SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

Myoprin 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Aspirin 100 mg

Excipients with known effect:

Myoprin contains sugar (lactose monohydrate 40,00 mg per tablet).

Myoprin contains sweetener (saccharin sodium 1,00 mg per tablet).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

White, flat bevelled edge round tablet with break line on one side and plain on the other.

Do not break the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The indications relate to inhibition of platelet aggregation:

- To reduce the risk of myocardial infarctions in patients with unstable angina or in patients who have previous myocardial infarction.
- To reduce the risk of recurrent transient ischaemia 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

100 mg to 300 mg to be taken every day, preferably at the same time each day:

- 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 aortocoronary by-pass surgery.

In some circumstances a higher dose may be appropriate, especially in the short term, and up to 300 mg 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.

Method of administration

The tablet should be swallowed whole.

4.3 Contraindications

- Hypersensitivity to aspirin, or to any of the excipients in Myoprin (see section 6.1)
- Patients with an intolerance to aspirin (especially aspirin-sensitive asthmatics)
- Patients with aspirin induced nasal polyps
- A history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory medicines
- Heart failure that is not well controlled
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including Myoprin
- Active or history of recurrent ulcer/haemorrhage/perforations
- Patients with gout
- Haemorrhagic diathesis
- Severe renal impairment
- Severe hepatic impairment
- Combination with methotrexate at doses of 15 mg/week or more (see section 4.5)
- Myoprin should not be taken from 20 weeks' gestation or later in pregnancy and during lactation (see section 4.6).

4.4 Special warnings and precautions for use

In the event of overdose 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.

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 Myoprin therapy. In view of the Myoprin's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

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 Myoprin after careful consideration.

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

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of Myoprin, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving Myoprin, treatment with Myoprin should be stopped.

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

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Myoprin should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

The administration of Myoprin around 20 weeks or later in pregnancy may cause foetal renal dysfunction, which may progress to renal failure with oligohydroamniosis, and in some cases neonatal renal impairment.

Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation.

Oligohydramnios may, but not always be reversible with Myoprin treatment discontinuation.

Myoprin use during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed, and its duration increased.

Myoprin may precipitate bronchospasm and induce asthma attacks and 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.

Myoprin should be used with particular caution in the following cases:

- hypersensitivity to analgesics/ anti-inflammatory medicines/ anti-rheumatic medicines and in the presence of other allergies;
- impaired hepatic function;
- ibuprofen may interfere with the acetylsalicylic acid's inhibitory effect on platelet aggregation. Patients should tell their doctor if they are on a Myoprin regimen and take ibuprofen for pain.

Myoprin should be discontinued one week before scheduled surgical procedures (including minor surgeries, e.g. dental extractions).

Neuraxial regional anaesthetic techniques:

Myoprin should be assumed to have decreased platelet function for one week after the last dose. Consider stopping Myoprin for 1 week before a neuraxial regional anaesthetic procedure.

Appropriate neurological monitoring must take place for 24 hours post procedure. Co-administration with any other antihaemostatic / antiplatelet medicine increases the risk of bleeding.

Myoprin has been implicated in Reye's syndrome, a rare but serious illness in children and teenagers less than eighteen years of age with chickenpox and influenza. A doctor should be consulted before Myoprin is used in such patients. Should persistent vomiting occur with such diseases, this may be a sign of Reye's syndrome.

Myoprin may enhance the coumarin anticoagulants, sulphonylurea, hypoglycaemic medicines, methotrexate, phenytoin and valproic acid.

Myoprin diminishes the effects of uricosuric medicines such as probenecid and sulphinpyrazone.

It should be administered with caution to patients with impaired renal function, dyspepsia, anaemia and when the patient is dehydrated.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as MYOPRIN. 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. Eosinophillia 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 MYOPRIN and evaluate the patient immediately.

Myoprin contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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).

Ibuprofen:

The concomitant administration of ibuprofen antagonises the irreversible platelet inhibition induced by acetylsalicylic acid. Treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of Myoprin.

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

Increased risk of bleeding.

Other non-steroidal anti-inflammatory medicines with MYOPRIN at high doses:

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

Selective Serotonin Reuptake Inhibitors (SSRIs): Increased risk of upper gastrointestinal bleeding due to possibly synergistic effect.

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

Antidiabetics, e.g. insulin, sulphonylureas: Increased hypoglycaemic effect by high doses of acetylsalicylic acid via hypoglycaemic action of acetylsalicylic acid and displacement of sulfonylurea from its plasma protein binding.

Diuretics in combination with Myoprin at higher doses: 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 or salicylates by corticosteroids.

Angiotensin converting enzyme inhibitors (ACE) in combination with Myoprin at higher doses: Decreased glomerular filtration via inhibition of vasodilator prostaglandins. Furthermore, decreased antihypertensive effect.

