SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alka-Seltzer XS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains acetylsalicylic acid (aspirin) 267 mg, paracetamol 133 mg and caffeine 40 mg.

Excipient with known effect: Sodium 472 mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For rapid relief of pain including migraine, headache, period pains, neuralgia, toothache, sore throat.

Symptomatic relief of rheumatic pain, sciatica, lumbago, fibrositis, muscular aches and pains.

Symptomatic relief of influenza, feverishness, feverish colds.

4.2 Posology and method of administration

Alka-Seltzer XS is for oral ingestion after dissolution in water. It dissolves more quickly in warm water.

Adults: Two tablets in water. This dose may be repeated every four hours up to four doses in 24 hours but the dosage should not be continued for more than three days without consulting a doctor. Do not exceed the stated dose.

Do not give to children under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).

4.3 Contraindications

Alka-Seltzer XS should not be administered to patients:

- with known hypersensitivity (e.g. bronchospasm, rhinitis, urticaria) to acetylsalicylic acid or other salicylates, paracetamol, caffeine or to any other components of the product
- with a history of hypersensitivity reactions (e.g. asthma, rhinitis, urticaria) induced by the administration of salicylates, or substances with similar actions, notably non-steroidal anti-inflammatory drugs.
- with active or a history of peptic ulcers.
- with haemorrhagic diathesis such as haemophilia.
- with severe renal failure.
- with severe hepatic failure.
- with severe cardiac failure.
- in the third trimester of pregnancy (see section 4.6).
- who are breastfeeding.
- receiving doses of methotrexate at 15mg/week or greater (see section 4.5).

4.4 Special warnings and precautions for use

Caution should be exercised in the following cases:

- hypersensitivity to analgesics / anti-inflammatory agents / anti-rheumatics and in the presence of other allergies,
- with a history of gastrointestinal disorders,
- with concomitant treatment with anticoagulants (e.g. coumarin derivatives or heparin) (see section 4.5),
- 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 haemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment,
- patients with impaired hepatic function. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease,
- in the first or second trimester of pregnancy (see section 4.6)

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.

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 aged under 16 years unless specifically indicated (e.g. Kawasaki's disease).

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.

Alka-Seltzer XS contains paracetamol and so other paracetamol-containing preparations should be avoided. The maximum dose of paracetamol for adults is 4g daily.

Do not exceed the recommended dose. If symptoms persist consult your doctor. Keep out of the reach of children.

Leaflet warning: Talk to a doctor at once if you take too much of this medicine, even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage.

Label warning: Do not take anything else containing paracetamol while taking this medicine. Talk to a doctor at once if you take too much of this medicine, even if you feel well.

This medicinal product contains 472 mg sodium per tablet, equivalent to 23.6% 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

Acetylsalicylic acid:

Contraindicated 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.

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 sulphonylurea from its plasma protein binding.

Diuretics in combination with acetylsalicylic acid at higher doses:
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.

Corticosteroids:
Potentiate the risk of gastro-intestinal bleeding during concomitant therapy with corticosteroids.

Angiotensin converting enzyme inhibitors (ACE) in combination with acetyl-salicylic acid at higher doses:
Decreased glomerular filtration via inhibition of vasodilatory prostaglandins. Furthermore, decreased antihypertensive effect.

Valproic acid and Phenytoin:

Increased toxicity of valproic acid due to displacement from protein binding sites. Phenytoin is also extensively bound to plasma proteins therefore it can be displaced by acetylsalicylic acid from plasma binding.

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).

Paracetamol

The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.

4.6 Fertility, pregnancy and lactation

Alka-Seltzer XS should not be taken by pregnant or nursing women unless directed by a doctor.

Pregnancy

Acetylsalicylic acid:
Doses of 500 mg/day and above:
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.
During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic 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.

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;

the mother and the neonate, at the end of pregnancy, to:

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

Consequently, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

Paracetamol:
Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, patients should follow the advice of their doctor regarding its use.

Breastfeeding

Acetylsalicylic acid:
Breastfeeding is contraindicated at high doses because of the theoretical risk of affecting clotting mechanisms.
The intake of acetylsalicylic acid by breastfeeding patients should be avoided as there is a risk of Reye's syndrome. Regular use of high doses could impair platelet function and produce hypoprothrombinaemia in the infant if neonatal vitamin K stores are low.

Paracetamol:
Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data on paracetamol does not contraindicate it for breastfeeding.

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.

