

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Aspirin 75mg Gastro-resistant Tablets
Boots Aspirin 75mg Gastro-resistant Tablets
Lloyds Pharmacy Aspirin Enteric Coated Tablets 75mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains aspirin 75mg

For the full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

White circular tablet, plain on both sides.

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 75mg-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:

Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease). See Section 4.4

Method of administration:

Aspirin 75 mg is for oral administration to adults only.

Take the tablet with water, do not cut, chew or crush the tablet. Swallow whole.

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), to any of the excipients (see section 6.1)
- Active, or history of peptic ulceration and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia or concurrent anticoagulant therapy
- Patients who are suffering from gout
- Severe hepatic impairment
- Severe renal impairment
- Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).
- Doses >100 mg/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 tablets is not suitable for use as an anti-inflammatory/analgesic/antipyretic.

Caution should be exercised in patients with allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration, 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 also precipitate bronchospasm or induce attacks of asthma in susceptible subjects or promote 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 Tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

The elderly may be more susceptible to the toxic effects of salicylates. Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Where prolonged therapy is required, patients should be reviewed regularly.

Caution should be taken in patients with glucose-6-phosphate dehydrogenase deficiency as haemolytic anaemia may occur.

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

Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation and therefore it should be discontinued several days before scheduled surgical procedures. Haematological & haemorrhagic effects can occur, and may be severe. Use with caution before surgery, including tooth extraction. Patients should report any unusual bleeding symptoms to their physician.

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. for Kawasaki's disease).

Aspirin is to be used with caution in cases of hypertension and patients with a stomach ulcer or a history of stomach ulcers or duodenal ulcer or haemorrhagic episodes or 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.

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.

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).

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 75mg tablets taken at over dosage (see section 4.5).

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

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, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin 75 mg tablets is contraindicated (see section 4.3).

Not recommended combinations:

Uricosuric agents, e.g. probenecid and sulfinpyrazone

Salicylates reverse the effect of probenecid and sulfinpyrazone. 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. sulphonylureas

Salicylics may increase the hypoglycaemic effect of sulphonylureas.

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.

Other non-steroidal anti-inflammatory drugs (NSAIDs):

Concurrent administration can increase side effects. Use of two or more NSAIDs increases risk of gastrointestinal haemorrhage.

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.

Systemic Corticosteroids:

The risk of gastrointestinal bleeding and ulceration is increased when acetylsalicylic acid and corticosteroids are co-administered (see section 4.4). Corticosteroids reduce the plasma salicylate concentration and salicylate toxicity may occur following withdrawal of corticosteroids.

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.

Carbonic anhydrase inhibitors:

Reduced excretion of acetazolamide; salicylate intoxication has occurred in patients on high dose salicylate regimes and carbonic anhydrase inhibitors. Concurrent administration of carbonic anhydrase inhibitors such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.

Antacids and adsorbents:

The excretion of aspirin is increased in alkaline urine; kaolin possibly reduces absorption. Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

Mifepristone:

The manufacturer of mifepristone recommends that aspirin should be avoided until eight to twelve days after mifepristone has been discontinued.

Alcohol:

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

Antiemetics:

Metoclopramide enhances the effects of aspirin by increasing the rate of absorption.

Anti-epileptics:

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.

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

Leukotriene antagonists:

The plasma concentration of zafirlukast is increased.

Antibacterials:

The toxicity of sulphonamides may be increased

Thyroid function tests:

Aspirin may interfere with thyroid function tests

4.6. Pregnancy and Lactation

Pregnancy

Low doses (up to 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 100- 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 preand 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.

Lactation

As aspirin is excreted in breast milk, Aspirin should not be taken by patients who are breast-feeding, as there is a risk of Reye's syndrome in the infant. High maternal doses may impair platelet function in the infant.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	<i>Common:</i> Increased bleeding tendencies. <i>Rare:</i> Thrombocytopenia, granulocytosis, aplastic anaemia. <i>Not known:</i> Cases of bleeding with prolonged bleeding time such as epistaxis, haematuria, purpura, ecchymoses, haemoptysis, haematoma, cerebral haemorrhage and 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. Aspirin decreases platelet adhesiveness and, in large doses, may cause hypoprothrombinaemia. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses). Haemolytic anaemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
Immune system disorders	<i>Rare:</i> Hypersensitivity reactions, , skin rashes, urticarial, asthma, bronchospasm, angio-oedema, allergic oedema, anaphylactic reactions including shock.

