PROFESSIONAL INFORMATION FOR AZPAMIN

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE
AZPAMIN Enteric coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each enteric coated tablet contains 81 mg aspirin.
Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Orange coloured, round shaped, enteric coated tablet having “81” engraved on one side and plain on other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Indications related to inhibition of platelet aggregation:
To reduce the risk of myocardial infarction in patients with unstable angina or in patients who have had a previous myocardial infarction. To reduce the risk of recurrent transient ischaemic attacks or stroke in men who have had transient ischaemia of the brain due to fibrin platelet emboli. To reduce the risk of graft occlusion following aorta coronary by-pass surgery.

4.2 Posology and method of administration
For inhibition of platelet aggregation:
Adults:
One to three tablets as directed by the doctor to be taken every day, preferably at the same time each day.

Warning:
The optimal dose for inhibition of platelet aggregation in humans is not known. Do not use this product for indications related to the inhibition of platelet aggregation unless directed by a doctor.

Method of administration:
For oral administration in adults only.

4.3 Contraindications
- Hypersensitivity to aspirin, salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint), or to any of the excipients (see section 6.1).
- Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages.
- Should not be administered to patients with haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia.
- Severe hepatic impairment.
- Severe renal impairment.
- Gout.
- Severe cardiac insufficiency.
- Methotrexate used at doses > 15 mg/week (see section 4.5).

- Aspirin should not be taken during the first and third trimesters of pregnancy and during lactation.
- Aspirin should be discontinued one week before scheduled surgical procedures.
- In the event of overdosage and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital, or Poison Control Centre must be contacted immediately.
- Do not exceed the recommended daily dose.

4.4 Special warnings and precautions for use

Aspirin has been implicated in Raye's syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza. A doctor should be consulted before aspirin is used in such patients.

There is an increased risk of haemorrhage and prolongation of bleeding time particularly during or after surgery (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.

AZPAMIN is not recommended during menorrhagia where it may increase menstrual bleeding.

AZPAMIN is to be used with caution in cases of uncontrolled 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 medical practitioner. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

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 less frequently been reported in association with the use of aspirin. AZPAMIN should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Concomitant treatment with AZPAMIN and other medicines that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet medicines, anti-inflammatory medicines 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 (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 AZPAMIN taken at over dosage (see section 4.5). Aspirin should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as aspirin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue AZPAMIN and evaluate the patient immediately.

Special population

Renal and hepatic impairment

Aspirin should be used with caution in patients with moderately impaired renal or hepatic function (contraindicated if severe, see section 4.3), 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.

Elderly

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including aspirin especially gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

Pregnancy

Aspirin should be avoided in early and late pregnancy and generally during breastfeeding (see sections 4.3 and 4.6).

Excipient warning

AZPAMIN contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Contraindicated combinations

Methotrexate (used at doses >15 mg/week):

The combined medicines, 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 >15 mg/week) with AZPAMIN is contraindicated (see section 4.3).

Not recommended combinations

Uricosuric medicines, e.g. probenecid, 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 and thrombolytics e.g. coumarin, heparin, warfarin, alteplase:

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). Particularly, treatment with aspirin should not be initiated within the first 24 hours after treatment with alteplase in acute stroke patients. Concomitant use is therefore not recommended.

Anti-platelet medicines (e.g. clopidogrel, ticlopidine, cilostazol 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 and insulin:

Salicylics may increase the hypoglycaemic effect of antidiabetics. Thus, some downward readjustment of the dosage of the antidiabetic may be appropriate if large doses of salicylates are used. Increased blood glucose controls are recommended.

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 medicines. Blood pressure should be well monitored.

Concomitant administration with ACE-inhibitors, angiotensin II receptor antagonists and calcium channel blocker increases the risk of acute renal insufficiency in combination with high-dose aspirin.

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. In case of association with verapamil the bleeding time should be monitored.

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 <15 mg/week):
The combined medicines, 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 ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

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

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 medicines and aspirin.

Antacids:
The excretion of aspirin is increased by alkaline urine, which can occur with some antacids.

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:

AZPAMIN should not be taken during the first and third trimesters of pregnancy.

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.

