Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aspirin Migraine Effervescent Tablets 500 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains acetylsalicylic acid 500 mg.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Effervescent tablets
White, round, flat effervescent tablets with Bayer cross embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the symptomatic relief of headache associated with migraine.

4.2 Posology and method of administration

Adults:
1,000 mg as single dose (corresponding to two effervescent tablets).

If the attack persists the dose may be repeated at intervals of 4 - 8 hours.
A maximum daily dose of 3 g (six tablets) must not be exceeded.

Aspirin Migraine tablets must not be taken for more than 3 days without consulting a physician. If migraine attacks occur frequently, if frequency of attacks increase or if symptoms persist, a physician should be consulted and an alternative treatment should be considered.

CHILDREN:
The use of Aspirin Migraine tablets is not recommended in children as no studies have included this population.

Aspirin Migraine tablets must be dissolved in a glass of water before taking.

4.3 Contraindications

- Active peptic ulcers;
- Haemorrhagic diathesis;
- Hypersensitivity to acetylsalicylic acid, to other salicylates, or to any other components of the product;
- A history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory drugs;
- Severe hepatic failure;
- Severe renal failure;

- Severe uncontrolled 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

- Concomitant treatment with anticoagulants;

- History of gastro-intestinal ulcers including chronic or recurrent ulcer disease or history of gastro-intestinal bleedings;

- Impaired renal function;

- Impaired hepatic function;

- Hypersensitivity to anti-inflammatory or antirheumatic drugs or other allergens.

Medicinal products containing acetylsalicylic acid should be used in children and adolescents with febrile diseases only after careful risk-benefit evaluation because of the possibility of Reye's syndrome, a rare but serious illness.

Acetylsalicylic acid may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are present bronchial asthma, hay fever, nasal polyps, or chronic respiratory disease.

This applies also for patients showing allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances.

Due to its inhibitory effect on platelet aggregation 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 trigger gout in patients who already tend to have a low uric acid excretion.

Chronic intake of analgesics may cause headache which can lead to renewed dosing and thus to a continuation of headache.

Habitual use of analgesics (particularly combinations of different analgesic drugs) may permanently damage the kidneys (analgesic nephropathy).

The product contains 1086 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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, e.g. coumarin, heparin:
Increased risk of bleeding via inhibition of platelet function, damage to gastroduodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites.

- Other non-steroidal anti-inflammatory drugs with salicylates at high doses (≥3g/day):
Increased risk of ulcers and gastrointestinal bleeding due to synergistic effect.

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

- 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.

- Thrombolytics / Other antiplatelet agents, e.g. ticlopidine:
Increased risk of bleeding.

- Diuretics in combination with acetylsalicylic acid at doses of 3g/day or more:
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):
At doses of 3g/day and more, decreased glomerular filtration via inhibition of vasodilator prostaglandins. Furthermore, 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.

4.6 Pregnancy and lactation

Pregnancy

Animal studies have revealed evidence of a teratogenic effect of acetylsalicylic acid.

First and second trimesters:

- Acetylsalicylic acid as occasional treatment:
Epidemiological study results appear to rule out any particular malformative effect of acetylsalicylic acid;

- Acetylsalicylic acid as chronic treatment:
Current data are numerically insufficient to evaluate any possible malformative effect of acetylsalicylic acid taken as chronic treatment at more than 150 mg/day.

Consequently,
- Acetylsalicylic acid can be prescribed if necessary as occasional treatment,
- As a precautionary measure, it is preferable not to use acetylsalicylic acid as chronic treatment at more than 150 mg/day.

Third trimester:

Acetylsalicylic acid at ≥ 500 mg per dose and per day, as other prostaglandin synthesis inhibitors, may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, potentially to the point of renal failure with oligo-hydramnios;
- Mother and baby, at the end of pregnancy, to possible lengthening of bleeding time. This anti-aggregant effect may occur even at very low doses.

