SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dispersible Aspirin 75 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains aspirin 75 mg as the active ingredient.

Excipients with known effect: Also contains lactose monohydrate 27.5 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Dispersible Tablets

White, flat tablets, debossed <F> on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the secondary prevention of thrombotic cerebrovascular or cardiovascular disease and following by –pass surgery.

4.2 Posology and method of administration

Posology

For the management of cardiovascular or cerebrovascular disease:

The advice of a doctor should be sought before commencing therapy for the first time. The usual dosage, for long term use, is 75-150mg once daily. In some circumstances a higher dose may be appropriate, especially in the short term, and up to 300mg a day may be used on the advice of a doctor. In general, acetylsalicylic acids should be used with caution in elderly patients who are more prone to adverse events. The usual adult dose is recommended in the absence of severe renal or hepatic insufficiency (see sections 4.3 and 4.4). Treatment should be reviewed at regular intervals.

Children:
Aspirin 75mg Tablets is not indicated for use in children and young people less than 16 years of age (see 'Special Warnings and Precautions for Use').

Method of administration
Oral administration, after dissolution in water.

4.3 Contraindications

- Hypersensitivity to salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria) and to any of the excipients listed in section 6.1
- Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages.
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia
- Patients who are suffering from gout
- Severe hepatic impairment
- Severe renal impairment
- Doses >100mg/day during the third trimester of pregnancy (see section 4.6);
- Methotrexate used at doses >15mg/week (see section 4.5)

4.4 Special warnings and precautions for use

Aspirin 75 mg is not suitable for use as an anti inflammatory/analgesic/antipyretic.

Recommended for use in adults and adolescents from 16 years of age. This medicinal product is not recommended for use in adolescents/children under 16 years unless the expected benefits outweigh the risks. Acetylsalicylic acid may be a contributory factor in the causation of Reye's Syndrome in some children.

There is an increased risk of haemorrhage particularly during or after operative procedures (even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.

Aspirin 75 mg is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin 75 mg is to be used with caution in cases of hypertension and when patients have a past history of gastric or duodenal ulcer or haemorrhagic episodes or are undergoing therapy with anticoagulants.

Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn. Acetylsalicylic acid should be used with caution in patients with moderately impaired renal or hepatic function (contraindicated if severe), or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Acetylsalicylic acid may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid (see section 4.8). Aspirin 75mg should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Where prolonged therapy is required, patients should be reviewed regularly.

Concomitant treatment with Aspirin 75mg and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage (see section 4.5). If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox (see section 4.5).

Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks (see section 4.5).

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin 75 mg taken at over dosage (see section 4.5).

Aspirin should be avoided in late pregnancy and generally during breast feeding (see section 4.6).

This medicinal product contains Lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

Methotrexate (used at doses >15 mg/week)

The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin 75mg Tablets is contraindicated (see section 4.3).

Not recommended combinations

Uricosuric agents, e.g. probenecid

Salicylates reverse the effect of probenecid. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

Anticoagulants: e.g. coumarin, heparin, warfarin and phenindione

Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored (see section 4.4).

Anti-platelet agents (e.g clopidogrel and dipyridamole) and selective serotonin re-uptake inhibitors (SSRIs; such as sertraline or paroxetine)

Increased risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics, e.g. sulfonylureas

Salicylics may increase the hypoglycaemic effect of sulfonylureas.

Digoxin and lithium

Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

Diuretics and antihypertensives
NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.

Diuretics: Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

Carbonic anhydrase inhibitors (acetazolamide)
May result in severe acidosis and increased central nervous system toxicity.

Systemic corticosteroids
The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered (see section 4.4).

Methotrexate (used at doses <15 mg/week)
The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Other non-steroidal anti-inflammatory drugs (NSAIDS)
Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

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)

Ciclosporin, tacrolimus
Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Valproate
Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin (an antiepileptic)
Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Alcohol:
Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

Metamizole:
Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardioprotection.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Low doses (up to and including 100 mg/day):
Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of above 100mg/day and up to 500 mg/day:
There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

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.

From the 20th week of pregnancy onward, acetylsalicylic acid 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 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to acetylsalicylic acid for several days from gestational week 20 onward. acetylsalicylic acid 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 (with premature closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis (see above);

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 higher than 100 mg/day is contraindicated during the third trimester of pregnancy (see sections 4.3). Doses up to and including 100 mg/day may only be used under strict obstetric monitoring

Breast-feeding
Low quantities of salicylates and of their metabolites are excreted into the breast milk. Since adverse effects for the infant have not been reported up to now, short term use of the recommended dose does not require suspending breastfeeding. In cases of long term use and/or administration of higher doses, breast feeding should be discontinued.

4.7 Effects on ability to drive and use machines

Aspirin does not usually affect the ability to drive or operate machinery.

4.8 Undesirable effects

Side effects are grouped on the basis of System Organ Class. Within each system organ class the frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data)

Blood and lymphatic system disorders	*Common:* Increased bleeding tendencies. *Rare:* Thrombocytopenia, granulocytosis, aplastic anaemia. *Not known:* Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).
Immune system disorders	*Rare:* Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock.
Metabolism and digestive system disorders	*Not known:* Hyperuricemia.
Nervous system disorders	*Rare:* Intracranial haemorrhage *Not known:* Headache, vertigo.
Ear and labyrinth disorders	*Not known:* Reduced hearing ability; tinnitus.
Vascular disorders	*Rare:* Hemorrhagic vasculitis.

