevated rate of malformations.

Animal studies have shown reproductive toxicity *(see Section 5.3 Preclinical Safety Data)*.

During the first and second trimester of pregnancy, acetylsalicylic acid containing drugs should not be given unless clearly necessary.

If acetylsalicylic acid containing drugs are 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;

Prostaglandin synthesis inhibitors may expose both the mother and the child, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even after very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour

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

Breast-feeding

Salicylate 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. However, on regular use or on intake of high doses, breast feeding should be discontinued early.

Fertility
There is some evidence that drugs 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

None known.

4.8 Undesirable effects

The listed adverse drug reactions are based on spontaneous reports, thus an organization according to CIOMS III categories of frequency is not possible.

Blood and lymphatic system disorders
Haemorrhagic anaemia, iron deficiency anaemia with the respective laboratory and clinical signs and symptoms. Haemolysis, haemolytic anaemia

Cardiac disorders
Cardio-respiratory distress

Ear and labyrinth disorders
Tinnitus

Gastrointestinal disorders
Dyspepsia, gastrointestinal pain, abdominal pain, gingival bleeding, gastrointestinal inflammation, gastrointestinal ulcer, gastrointestinal ulcer haemorrhage, gastrointestinal ulcer perforation with the respective laboratory and clinical signs and symptoms, intestinal diaphragm disease

Hepatobiliary disorders
Liver disorder, transaminases increased

Immune system disorders
Hypersensitivity, drug hypersensitivity, allergic edema and angioedema, anaphylactic reaction, anaphylactic shock with respective laboratory and clinical manifestations

Injury, poisoning and procedural complications
See overdose section

Nervous system disorders
Cerebral and intracranial hemorrhage, dizziness

Renal and urinary disorders
Urogenital haemorrhage, renal impairment, renal failure acute

Respiratory, thoracic and mediastinal disorders
Epistaxis, analgesic asthma syndrome, rhinitis, nasal congestion

Skin and subcutaneous tissue disorders
Rash, urticaria, pruritus

Vascular disorders
Haemorrhage, operative haemorrhage, haematoma, muscle haemorrhage

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

Salicylate toxicity (> 100 mg/kg/day over 2 days may produce toxicity) may result from chronic, therapeutically acquired, intoxication, and from, potentially life-threatening, acute intoxications (overdose), ranging from accidental ingestions in children to incidental intoxications.

Chronic salicylate poisoning can be insidious as signs and symptoms are non-specific. Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses. Symptoms include dizziness, vertigo, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage. Tinnitus can occur at plasma concentrations of 150 to 300 micrograms/mL. More serious adverse events occur at concentrations above 300 micrograms/mL.

The principal feature of acute intoxication is severe disturbance of the acid-base balance, which may vary with age and severity of intoxication. The most common presentation for a child is metabolic acidosis. The severity of poisoning cannot be estimated from plasma concentration alone. Absorption of acetylsalicylic acid can be delayed due to reduced gastric emptying, formation of concretions in the stomach, or as a result of ingestion of enteric-coated preparations. Management of acetylsalicylic acid intoxication is determined by its extent, stage and clinical symptoms and according to standard poisoning management techniques. Predominant measures should be the accelerated excretion of the drug as well as the restoration of the electrolyte and acid-base metabolism.

Due to the complex pathophysiologic effects of salicylate poisoning, signs and symptoms/investigational findings may include:

SIGNS AND SYMPTOMS	**INVESTIGATIONAL FINDINGS**	**THERAPEUTIC MEASURES**
Mild to moderate intoxication		Gastric lavage, repeated administration of activated charcoal, forced alkaline diuresis
Tachypnoea, hyperventilation, respiratory alkalosis	Alkalemia, alkaluria	Fluid and electrolyte management
Diaphoresis		
Nausea, vomiting		
Moderate to severe intoxication		Gastric lavage, repeated administration of activated charcoal, forced alkaline diuresis, hemodialysis in severe cases
Respiratory alkalosis with compensatory metabolic acidosis,	Acidemia, aciduria	Fluid and electrolyte management
Hyperpyrexia		Fluid and electrolyte management
Respiratory: ranging from hyperventilation, non-cardiogenic pulmonary edema to respiratory arrest, asphyxation		
Cardiovascular: ranging from dysarrhythmias, hypotension to cardiovascular arrest	e.g. Blood pressure, ECG alteration	
Fluid and electrolyte loss: dehydration, oliguria to renal failure	e.g. Hypokalemia, hypernatremia, hyponatremia, altered renal function	Fluid and electrolyte management
Impaired	Hyperglycemia,	

glucose metabolism, Ketosis	hypoglycemia (especially in children) Increased ketone levels	
Tinnitus, deafness		
Gastrointestinal: GI bleeding		
Hematologic: ranging from platelet inhibition to coagulopathy	e.g. PT prolongation, hypoprothrombinemia	
Neurologic: Toxic encephalopathy and CNS depression with manifestations ranging from lethargy, confusion to coma and seizures		

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 nonsteroidal 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.

Acetylsalicylic acid in oral doses of in general 0.3 to 1.0 g is used for the relief of pain and in minor febrile conditions, such as colds or influenza, for the reduction of temperature and relief of the joint and muscle pains.

It is also used in acute and chronic inflammatory disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

Acetylsalicylic acid also inhibits platelet aggregation by blocking thromboxane A_2 synthesis in platelets. Thus, it is used for various vascular indications at doses of in general 75 to 300 mg daily.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of ASA 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 from regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

Following oral administration, acetylsalicylic acid is absorbed rapidly and completely from the gastro-intestinal tract. During and after absorption acetylsalicylic acid is converted into its main active metabolite, salicylic acid. Maximal plasma levels are reached after 10 - 20 minutes for acetylsalicylic acid and after 0.3-2 hours for salicylic acid, respectively.

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.

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 caused kidney damage at high dosages but no other organic lesions. 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 and a number of different species. 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

Povidone
Dimeticone
Calcium silicate
Docusate sodium
Sodium benzoate (E211)
Sodium saccharin
Natural and artificial lemon flavour
Natural and artificial lime flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf-life of the product as packaged for sale is 3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Aluminium foil pouches, each containing two tablets. Available in pack sizes of 10 or 20 tablets.

Primary packaging material: composite aluminium foil laminate consisting of 40g/m^2 paper, 14g/m^2 polyethylene and 25 microM aluminium foil with 18g/m^2 surlyn heat-seal.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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