PROFESSIONAL INFORMATION FOR AZPAMIN 100

PROFESSIONAL INFORMATION FOR AZPAMIN 100

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

AZPAMIN 100 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg acetylsalicylic acid (aspirin).

AZPAMIN 100 contains salt (sodium, 0,29 mg per tablet)

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

White to off-white coloured, round shaped, uncoated tablet, plain on-one side and break line on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- 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

Posology:

The usual dose is 100 mg daily.

For reducing the risk of myocardial ischaemic events in people with increased cardiovascular risk:

100 mg to be taken every day preferably at the same time each day accordingly to the individual needs of the patient, as determined by the medical practitioner.

Special populations:

Patients with hepatic impairment:

AZPAMIN 100 should be used with caution in patients with abnormal hepatic function (see section 4.4).

Patients with renal impairment:

AZPAMIN 100 should be used with caution in patients with abnormal renal function (see section 4.4).

Paediatric population:

AZPAMIN 100 should not be given to children under the age 16 unless specifically

indicated.

Method of administration:

For oral use.

The tablets should preferably be taken at least 30 minutes before meals, with plenty of water.

4.3 Contraindications

- Hypersensitivity to acetylsalicylic acid or other salicylates, or to any other components of AZPAMIN 100 (see section 6.1).
- Should not be administered to patients with haemorrhagic diathesis, haemophilia, or a history of haemorrhagic disorders, with gout, or a history of asthma induced by the administration of aspirin (salicylates) or substances with a similar action, including non-steroidal anti-inflammatory medicines
- Patients with severe impaired renal or hepatic function.
- Last trimester of pregnancy (see section 4.6).
- Acute gastrointestinal ulcers and active or history of recurrent ulcer/haemorrhage/perforation.
- Patients receiving oral anti-coagulant therapy
- Heart failure
- Combination with methotrexate at doses of 15 mg/week or more
- History of gastrointestinal perforation, ulceration or bleeding related to previous NSAIDs use, including AZPAMIN
- Patients with aspirin-induced nasal polyps.

PROFESSIONAL INFORMATION FOR AZPAMIN 100

4.4 Special warnings and precautions for use

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.

AZPAMIN 100 should be administered with caution in the following cases:

- Hypersensitivity to analgesics / anti-inflammatory medicines/ anti-rheumatic and in the presence of other allergies
- Patients with impaired cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume depletion, major surgery, sepsis or major haemorrhagic events), since acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure,

AZPAMIN 100 may precipitate bronchospasm and induce asthma attacks or other hypersensitivity reactions. Risk factors are pre-existing asthma, hay fever, nasal polyps, or chronic respiratory disease. This also applies to patients exhibiting allergic reactions (e.g. cutaneous reactions, itching, urticaria) to other substances.

AZPAMIN 100 should be withdrawn 1 week before surgery.
Due to its inhibitory effect on platelet aggregation which persists for several days after administration, AZPAMIN 100 may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g. dental

extractions).

At low doses, AZPAMIN 100 reduces the excretion of uric acid. This can possibly trigger gout attacks in predisposed patients.

In view of the medicine's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.
AZPAMIN 100 should be administered with caution to patients with impaired renal function, dyspepsia, anaemia, and when the patient is dehydrated.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with aspirin as in AZPAMIN 100 therapy.

Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with aspirin after careful consideration.

In patients suffering from severe glucose-6-phosphatedehydrogenase (GP6PD) deficiency, AZPAMIN 100 may induce haemolysis or haemolytic anaemia. Factors that may increase the risk of haemolysis are high dosage, fever, or acute infections.

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal. The risk of

gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of AZPAMIN 100 in patients with a history of ulcer and the elderly. When gastrointestinal bleeding or ulceration occurs in patients receiving AZPAMIN 100, treatment with AZPAMIN 100 should be stopped.

AZPAMIN 100 should be given with caution to patients with a history of gastrointestinal diseases (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the conditions may be exacerbated.

Dermatological effects:
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis may occur with the use of NSAIDs. AZPAMIN 100should be discontinued at the first appearance of skin rash, mucosal lesions or any other hypersensitivity.

Special populations

Paediatric population

AZPAMIN 100 should not be used in children and adolescents for viral infections with or without fever without consulting a doctor. In certain viral illnesses, especially influenza A, influenza B and varicella, there is a risk of Reye's syndrome, a possibly life-threatening illness requiring immediate medical action. The risk may be increased when AZPAMIN 100 is given concomitantly. Should persistent vomiting occur with such diseases, this may be a sign of Reye's syndrome.

Excipient warning

PROFESSIONAL INFORMATION FOR AZPAMIN 100

AZPAMIN 100 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 interactions:

Methotrexate used at doses of 15 mg/week or more:

Increased haematological toxicity of methotrexate (decreased renal clearance of methotrexate by anti-inflammatory medicines in general and displacement of methotrexate from its plasma protein binding by salicylates), (see section 4.3).