Consequently, apart from extremely limited cardiologic and obstetric uses which justify a medical advice and a specialist monitoring, all medicines containing acetylsalicylic acid are contraindicated during the last 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. However, on regular use or on intake of high doses, breast feeding should be discontinued early.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Gastrointestinal effects:
Abdominal pain, heartburn, nausea, vomiting.
Evident (hematemesis, melena) or occult gastro-intestinal bleeding which may cause iron deficiency anaemia. Such bleeding is commoner when the dosage is higher.
Gastro-duodenal ulcer and perforation.

Effects on the central nervous system:
Headache, vertigo, feelings of impaired hearing, tinnitus, which are usually indicative of overdose.

Haematological effects:
Bleeding syndromes (epistaxis, gingival bleeding, purpura, etc.) with prolonged bleeding time. This action may persist for 4 to 8 days after acetylsalicylic acid is stopped. It may result in the risk of bleeding during surgery.

Hypersensitivity reactions:.
Urticaria, skin reactions, anaphylactic reactions, asthma, Quincke oedema.

4.9 Overdose

Poisoning must be feared in the elderly and above all in young children (therapeutic overdose or frequent accidental poisoning) in whom it may be fatal.

Symptomatology:

Moderate poisoning:
tinnitus, feeling of impaired hearing, headache, vertigo and mental confusion are observed in case of overdose and can be controlled by a dosage reduction.

Severe poisoning:
fever, hyperventilation, ketosis, respiratory alkalosis, metabolic acidosis, coma, cardiovascular shock, respiratory failure, severe hypoglycaemia.

Emergency management:

Immediate transfer to hospital specialist unit, gastric lavage, administration of activated charcoal, check of acid-base balance, alkaline diuresis so as to obtain a urine pH between 7.5 and 8, forced alkaline diuresis should be considered when the plasma salicylate concentration is greater than: 500 mg/litre (3.6 mmol/litre) in adults or 300 mg/litre (2.2 mmol/litre) in children, possibility of hemodialysis in severe poisoning, fluid losses should be replaced, symptomatic treatment.

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 0.5 to 1.0 g is used for the relief of mild to moderate 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. Generally high doses of 4 to 8 g daily in divided doses are used for these disorders.

Acetylsalicylic acid also inhibits platelet aggregation by blocking thromboxane A_2 synthesis in platelets. Thus, it is used for various cardiovascular indications at doses of in general 75 to 100 mg daily. The use of Aspirin Migraine is not recommended for platelet aggregation inhibition.

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, resp.

Both acetylsalicylic acid and salicylic acid are extensively bound to plasma proteins and rapidly distributed to all body parts. Salicylic acid appears in breast milk and crosses the placenta.

Salicylic acid is mainly eliminated by hepatic metabolism; metabolites include salicyluric acid, salicyl phenolic glucuronide, salicyl acyl glucuronide, gentisic acid, and gentisuric acid.
The elimination kinetics of salicylic acid is dose-dependent, as the metabolism is limited by the capacity of liver enzymes. Thus, the elimination half-life varies between 2 to 3 hours after low doses 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 tests salicylates caused kidney damage but no other organic lesions.

Acetylsalicylic acid has been adequately tested for mutagenicity and carcinogenicity; no relevant evidence of a mutagenic or carcinogenic potential was found.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monosodium Citrate
Sodium Hydrogen Carbonate
Citric Acid, anhydrous
Sodium Carbonate, anhydrous

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.

6.5 Nature and contents of container

Strips (Paper/Polyethylene/Aluminium/Copolymer), each containing 2 effervescent tablets.
Strips are packed into cardboard outers in packs of 6x2/12x2 effervescent tablets.

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 plc
Trading as Bayer plc, Consumer Care Division
Bayer House
Strawberry Hill
Newbury
Berkshire RG14 1JA
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 21/51/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2001

Date of last renewal: 29 January 2003

10 DATE OF REVISION OF THE TEXT

January 2003