Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Aspirin 75mg Dispersible Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 75 mg acetylsalicylic acid (aspirin)

Excipients: also contains lactose 34.25mg per tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersible Tablet
White, circular, flat bevelled-edge uncoated tablets impressed with the word “C” and identifying letters “AY” on one face.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Aspirin has analgesic, antipyretic and anti-inflammatory actions and an antithrombotic effect through inhibition of platelet activation. This preparation is indicated for the prophylactic management of cardiovascular disease or myocardial infarction.

4.2 Posology and method of administration

The tablets should be dispersed in water before administration, and taken immediately.
Adults: The usual dose is 75 mg daily.
Elderly: NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. See also section 4.4. Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.
Do not give to children and adolescents aged under 16 years, except on medical advice, where the benefit outweighs the risk.
Undesirable effects may be minimised by using the shortest duration necessary to control symptoms (see section 4.4).

4.3 Contraindications

Aspirin should not be taken by patients with the following conditions:
- Known hypersensitivity to aspirin, other ingredients in the product, other salicylates or non-steroidal anti-inflammatory drugs (a patient may have developed anaphylaxis, angioedema, asthma, rhinitis or urticaria induced by aspirin or other NSAIDs).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Severe heart failure.

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Before commencing long-term aspirin therapy for the management of cardiovascular or cerebrovascular disease, patients should consult their doctor who can advise on the relative benefits versus the risks for the individual patient.
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.
Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration necessary to control symptoms (see section 4.2, GI and cardiovascular below). Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).
In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.
As NSAIDs can interfere with platelet function, they should be used with caution in patients with intercranial haemorrhage and bleeding diathesis.
The use of aspirin with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.
Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.
The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and 4.5).
Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.
Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as aspirin (see section 4.5).
When GI bleeding or ulceration occurs in patients receiving aspirin, the treatment should be withdrawn.
NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).
Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Aspirin should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
Cardiovascular and cerebrovascular effects
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for aspirin.
Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with aspirin after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).
Aspirin should be used with caution in patients with:

- allergic disease
- anaemia (may be exacerbated by GI blood loss)
- asthma (increased risk of bronchospastic sensitivity reactions)
- cardiac failure (conditions which predispose to fluid retention as NSAIDs may exacerbate this)
- dehydration
- dyspepsia

- glucose-6-phosphate dehydrogenase deficiency (aspirin rarely causes haemolytic anaemia)
- gout (serum urate may be increased)
- haemophilia or other haemorrhagic disorder (including thrombocytopenia) as there is an increased risk of bleeding
- nasal polyps associated with asthma (high risk of severe sensitivity reactions)
- surgery. Aspirin should be discontinued several days before scheduled surgery (including dental extractions)
- systemic lupus erythematosus and other connective tissue disorders (hepatic and renal function may be impaired in these conditions)

In patients with strokes, aspirin should not be given until the possibility of cerebral haemorrhage has been excluded.

4.5 Interaction with other medicinal products and other forms of interaction

The following drug interactions should be considered when prescribing aspirin:
It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

- Alcohol - may enhance gastro-intestinal side effect of aspirin.
- Analgesics - avoid concomitant administration of other salicylates or other NSAIDs (including topical formulations eg ibuprofen) as increased risk of side effects.
- Alkalizers of urine (eg carbonic anhydrase inhibitors such as acetazolamide, antacids, citrates eg sodium citrate) - increased excretion of aspirin.
- Anticoagulants - NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).
- Antiepileptic drugs (eg phenytoin, sodium valproate) - increased effect.
- Antihypertensives - reduced anti-hypertensive effect.
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).
- Corticosteroids eg hydrocortisone, prednisone - increased risk of gastro-intestinal bleeding or ulceration (see section 4.4).
- Diuretics: furosemide and acetazolamide (risk of toxic effects), spironolactone (antagonized diuretic action). All diuretics can cause nephrotoxicity.
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.
- Lithium: decreased elimination of lithium
- Oral hypoglycaemics eg glibenclamide, gliclazide - enhanced activity. Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia
- Methotrexate: decreased elimination of methotrexate, increased toxicity.
- Ciclosporin: increased risk of nephrotoxicity with NSAIDs.
- Other NSAIDs: avoid concomitant use of two or more NSAIDs.
- Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.
- Probenecid: reduction in metabolism and elimination of NSAID and metabolites.
- Mifepristone - avoid aspirin until 8-12 days after mifepristone.
- Metoclopramide and domperidone - increased rate of absorption of aspirin.
- Ototoxic medicine (eg vancomycin) - potential for ototoxicity increased. Hearing loss may occur and may progress to deafness even after discontinuation of the medication. Effects may be reversible but are usually permanent.
- Uricosurics (eg sulfinpyrazone) - effects of uricosurics reduced.
- Laboratory investigations - aspirin may interfere with some laboratory tests such as urine 5-hydroxyundoleacetic acid determinations and copper sulphate urine sugar tests.