Combinations requiring precautions for use:

Methotrexate used at doses of less than 15 mg/week:

Increased haematological toxicity of methotrexate (decreased renal clearance of methotrexate by anti-inflammatory medicines in general and displacement of methotrexate from its plasma protein binding by salicylates).

Anticoagulants, thrombolytics/other inhibitors of platelet aggregation/haemostasis:

Increased risk of bleeding.

AZPAMIN 100 may enhance the effects of coumarin anti-coagulants such as warfarin.

Other non-steroidal anti-inflammatory drugs with salicylates:

Increased risk of ulcers and gastrointestinal bleeding due to synergistic effect.

PROFESSIONAL INFORMATION FOR AZPAMIN 100

Selective Serotonin Re-uptake Inhibitors (SSRIs):

Increased risk of upper gastrointestinal bleeding due to a possible synergistic effect.

Digoxin:

Plasma concentrations of digoxin are increased due to a decrease in renal excretion.

Antidiabetic Medicines, e.g. insulin, sulphonylureas:

Increased hypoglycaemic effect by high doses of AZPAMIN via hypoglycaemic action of AZPAMIN and displacement of sulphonylurea from its plasma protein binding sites.

Diuretics in combination with AZPAMIN 100

Decreased glomerular filtration via decreased renal prostaglandin synthesis.

Systemic glucocorticoids, except hydrocortisone used as replacement therapy in Addison's disease:

Decreased blood salicylate levels during corticosteroid treatment and risk of salicylate overdose, after this treatment is stopped, via increased elimination of salicylates by corticosteroids.

Angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers in combination with acetylsalicylic acid:

Decreased glomerular filtration via inhibition of vasodilatory prostaglandins. Furthermore, decreased antihypertensive effect.

PROFESSIONAL INFORMATION FOR AZPAMIN 100

Valproic acid:

Increased toxicity of valproic acid due to displacement from protein binding sites.

Alcohol:

Increased damage to gastro-intestinal mucosa and prolonged bleeding time due to additive effects of AZPAMIN and alcohol.

Uricosurics such as benzbromarone, probenecid:

Decreased uricosuric effect (competition of renal tubular uric acid elimination). Aspirin diminishes the effects of uricosuric medicines such as probenecid and sulphinpyrazone.

NSAIDs

The use of two or more NSAIDs concomitantly could result in an increase in side effects.

Ibuprofen

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly.

Metoclopramide

May enhance the effect of AZPAMIN 100.

Phenytoin

Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to

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.

Alkaliser of urine such antacids, citrates

Increased excretion of aspirin.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from studies raise concern about an increased risk of mis-carriage and of malformations after the use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. During the first and second trimester of pregnancy, AZPAMIN 100 should not be given. If AZPAMIN 100 is used by a woman attempting to conceive, or during the first and second trimesters of pregnancy, the dose should be kept as low, and the duration of treatment kept 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 andpulmonary hypertension),
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

PROFESSIONAL INFORMATION FOR AZPAMIN 100

Prostaglandin synthesis inhibitors may expose both the mother and the child at the end of pregnancy to:

- possible prolongation of bleeding time/increased INR, an anti-aggregating effectwhich may occur even after very low doses,
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, AZPAMIN 100 is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation:

Safety in breastfeeding has not been established. Salicylates and their metabolites pass into breast milk in small quantities. Mothers on treatment with AZPAMIN 100 should not breastfeed their babies.

Fertility:

Limited data available. Studies in humans showed no consistent effect of aspirin as in AZPAMIN 100 on impairment of fertility and there is no conclusive evidence from animal studies.

4.7 Effects on ability to drive and use machines:

AZPAMIN 100 has none to negligible influence on the ability to drive and use of machines. However, due to side effect such as dizziness, patients should check how they react to AZPAMIN 100 before driving a vehicle or operating machinery.

4.8 Undesirable effects

PROFESSIONAL INFORMATION FOR AZPAMIN 100

The most frequent adverse effects occurring with therapeutic doses of aspirin are gastrointestinal disturbances such as nausea, hepatotoxicity particularly in patients with juvenile arthritis and other connective tissue disorders.

