

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Resprin Suppositories 300mg (Aspirin Suppositories 300mg)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains acetylsalicylic acid (aspirin) 300 mg in combination with hard fat (suppository base).

3 PHARMACEUTICAL FORM

Uniform white suppositories.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Mild to moderate pain including headache, neuralgia and sore throat; pyrexia as in colds and influenza; pain and inflammation in rheumatic disease, arthritis, sciatica.

4.2 Posology and method of administration

Dosage

Over 16 years, adults and the elderly:

3-4 suppositories every 4 hours. Not more than 24 suppositories to be used in any 24 hours.

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

Children (under 16 years):

Not recommend except under medical supervision for use for example in juvenile rheumatoid arthritis.

Method of Administration

Remove from plastic mould and insert rectally.

4.3 Contraindications

- 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).
- Nasal polyps associated with asthma (high risk of severe sensitivity reactions).
- Active peptic ulceration or a past history of ulceration or dyspepsia.
- Haemophilia or other haemorrhagic disorder (including thrombocytopenia) as there is an increased risk of bleeding.
- Concurrent anticoagulant therapy should be avoided.
- Severe hepatic impairment
- Severe renal impairment
- Severe cardiac failure
- Third trimester of pregnancy
- Methotrexate used at doses >15mg/week (see section 4.5).
- Children under 16 years old, unless specifically indicated (e.g. Kawasaki's disease).

4.4 Special warnings and precautions for use

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 on the advice of a doctor e.g. Kawasaki's Syndrome

Aspirin Suppositories should be used with caution in patients with:

- 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).
- Anaemia (may be exacerbated by gastrointestinal blood loss)
- Cardiac failure (conditions which predispose to fluid retention)
- Dehydration
- Glucose-6-phosphate dehydrogenase deficiency (aspirin rarely causes haemolytic anaemia)

- Gout (serum urate may be increased)
- 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.
- 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.
- Systemic lupus erythematosus and other connective tissue disorders (hepatic and renal function may be impaired in these conditions)
- Thyrotoxicosis (may be exacerbated by large doses of salicylates)
- 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.
- 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.
- Vaccine recipients should avoid use of salicylates for 6 weeks after varicella vaccination (see section 4.5).
- Acetylsalicylic acid is not recommended during menorrhagia where it may increase menstrual bleeding.
- Acetylsalicylic acid 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.
- Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid (see section 4.8). Acetylsalicylic acid should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- Concomitant treatment with acetylsalicylic acid 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 acetylsalicylic acid taken at over dosage (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

- Analgesics - avoid concomitant administration of other salicylates or other NSAIDs (including topical formulations) as increased risk of side effects.
- Alkalizers of urine (e.g. antacids, citrates) - increased excretion of aspirin.
- Metoclopramide and domperidone - increased rate of absorption of aspirin.
- Mifepristone - avoid aspirin until 8-12 days after mifepristone.
- Ototoxic medicine (e.g. 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.
- Laboratory investigations - aspirin may interfere with some laboratory tests such as urine 5-hydroxyindoleacetic acid determinations and copper sulfate urine sugar tests.
- Calcium-channel blockers – reduced hypotensive effects, increased antiplatelet effect which rarely results in pro-longed bleeding time.
- Varicella vaccine - Vaccine recipients should avoid use of salicylates for 6 weeks after vaccination with varicella vaccine as Reye's syndrome has been reported following use of salicylates during wild-type varicella infection (see section 4.4).
- Ginkgo Biloba – possible increase in risk of bleeding.

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 acetylsalicylic acid 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. sulfonylureas

Salicylics may increase the hypoglycaemic effect of sulfonylureas.

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

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

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.

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 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 acetylsalicylic acid 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

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 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, 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.

Regular or high dose use of salicylates late in pregnancy may result in:

- kernicterus in jaundiced neonates

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, acetylsalicylic acid at doses of 100 mg/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. Adverse effects for the infant have not been reported up to now. However, aspirin should be avoided during lactation because of the possible risk of Reye's syndrome.

In cases of long-term use and/or administration of higher doses, breastfeeding should be discontinued. Regular use of high doses of aspirin could impair platelet function and produce hypoprothrombinaemia in the infant neonatal vitamin K stores are low.