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).

4.6 Fertility, pregnancy and lactation

Salicylates readily cross the placenta and have been shown to be teratogenic in animals. Although some studies and anecdotal reports have implicated aspirin in the formation of congenital abnormalities, most large studies have failed to find any significant risk or evidence of teratogenicity. Ingestion of aspirin during the last two weeks of pregnancy may increase the risk of foetal or neonatal haemorrhage.

Regular or high dose use of salicylates late in pregnancy may result in constriction or premature closing of the foetal ductus arteriosus, increased risk of still birth or neonatal death, decreased birth weight, prolonged labour, complicated deliveries and increased risk of maternal or foetal haemorrhage and possibly persistent pulmonary hypertension of newborn or kernicterus in jaundiced neonates. Pregnant women should be advised not to take aspirin in the last three months of pregnancy unless under medical supervision.
Aspirin is distributed in breast milk. Aspirin should be avoided while breastfeeding.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Adverse effects of aspirin treatment which have been reported include:

- Allergic reactions - rhinitis, urticaria, angioneurotic oedema and worsening of asthma. Aspirin may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions in susceptible individuals.
- Effects on GI system - the most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (se section 4.4). Nausea, vomiting, diarrhoea, flatulence constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.
- Effects on blood - anaemia, haemolytic anaemia, hypoprothrombinaemia, thrombocytopenia, aplastic anaemia, pancytopenia.
- Effects on sensory system - tinnitus.
- Effects on heart – oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.
- Effects on the skin – bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rare).
- Salicylism - mild chronic salicylate intoxication may occur after repeated administration of large doses. Symptoms include dizziness, tinnitus, deafness, sweating, nausea, vomiting, headache and mental confusion, and may be controlled by reducing the dose.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

4.9 Overdose

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (95.1 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 4 years. In children aged 4 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, thrombocytopenia, 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 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 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 10 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

ATC Code: N02B A01 Salicylic acid and derivatives.
Aspirin is an anti-inflammatory analgesic and antipyretic. It inhibits prostaglandin synthetase and platelet aggregation.

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 400 mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81 mg), 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 conclusion 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

Absorption
Acetylsalicylic acid is rapidly absorbed from the gastrointestinal tract. Following oral administration, the absorption of non-ionised acetylsalicylic acid will occur in the stomach and the intestine. Absorption is delayed by the presence of food and reduced in patients suffering from migraine. The rate of absorption is increased in patients who suffer from achlorhydria or in patients undergoing treatment with polysorbates or antacids. Peak serum concentration for acetylsalicylic acid is achieved within half an hour and within 1-2 hours for salicylic acid.

Distribution
Acetylsalicylic acid has a plasma protein binding of 80-90%. The distribution volume has been reported at 170 ml/kg bodyweight in adults. When the plasma concentration increases, the proteins' binding sites become saturated resulting in increased distribution volume. The salicylates are largely bound to plasma proteins and are rapidly distributed throughout the body. Salicylates are found in mother's milk and can cross the placenta barrier.

Metabolism
Some acetylsalicylic acid is hydrolysed to salicylate in the gut wall. After absorption aspirin is rapidly converted to salicylate but during the first 20 minutes aspirin is the predominant form of the drug in the plasma. Aspirin is bound to

plasma proteins and is widely distributed. Plasma-aspirin concentrations decline rapidly (half-life 15-20 minutes) as plasma salicylate concentrations increase. Both aspirin and salicylate have pharmacological activity; only aspirin has an antiplatelet effect.

Elimination
Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, gentisic acid, and gentisuric acid. The steady state plasma salicylate concentration will therefore increase disproportionally with dose level. At a dose level of 325 mg acetylsalicylic acid, elimination follows the first order kinetics and the half-life for plasma salicylate is 2-3 hours. At high doses of acetylsalicylic acid, the half-life increases to 15-30 hours. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Citric acid
Lactose
Maize starch
Saccharin sodium
Calcium carbonate (E170)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

PP tablet container with a PE closure. A 2g silica gel container is included in each pack.
Pack size: 1000 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

Disperse in water immediately before use.

7 MARKETING AUTHORISATION HOLDER

Actavis UK Ltd
Trading as Actavis
Whiddon Valley
BARNSTAPLE
North Devon EX32 8NS
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0176/015/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 27 August 2010

10 DATE OF REVISION OF THE TEXT

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