4.8 Undesirable effects

Acetylsalicylic acid:

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
Increased risk of bleeding (due to effect on platelet aggregation). In the context of bleeding: haemorrhagic anaemia, iron deficiency anaemia with the respective laboratory and clinical signs and symptoms. In the context of glucose-6-phosphate dehydrogenase (G6PD) deficiency: haemolysis, haemolytic anaemia

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

Nervous system disorders
Cerebral and intracranial haemorrhage, dizziness

Ear and labyrinth disorders
Tinnitus

Cardiac disorders
In the context of severe allergic reactions: cardio-respiratory distress

Vascular disorders
Haemorrhage, operative haemorrhage, haematoma, muscle haemorrhage

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

Gastrointestinal disorders
Dyspepsia, gastrointestinal pain, abdominal pain, gingival bleeding, gastrointestinal inflammation, gastrointestinal ulcer, gastrointestinal haemorrhage, gastrointestinal ulcer perforation with the respective laboratory and clinical signs and symptoms, nausea, diarrhoea, vomiting

Hepatobiliary disorders
Liver disorder, transaminases increased

Skin and subcutaneous tissue disorders
Rash, urticaria, pruritus, severe skin reactions

Renal and urinary disorders
Impaired renal function

Injury, poisoning and procedural complications
See overdose section

Paracetamol:

Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur.

Very rare cases of serious skin reactions have been reported.

There have been reports of blood dyscrasis including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Paracetamol

Liver damage is possible in adults who have taken 10g or more of paracetamol.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention and any patient who had ingested around 7.5g or more of paracetamol in the preceding 4 hours should undergo gastric lavage. Administration of oral methionine or intravenous N-acetylcysteine which may have a beneficial effect up to at least 48 hours after the overdose, may be required. General supportive measures must be available.

Acetylsalicylic acid

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Symptoms

Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory

rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of four years. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Management

Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under ten years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The therapeutic uses of Alka-Seltzer XS are based on the following pharmacological properties of the active ingredients:

Acetylsalicylate	- analgesic, antipyretic and anti-inflammatory.
Paracetamol	- analgesic, antipyretic.
Caffeine	- central nervous system stimulant.

The buffer converts acetylsalicylic acid to sodium acetylsalicylate and promotes gastric emptying.

5.2 Pharmacokinetic properties

Acetylsalicylate is rapidly absorbed from the small intestine after oral ingestion of Alka-Seltzer XS and rapidly distributed to all body tissues.

Acetylsalicylate is hydrolysed to its active primary metabolite salicylic acid and completely excreted in the urine, principally as glucoronic acid and glycine conjugates of salicylic acid, but also as salicylic acid itself. Salicylates are extensively bound to plasma proteins. Peak plasma levels occur at approximately 20 minutes. Following administration of acetylsalicylic acid, salicylic acid can be detected in breast milk, cerebral spinal fluid and synovial fluid. The substance crosses the placenta.

Paracetamol is rapidly absorbed from the upper gastrointestinal tract after oral administration of Alka-Seltzer XS, with the small intestine being an important site of absorption. Peak plasma concentration occurs about 30 minutes to 2 hours after ingestion. It is rapidly distributed throughout the body and is primarily metabolised in the liver with excretion via the kidney. Elimination half-life varies from about 1 to 4 hours. Paracetamol crosses the placental barrier and is present in breast milk.

Caffeine is readily absorbed after oral administration and passes readily into the central nervous system. Excretion is renal.

5.3 Preclinical safety data

Acetylsalicylic acid

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.

Paracetamol

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric Acid

Sodium Hydrogen Carbonate

6.2 Incompatibilities

None known.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Laminated paper/polyethylene/aluminium surlyn heat sealed foil :

Do not store above 25^{o}C. Store in the original package.

Laminated aluminium/polyethylene surlyn heat sealed foil:

Do not store above 25^{o}C. Store in the original package.

6.5 Nature and contents of container

Laminated paper/polyethylene/aluminium surlyn heat sealed foil, or laminated aluminium/polyethylene surlyn heat sealed foil.

Aluminium foil pouches containing one or two tablets. Pack sizes available are 2, 10, 12, 20, and 30 tablets.

6.6 Special precautions for disposal

None applicable.

7 MARKETING AUTHORISATION HOLDER

Bayer plc
400 South Oak Way
Reading
RG2 6AD

8 MARKETING AUTHORISATION NUMBER(S)

PL 00010/0510

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st June 2006

Date of last renewal:

10 DATE OF REVISION OF THE TEXT

17/09/2024