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 Acetylsalicylic acid. Based on the pharmacodynamic properties and the side effects of acetylsalicylic acid, 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 ($\geq 1/10$), 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)

<p>Blood and lymphatic system disorders</p>	<p><i>Common:</i></p> <p>Increased bleeding tendencies.</p> <p><i>Rare:</i></p> <p>Thrombocytopenia, agranulocytosis, aplastic anaemia.</p> <p><i>Not known:</i></p> <p>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.</p> <p>Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).</p> <p>Anaemia, haemolytic anaemia, hypoprothrombinaemia, pancytopenia, occult blood loss, elevated transaminase levels</p>
<p>Immune system disorders</p>	<p><i>Rare:</i></p> <p>Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock.</p>

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> Haemorrhagic 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. <i>Not known:</i> Gastric or duodenal ulcers and perforation which can occasionally be major (may develop bloody or black tarry stools, severe stomach pain and vomiting blood), gastrointestinal irritation (mild stomach pain), erosions, heartburn, Fatalities have occurred.
Hepatobiliary disorders	<i>Not known:</i> Hepatic insufficiency, hepatitis (particularly in patients with SLE or connective tissue disease)
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

Body as a whole – general disorders	<i>Not known:</i> 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)
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Children

Aspirin may be associated with the development of Reye’s Syndrome (encephalopathy and hepatic failure) in children presenting with an acute febrile illness.

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; www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Although considerable inter-individual variations are involved, it can be considered that the toxic dose is about 200 mg/kg in adults and 100 mg/kg in children. The lethal dose of acetylsalicylic acid is 25-30 grams. Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Plasma concentrations above 500 mg/l in adults and 300 mg/l in children generally cause severe toxicity. Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 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 four years. In children aged 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.

Other symptoms may include: headache, nausea, or abdominal pain.

Central nervous system features including confusion, restlessness, hallucinations, disorientation, coma, cardiovascular collapse, respiratory arrest and convulsions are less common in adults than in children.

Management:

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 mg/L (5.1 mmol/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.

Other symptoms to be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Acetylsalicylic acid

ATC code: N02BA01

Mechanism of action

Aspirin is an anti-inflammatory analgesic and antipyretic.

Aspirin is analgesic, anti-inflammatory, antipyretic and an inhibitor of platelet aggregation. It prolongs the bleeding time. It inhibits fatty acid cyclooxygenase by acetylation of the active site of the enzyme, and most of its pharmacological effects are due to inhibition of the formation of cyclooxygenase products including thromboxanes, prostaglandins and prostacyclin.

Pharmacodynamic effects

The effect on platelets is cumulative over their 8-day life span because they have no capacity to resynthesize the cyclo-oxygenase enzyme. Aspirin has an active metabolite (salicylate) which, in addition to possessing some anti-inflammatory properties in its own right, also has important effects on respiration, acid-base balance and the stomach. Salicylates stimulate respiration by a direct effect on the medulla, and at high concentrations, uncouple oxidative phosphorylation in muscle, increasing oxygen consumption and carbon dioxide production. Hyperventilation causes respiratory alkalosis which is compensated by renal excretion of bicarbonate.

When large toxic doses of salicylate are ingested and carbohydrate metabolism is deranged, lactic and pyruvic acids accumulate and renal function is impaired, resulting in metabolic acidosis. Salicylates have a direct irritant effect on the gastric mucosa and further predispose to ulceration by inhibiting synthesis of vasodilator and cytoprotective prostaglandins.

Clinical efficacy and safety

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid 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

After absorption, aspirin is rapidly converted to salicylate. Plasma-aspirin concentrations decline rapidly (half-life 15-20 minutes) as plasma salicylate concentrations increase. Salicylates are extensively bound to plasma proteins and are rapidly distributed to all body parts. Salicylates appear in breast milk and cross the placenta.

Salicylate is mainly eliminated by hepatic metabolism: the metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid, and gentisuric acid. Following a single suppository, elimination is a firstorder process and the serum-salicylate half-life is about two to three hours; at high aspirin doses, the half-life increases to fifteen to thirty 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. Salicylates are removed by haemodialysis.

5.3 Preclinical safety data

Aspirin is a well established drug substance whose preclinical profile has been investigated thoroughly and is established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard Fat suppository base.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Suppositories are presented in strips of five peel-apart, plastilaminated moulds. The plastilaminated consists of a contact layer of polyethylene, an outer layer of polyvinylchloride and a polyurethane adhesive layer.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals Limited
Bampton Road, Harold Hill
Essex
RM3 8UG
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00156/0374

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21/09/1989

Renewal of the authorisation: 12/08/2004

10 DATE OF REVISION OF THE TEXT

01/02/2024