Metabolism and digestive system disorders	<i>Not known:</i> Hyperuricemia.
Nervous system disorders	<i>Rare:</i> Intracranial haemorrhage <i>Not known:</i> Headache, vertigo
Ear and labyrinth disorders	<i>Not known:</i> Reduced hearing ability; tinnitus
Vascular disorders	<i>Rare:</i> Hemorrhagic vasculitis.
Respiratory, thoracic and mediastinal disorders	<i>Uncommon:</i> Rhinitis, dyspnoea. <i>Rare:</i> Bronchospasm, asthma attacks.
Reproductive System and mammary disorders	<i>Rare:</i> Menorrhagia
Gastrointestinal disorders	<i>Common:</i> Dyspepsia. <i>Rare:</i> Severe gastrointestinal haemorrhage, nausea, vomiting, gastritis <i>Not known:</i> Gastric or duodenal ulcers and perforation, diarrhoea
Hepatobiliary disorders	<i>Not known:</i> Hepatic insufficiency
Skin and subcutaneous tissue disorders	<i>Uncommon:</i> Urticaria. <i>Rare:</i> Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.
Renal and urinary tract disorders	<i>Not known:</i> Impaired renal function, salt and water retention, urate kidney stones.

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

Salicylate poisoning is usually associated with plasma concentrations $>350\text{mg/L}$ (2.5mmol/L). 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.

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 or children over the age of four years. In children 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, 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.

Treatment

Give activated charcoal if an adult presents 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 alkalisation, 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 $>700\text{mg/L}$ (5.1mmol/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

ATC Code: B01A C

Pharmacotherapeutic group: Blood and blood forming organs – antithrombotic agents

Aspirin has analgesic, anti-inflammatory and anti-pyretic activity. It also has an antithrombotic action, mediated through inhibition of platelet activation, which has been shown to be useful in secondary prophylaxis following myocardial infarction and in patients with unstable angina or ischaemic stroke including cerebral transient attacks.

In the body it is rapidly converted to the salicylate form which has similar activity and works via the inhibition of the enzyme cyclo-oxygenase, inhibiting prostaglandin synthesis.

The enteric coat is intended to resist gastric fluid whilst allowing disintegration in the intestinal fluid. Owing to the delay that the coating imposes on the release of the active ingredient, enteric coated tablets are unsuitable for the short-term relief of pain.

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 30min 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: Aspirin is rapidly absorbed after oral administration, with some hydrolysis to salicylate before absorption. Absorption is delayed by the presence of food and is impaired in patients suffering migraine attacks. Absorption is more rapid in patients with achlorhydria and also following administration of polysorbates and antacids.

Blood concentration: Single and multiple 100 mg doses of enteric-coated aspirin give systemic bioavailabilities of between 15% and 20% of that seen with immediate release aspirin preparations. C_{max} of aspirin for several enteric-coated preparations has been shown to be approximately 100 - 200 ng/ml with a half-life of approximately 1.7 hours. Plasma concentrations of salicylic acid increase disproportionately with dose - a 325 mg dose having a half-life of 2-3 hours and higher doses showing lower plasma concentrations in the presence of an increased half-life due to a disproportionate increase in volume of distribution.

Distribution: Aspirin is found in the saliva, milk, plasma and synovial fluid at concentrations less than blood and crosses the placenta.

Salicylate - extensive protein binding.

Aspirin - protein binding to a small extent.

Metabolism: In the blood, rapid hydrolysis to salicylic acid; glucuronic acid/ glycine conjugation to form glucuronides and salicyluronic acid; oxidation of a small proportion.

Excretion: Excreted in the urine mainly as salicyluronic acid. Salicylate reabsorbed by renal tubules in acid urine, and alkaline diuresis will increase the rate of excretion; 85% of dose excreted as free salicylate.

5.3. Preclinical Safety Data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch

Calcium hydrogen phosphate dihydrate E341

Microcrystalline cellulose E460

Talc E553b

Methacrylic acid - ethylacrylate -copolymer (1: 1) (also contains: Sodium lauryl sulphate and polysorbate 80)

Macrogol

30% Simeticone emulsion

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
32, 56 or 84 tablets in a blister pack.

Blister strips consist of a 35gsm paper/9µ soft tempered aluminium foil 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

6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0157

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