Breastfeeding:

Low quantities of aspirin and its 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, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines:

AZPAMIN may cause side effects such as dizziness. Caution is advised before driving a vehicle or operating machinery.

4.8 Undesirable effects

The most common adverse effects occurring with therapeutic doses of aspirin are gastrointestinal disturbances such as nausea, dyspepsia and vomiting.

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequent	Increased bleeding tendencies
	Less frequent	Thrombocytopenia, granulocytosis, aplastic anaemia.
	Frequency unknown	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	Less frequent	Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock

Metabolism and nutrition disorders	Frequency unknown	Hyperuricemia, hypoglycaemia
Nervous system disorders	Less frequent Frequency unknown	Intracranial haemorrhage Headache, vertigo
Ear and labyrinth disorders	Frequency unknown	Reduced hearing ability; tinnitus
Vascular disorders	Less frequent	Haemorrhagic vasculitis
Respiratory, thoracic and mediastinal disorders	Less frequent	Rhinitis, dyspnoea, bronchospasm, asthma attacks
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Dyspepsia, nausea, vomiting, diarrhoea Severe gastrointestinal haemorrhage Gastric or duodenal ulcers and perforation
Hepato-biliary disorders	Less frequent Frequency unknown	Reye's syndrome Hepatic insufficiency, hepatic enzyme increased
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Urticaria, Steven-Johnsons syndrome, Lyell's syndrome, purpura, erythema nodosum, erythema multiforme Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4)
Renal and urinary disorders	Frequency unknown	Impaired renal function, salt and water retention.
Reproductive system and breast disorders	Less frequent	Menorrhagia

Reporting of suspected adverse reactions:
Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose
Mild chronic salicylate intoxication usually occurs only after repeated administration of large doses. Symptoms include dizziness, tinnitus, deafness, sweating, nausea, headache, vomiting and mental confusion.

Symptoms of more acute or severe intoxication following overdosage include hyperventilation, fever, restlessness, ketosis, respiratory alkalosis and metabolic acidosis. Depression of the central nervous system may lead to coma, cardiovascular collapse or respiratory failure.

In children drowsiness and metabolic acidosis commonly occur, hypoglycaemia may be severe.

In cases or overdosage consult a doctor immediately.

Fluid and electrolyte management is the mainstay of treatment with the immediate aim being correction of acidosis, hyperpyrexia, hypokalaemia and dehydration. Salicylate remaining in the stomach may be adsorbed by activated charcoal. Alkaline diuresis, haemodialysis and haemoperfusion are effective methods of removing salicylate from the plasma.

5. PHARMACOLOGICAL PROPERTIES

A 8 Medicines acting on the blood and haemopoietic system.
Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors excl. heparin
ATC code: B01AC06.

5.1 Pharmacodynamic properties

Aspirin inhibits platelet aggregation by inactivation of platelet cyclo-oxygenase, the enzyme that produces the cyclic endoperoxide precursor of thromboxane A2.

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 tablets the maximum plasma levels of aspirin and salicylic acid are reached after about 20 minutes and 1 hour, respectively, following administration 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. Maximum plasma concentration is reached after 0,3 – 2 hours (total salicylate). 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. 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.

Elimination

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet:

Cross Carmellose Sodium
Isopropyl Alcohol
Microcrystalline cellulose
Pregelatinised maize starch
Purified Talc
Sodium Lauryl sulphate

Enteric coating:
Wincoat WT-TR-5002
Wincoat WT-NAQ-6015 Orange

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at or below 25 °C.
Protect from heat, cold, moisture and light.
Preserve in tightly closed container.

6.5 Nature and contents of container
Blisters:
Aluminium-PVC/PE/PVDC foil blister pack of 10 tablets and such 3, 5 and or 10 blisters are packed in an outer carton.
Pack size: 30, 50 or 100 enteric coated tablets.

Bottle:
Enteric coated tablets are packed in a polypropylene bag inside a white HDPE bottle with a white cap. The bottle is packed in an outer carton.
Pack size: 200 or 1000 enteric coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION
Forrester Pharma (Pty) Ltd
2 Waterford Mews
Waterford Place
Century City
7441
Cape Town
South Africa

8. REGISTRATION NUMBERS
AZPAMIN: 56/8/0993

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of registration: 13 August 2024