

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aspirin 300mg Effervescent tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Acetylsalicylic Acid (aspirin) 300.00 mg.

Excipients with known effect:

Sodium 150 mg (6.5 mmol) per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent Tablet

White, circular tablets, with a scoreline on one face (to allow breaking for ease of swallowing) and the other side plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The symptomatic relief of influenza, feverishness, feverish colds, and of lumbago, sciatica, fibrositis, rheumatic pains, muscular aches and pains.

The relief of mild to moderate pain including headache, migraine, toothache, period pains, sore throat, neuralgia, aches and pains.

4.2 Posology and method of administration

Posology

Adults:

2 tablets in half a glass of water every 4 hours as required. Do not exceed 13 tablets in 24 hours unless directed by a doctor. Aspirin must not be taken for longer than 3-5 days without consulting your doctor. If symptoms persist consult your doctor. Medicines should not be taken in pregnancy without consulting your doctor.

Elderly:

As for adults.

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 warning and precautions for use".

Method of administration

Oral.

Tablets must be dissolved in water. The tablets should preferably be taken after meals.

4.3 Contraindications

Aspirin 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 15mg/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

Aspirin 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 haemolysis or haemolytic anaemia. Factors that may increase the risk of haemolysis 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 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 150 mg sodium per tablet, equivalent to 7.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 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) (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/haemostasis:

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 for 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 hypoglycaemic effect by high doses of acetylsalicylic acid via hypoglycaemic 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).

From the 20th week of pregnancy onward, acetylsalicylic acid containing drug use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, 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.

Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to acetylsalicylic acid containing drugs for several days from gestational week 20 onward. Acetylsalicylic acid containing drugs should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above).

Prostaglandin synthesis inhibitors may expose 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 (see sections 4.3 and 5.3).

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 stated.

4.8 Undesirable effects

The listed adverse drug reactions are based on spontaneous reports, thus an organisation 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 haemorrhage, gastrointestinal ulcer haemorrhage and 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 haemorrhage, dizziness

Renal and urinary disorders

Urogenital haemorrhage, renal impairment, renal failure acute

Respiratory, thoracic and mediastinal disorders

Epistaxis, analgaesic 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 principle 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 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	Alkalaemia, alkaluria	Fluid and electrolyte management
Diaphoresis		
Nausea, vomiting		
Moderate to severe intoxication		Gastric lavage, repeated administration of activated charcoal, forced alkaline diuresis, haemodialysis in severe cases
Respiratory alkalosis with compensatory metabolic acidosis,	Acidaemia, aciduria	Fluid and electrolyte management
Hyperpyrexia		Fluid and electrolyte management
Respiratory: ranging from hyperventilation, non-cardiogenic pulmonary oedema to respiratory arrest, asphyxiation		
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. Hypokalaemia, hypernatraemia, hyponatraemia, altered renal function	Fluid and electrolyte management
Impaired glucose metabolism, ketosis	Hyperglycaemia, hypoglycaemia (especially in children) Increased ketone levels	
Tinnitus, deafness		
Gastrointestinal: GI bleeding		

Haematologic: ranging from platelet inhibition to coagulopathy	e.g. PT prolongation, hypoprothrombina	
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 A₂ 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 for 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 foetotoxic effects and impairment of learning ability in the offspring after prenatal exposure have been described.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Malic acid
Povidone
Docusate sodium
Sodium carbonate
Sodium hydrogen carbonate
Saccharin sodium
Citric acid
Lemon flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

Tablets are packed in aluminium foil/polythene blister strips which are packed into cardboard cartons to contain 18 or 30 tablets.

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

Bayer Limited
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Co Dublin
A94 H2K7
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8 MARKETING AUTHORISATION NUMBER

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