SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Aspirin 75 mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gastro-resistant tablet contains 75 mg aspirin.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablet
Oval, white, biconvex film-coated tablets, 9.2 × 5.2 mm.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
− Secondary prevention of myocardial infarction.
− Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris.
− History of unstable angina pectoris, except during the acute phase.
− Prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG).
− Coronary angioplasty, except during the acute phase.
− Secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out.
Aspirin is not recommended in emergency situations. It is restricted to secondary prevention with chronic treatment.

4.2 Posology and method of administration
Adults
Secondary prevention of myocardial infarction:
The recommended dose is 75-160mg once daily.

Prevention of cardiovascular morbidity in patients suffering from stable angina pectoris:
The recommended dose is 75-160mg once daily.

History of unstable angina pectoris, except during the acute phase:
The recommended dose is 75-160mg once daily.
Prevention of graft occlusion after Coronary Artery Bypass Grafting (CABG):
The recommended dose is 75-160mg once daily.

Coronary angioplasty, except during the acute phase:
The recommended dose is 75-160mg once daily.

Secondary prevention of transient ischaemic attacks (TIA) and ischaemic cerebrovascular accidents (CVA), provided intracerebral haemorrhages have been ruled out:
The recommended dose is 75-325mg once daily.

Elderly
In general, aspirin 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.

Paediatric population
Aspirin should not be administered to children and adolescents younger than 16 years, except on medical advice where the benefit outweighs the risk (see section 4.4).

Method of administration
For oral use.
The tablets should be swallowed whole with sufficient fluid (1/2 glass of water). Due to the gastro-resistant coating the tablets should not be crushed, broken or chewed because coating prevents irritant effects on the gut.

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 to any of the excipients;
- 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;
- 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 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. Aspirin 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 is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin 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.

Aspirin 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.

Aspirin 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 aspirin (see section 4.8). Aspirin 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 aspirin 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 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).

Aspirin 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 taken at over dosage (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

*Methotrexate (used at doses >15mg/week)*: The combined drugs, methotrexate and aspirin, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by aspirin. Therefore, the concomitant use of methotrexate (at doses >15mg/week) with aspirin 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*  
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 reuptake inhibitors (SSRIs; such as sertraline or paroxetine)*  
Increased risk of gastrointestinal bleeding (see section 4.4).

*Antidiabetics, e.g. sulphonylureas*  
Salicylics may increase the hypoglycaemic effect of sulphonylureas.

*Digoxin and lithium*  
Aspirin 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 aspirin. 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 aspirin and corticosteroids are co-administered (see section 4.4).

*Methotrexate (used at doses <15mg/week)*:
The combined drugs, methotrexate and aspirin, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by aspirin. 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 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 aspirin.

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

Phenytoin
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 aspirin increases the risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Doses of 500mg/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, aspirin should not be given unless clearly necessary. If aspirin 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 oligohydroamniosis;

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

**Lactation**

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 lactation. In cases of long-term use and/or administration of higher doses, breastfeeding should be discontinued.

### 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed with aspirin.

Based on the pharmacodynamic properties and the side effects of aspirin, no influence on the reactivity and the ability to drive or use machines is expected.

### 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 aspirin 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 system and mammary disorders | Rare: Menorrhagia. |
| Gastrointestinal disorders            | Common: Dyspepsia.  
Rare: Severe gastrointestinal haemorrhage, nausea, vomiting.  
Not known: Gastric or duodenal ulcers and perforation. |
| 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. |

**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

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 aspirin is 25-30 grams. Plasma salicylate concentrations above 300mg/l indicate intoxication. Plasma concentrations above 500mg/l in adults and 300mg/l in children generally cause severe toxicity.

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

Symptoms of moderate intoxications
Tinnitus, hearing disorders, headache, vertigo, confusion and gastrointestinal symptoms (nausea, vomiting and abdominal pain).

Symptoms of severe intoxications
Symptoms are related to severe disruption of the acid-base balance. 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 occurs as a result of the presence of salicylate. 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: hyperthermia and perspiration, resulting in dehydration: feelings of restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system may lead to coma, cardiovascular collapse or respiratory arrest.

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. Afterwards, administer activated carbon (adsorbent) and sodium sulphate (laxative). Activated charcoal may be given as a single dose (50g for an adult, 1g/kg body weight for a child up to 12 years). Alkalisation of the urine (250mmol NaHCO₃, for three hours) whilst checking urine pH levels.

In the event of severe intoxication, haemodialysis is to be preferred. Other symptoms to be treated symptomatically.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors excl. heparin, ATC code: B01AC06.

Aspirin inhibits the platelet activation: 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 atheromatous 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 aspirin.

The repeated doses from 20 to 325mg 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.

Aspirin 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 aspirin 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, aspirin is rapidly and completely absorbed from the gastrointestinal tract. The principal site of absorption is the proximal small intestine.

However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process. The degree of hydrolysis is dependent on the rate of absorption.

After intake of Aspirin gastro-resistant tablets the maximum plasma levels of aspirin and salicylic acid are reached after about 5 hours and 6 hours, respectively, following administration in the fasted state. If the tablets are taken with food, maximum plasma levels are reached approximately 3 hours later than in the fasted state.
Distribution
Aspirin 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. The degree of protein binding of salicylic acid is strongly dependant of both the salicylic acid and albumin concentration. The volume of distribution of aspirin is ca. 0.16 L/kg of body weight. Salicylic acid slowly diffuses into the synovial fluid, crosses the placental barrier and passes into breast milk.

Biotransformation
Aspirin 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, and traces of gentisic acid.
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, 12 hours after usual analgesic doses and 15-30 hours after high therapeutic doses or intoxication.

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

5.3 Preclinical safety data
The preclinical safety profile of aspirin 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 aspirin 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.
Aspirin 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
Tablet core:
Microcrystalline cellulose
Maize starch
Silica, colloidal anhydrous
Stearic acid

Film-coating:
Methacrylic acid – ethyl acrylate copolymer (1:1)
Polysorbate 80
Sodium laurilsulfate
Triethyl citrate
Talc
6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.
Blister packs: Store in the original package in order to protect from moisture.
Tablet container: Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container
Blister (PVC/Aluminium).
Tablet container (HDPE) with plastic cap (LDPE).
Tablet container (LDPE) with plastic cap (PP).

*Pack sizes:*
Blisters: 10, 20, 28, 30, 50, 56, 60, 90, 100 gastro-resistant tablets.
Tablet containers: 10, 30, 50, 100, 500 gastro-resistant tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
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8 MARKETING AUTHORISATION NUMBER(S)
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