System Organ Class	Frequency	Side effects
Blood and the lymphatic system disorders	Frequency unknown	Hypoprothrombinaemia, thrombocytopenia, aplastic anaemia, agranulocytosis, pancytopenia
Immune system disorders	Frequency unknown	Various skin eruptions, pyrexia, angioedema, and oedema
Metabolism and Nutrition Disorders	Frequency unknown	Sodium retention and fluid retention
Nervous system disorders	Frequency unknown	Meningitis, headache and dizziness
Cardiac Disorders	Frequency unknown	Hypertension, cardiac failure
Vascular Disorders	Frequency unknown	Hypertension
Respiratory, Thoracic and Mediastinal Disorders	Frequency unknown	Respiratory tract reactivity, bronchospasm, asthma, dyspnoea, and rhinitis
Gastrointestinal disorders	Frequency unknown	Gastrointestinal disturbances including nausea, vomiting and dyspepsia. Gastrointestinal

PROFESSIONAL INFORMATION FOR AZPAMIN 100

		haemorrhage melaena, haematemesis, gastritis, diarrhoea, constipation, flatulence, peptic ulcer, and mouth ulceration (ulcerative stomatitis)
Hepato-biliary disorders	Less frequent Frequency unknown	Transaminases increased Hepatotoxicity
Skin and subcutaneous tissue disorders	Frequency unknown	Stevens-Johnson syndrome and toxic epidermal necrolysis, rash, urticaria and pruritis, drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4)
Renal and urinary disorders	Frequency unknown	Increased blood uric acid
Investigations	Frequency unknown	Bleeding time prolonged, platelet adhesiveness decreased

Reporting of suspected adverse reactions:

Reporting 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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Salicylate toxicity may result from chronic, therapeutically acquired intoxication, and from potentially life-threatening, acute intoxications (overdose), ranging from accidental ingestions in children to incidental intoxications.

Chronic salicylic intoxication

Chronic salicylate poisoning can be insidious as signs and symptoms are non-specific. Mild chronic salicylate intoxication, or salicylism, usually occurs only after repeated use of large doses.

Symptoms include dizziness, vertigo, tinnitus, deafness, sweating, nausea and vomiting, headache, and confusion, and may be controlled by reducing the dosage.

Acute salicylate intoxication

The principal feature of acute intoxication is severe disturbance of the acid-base balance, which may vary with age and severity of intoxication. Symptoms of acute or severe intoxication following overdose include hyperventilation, fever, ketosis, respiratory alkalosis and metabolic acidosis. Depression of the central nervous system may lead to coma, cardiovascular collapse, or respiratory failure. The most frequent presentation for a child is drowsiness and metabolic acidosis, hypoglycaemia may be severe. The severity of poisoning cannot be estimated from plasma concentration alone. Absorption of acetylsalicylic acid can be delayed due to reduced gastric emptying, formation of concretions in the stomach, or as a result

of ingestion of enteric-coated preparations.

Management of AZPAMIN 100 intoxication is determined by its extent, stage and clinical symptoms and according to standard poisoning management techniques.

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 absorbed by activated charcoal.

Alkaline diuresis, haemodialysis or haemoperfusion are effective methods of removing salicylate from the plasma.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A 8 Medicines acting on the blood and haemopoietic system.

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin

ATC code- N02BA01

Aspirin has analgesic, anti-pyretic and anti-inflammatory actions.
Acetylsalicylic acid belongs to the group of acidic nonsteroidal anti-inflammatory medicine (NSAIDs) with analgesic, antipyretic and anti-inflammatory properties. Its mechanism of action is based on irreversible inhibition of cyclo-oxygenase enzymes involved in prostaglandin synthesis. Acetylsalicylic acid inhibits platelet aggregation

by blocking thromboxane A_2 synthesis in platelets.

5.2. Pharmacokinetic properties

Following oral administration, acetylsalicylic acid is well and completely absorbed from the gastrointestinal tract. During and after absorption acetylsalicylic acid is converted into its main active metabolite, salicylic acid. Maximal plasma levels are reached after 18 – 30 minutes for acetylsalicylic acid and after 0,72 - 2 hours for salicylic acid, respectively.

Distribution

Both acetylsalicylic acid and salicylic acid are extensively bound to plasma proteins and are rapidly distributed throughout the body. Salicylic acid passes into breast milk and crosses the placenta.

Biotransformation

Acetylsalicylic acid is converted into its main metabolite salicylic acid. The acetyl group of acetylsalicylic acid begins to split off hydrolytically even during passage through the intestinal mucosa but mainly this process takes place in the liver.
Its metabolites are salicyluric acid, salicylic phenolic glucuronide, salicylacyl glucuronide, gentisic acid and gentisuric acid.

Elimination

The elimination kinetics of salicylic acid is dose-dependent, as metabolism is limited by liver enzyme capacity. The elimination half-life therefore varies from 2 to 3 hours after low doses to up to about 15 hours at high doses. Salicylic acid and its

metabolites are excreted mainly via the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cross Carmellose Sodium

Microcrystalline cellulose PH -102

Pre-gelatinised Starch

Purified Talc

Sodium Lauryl Sulphate

Stearic Acid

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

Aluminium-PVDC blister strips packed in an outer carton.

Pack size: 28 or 30 tablets.

PROFESSIONAL INFORMATION FOR AZPAMIN 100

White HDPE ribbed container with white cap: Pack size: 1 000 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

Tel: +27 21 943 0600

8. REGISTRATION NUMBERS

AZPAMIN 100: 57/8/0436

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: To be allocated by the SAHPRA.