Respiratory, thoracic and mediastinal disorders	*Uncommon:* Rhinitis, dyspnoea. *Rare:* Bronchospasm, asthma attacks.
Reproductive systemand mammary disorders	*Rare:* Menorrhagia
Gastrointestinal disorders	*Common:* Dyspepsia. *Rare:* Severe gastrointestinal haemorrhage, nausea, vomiting. *Not known:* Gastric or duodenal ulcers and perforation, diarrhoea.
Hepatobiliary disorders	*Not known:* Hepatic insufficiency
Skin and subcutaneous tissue disorders	*Uncommon:* Urticaria. *Rare:* Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.
Renal and urinary tract disorders	*Not known:* Impaired renal function, salt and water retention.

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

Although considerable inter-individual variations are involved, it can be considered that the toxic dose is about 200mg/kg in adults and 100mg/kg in children. The lethal dose of acetylsalicylic acid is 25-30 grams. Salicylate poisoning is usually associated with plasma concentrations >300mg/L (2.5mmol/L). Plasma concentrations above 500mg/l in adults and 300mg/l in children generally cause severe toxicity. Most adult deaths occur in patients whose concentrations exceed 700mg/L (5.1mmol/L). Single doses less than 100mg/kg are unlikely to cause serious poisoning.

Overdose may harmful for elderly patients and particularly for small children (therapeutic overdose or frequent accidental intoxications may be fatal).

Symptoms of moderate intoxications:
Common features of salicylate poisoning include vomiting, nausea, abdominal pain, dehydration, tinnitus, headache, vertigo, deafness, sweating, warm extremities with bounding pulses.

Symptoms of severe intoxications:
Some degree of acid-base disturbance is present in most cases. In the first instance hyperventilation occurs, which results in respiratory alkalosis. Respiratory acidosis ensues due to suppression of the respiratory centre. In addition 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 as a result of the presence of salicylate. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Since younger children are often not seen until they have reached a late stage of intoxication, they are usually in the stage of acidosis.

Furthermore, the following symptoms may occur: haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema, hyperthermia and perspiration, resulting in dehydration: feelings of restlessness, convulsions and hallucinations.

Central nervous system features including confusion, disorientation, convulsions may lead to coma cardiovascular collapse or respiratory arrest is less common in adults than in children.

Treatment of Overdose
If a toxic dose has been ingested, hospital admission is required. In the event of moderate intoxication, inducing the patient to vomit should be attempted.

If this fails, gastric lavage may be attempted during the first hour after ingestion of a substantial amount of the medicine.

Give activated charcoal (50g for an adult, 1g/kg body weight for a child up to 12 years) - within one hour of ingestion of more than 250mg/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 >700mg/L (5.1mmol/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.

Other symptoms to be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood and blood forming organs - antithrombotic agents: Platelet aggregation inhibitors excl. heparin,

ATC Code: BO1A C06

Aspirin inhibits platelet aggregation. Blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatosic lesions. Inhibition of TXA2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid.

The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption. Acetylsalicylic

acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

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 8 h 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

Absorption
After oral administration, acetylsalicylic acid is is rapidly absorbed from gastrointestinal tract. However significant portion of the dosage is already hydrolysed to salicylic acid in intestinal wall during the absorption process.

Distribution
Acetylsalicylic acid as well as the main metabolite salicylic acid, are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. Maximum plasma concentration is reached after 0.3 – 2 hours (total salicylate). The volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight.

Biotransformation
Acetylsalicylic acid is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. Salicylic acid is subsequently predominantly converted into glycine and glucuronic acid conjugates.
Elimination kinetics of salicylic acid is dose-dependent, because the metabolism is limited by liver enzyme capacity. Thus, elimination half-time varies and is 2-3 hours after low doses (75 mg – 160 mg).

Excretion
Salicylic acid and its metabolites are predominantly excreted via the kidneys.

5.3 Preclinical safety data

The nonclinical safety profile of acetylsalicylic acid is well documented.

In experimental animal studies, salicylates have shown no other organ injury than renal damage. In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications. Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Saccharin
Citric acid
Calcium Carbonate
Maize Starch
Purified Talc
Sodium Lauryl Sulfate
Lactose monohydrate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 25°C.

Blister packs: store in the original package.

Polypropylene/polyethylene containers: keep the container tightly closed.

6.5 Nature and contents of container

Polypropylene/polyethylene containers:

32, 50 & 100 tablets

Blister Pack: Blister strips consist of a 35gsm paper/9µ soft tempered aluminium oil lid and 250µ PVC film base in cartons

Or

Child resistant Aluminium/PVC blister packs: 20µm hard aluminium foil laminated to 15µm rigid PVC and 250µ PVC film base in cartons

Or

Child resistant Aluminium/PVC/PVDC blister packs: 20µm hard aluminium foil laminated to 15µm rigid PVC and PVC (250micron)/PVDC 90gsm film.

Blister packs: 12, 20, 24, 28, 30, 32, 48, 56 60, 84, 96, 98 and 100.

6.6. Special precautious for disposal and other handling

No special requirement.

7 MARKETING AUTHORISATION HOLDER

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