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 Myoprin and alcohol.

Uricosurics such as benzbromarone, probenecid: Decreased uricosuric effect (competition of renal tubular uric acid elimination).

4.6 Fertility, pregnancy and lactation

Pregnancy

The administration of Myoprin around 20 weeks or later in pregnancy may cause foetal renal dysfunction, which may progress to renal failure with oligohydroamniosis, and in some cases neonatal renal impairment (see 4.3 & 4.4).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. During the first and second trimester of pregnancy, acetyl salicylic acid containing medicines are not recommended.

If acetylsalicylic acid is used by a woman attempting to conceive, or during the first trimester of pregnancy up to 20 weeks' gestation, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, prostaglandin synthesis inhibitors, such as Myoprin, may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- the mother and the child, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even after very low doses
- inhibition of uterine contractions resulting in delayed or prolonged labour

Consequently, Myoprin is contraindicated from 20 weeks gestation and later in pregnancy.

Breastfeeding

Salicylates and its metabolites pass into breastmilk. Safety is unproven. Mothers on treatment with Myoprin should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

Chronic Myoprin overdose or use in sensitive individuals, may result in symptoms that may impair the ability to drive or to use machines safely. Symptoms such as dizziness, tinnitus, deafness, nausea, headache, vomiting and mental confusion.

4.8 Undesirable effects

Blood and lymphatic system disorders

Frequency unknown	Hypoprothrombinaemia, increased risk of bleeding. Bleedings, such as perioperative haemorrhage, haematomas, epistaxis, urogenital bleedings, gingival bleedings, have been observed. Haemorrhage may result in acute and chronic post haemorrhagic anaemia, iron deficiency anaemia (due to e.g. occult micro bleeding) with respective laboratory and clinical signs and symptoms, such as asthenia, pallor, hypoperfusion.

Immune system disorders

Frequency unknown	Hypersensitivity reactions which may include skin eruptions, rash, urticaria, pruritus, angio-oedema, rhinitis, paroxysmal bronchospasm and dyspnoea, nasal congestion, cardio-respiratory distress, and severe reactions, including anaphylactic shock.

Nervous system disorders

Less frequent	Cerebral haemorrhage (especially in patients with uncontrolled hypertension and/or on concomitant anti-haemostatic medicines), which in single cases may be potentially life-threatening.
Frequency unknown	Dizziness.

Cardiac disorders

Frequency unknown	Oedema, hypertension and cardiac failure.

Respiratory, thoracic and mediastinal disorders

Frequency unknown	Asthma syndrome (hypersensitivity) including paroxysmal bronchospasm, dyspnoea, rhinitis, and nasal congestion.

Gastrointestinal disorders

Frequent	Nausea, upper and lower gastrointestinal tract disorders such as common signs and symptoms of dyspepsia, gastrointestinal and abdominal pain.
Less frequent	Gastrointestinal tract haemorrhage, gastrointestinal inflammation, gastrointestinal ulcer.
Frequency unknown	Heamatemesis, melaena, gastrointestinal ulcer haemorrhage and perforation, with the respective laboratory and clinical signs and symptoms, vomiting, diarrhoea, flatulence, constipation, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

Hepato-biliary disorders

Frequent	Hepatotoxicity particularly in patients with juvenile arthritis and other connective tissue disorders.
Less frequent	Transient hepatic impairment with increase in liver transaminases.

Skin and subcutaneous tissue disorders

Frequency unknown	Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.
Frequency unknown	Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4)

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 "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Poisoning must be feared in the elderly and above all in young children (from accidental poisoning) in whom it may be fatal.

Symptoms of acute or severe intoxication following overdose includes hyperventilation, fever, 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 of 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 or haemoperfusion are effective methods of removing salicylate from the plasma.

Chronic Myoprin (salicylate) intoxication usually occurs after repeated administration of large doses. Symptoms include dizziness, tinnitus, deafness, sweating, nausea, headache, vomiting and mental confusion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excl. heparin: ATC: B01AC06

Myoprin 100 mg 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:

Following oral administration, acetylsalicylic acid is absorbed completely 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 10 to 20 minutes for acetylsalicylic acid and after 0,3 to 2 hours for salicylic acid, respectively.

Distribution:

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

Biotransformation:

Salicylic acid is eliminated predominantly by hepatic metabolism. Its metabolites are salicyluric acid, salicylic phenolic glucuronide, salicylacyl glucuronide, gentisic acid, and gentisuric acid. The elimination kinetics of salicylic acid is dose-dependent, as metabolism is limited by liver enzyme capacity.

Elimination:

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

Calcium carbonate heavy
Citric acid monohydrate
Lactose monohydrate
Maize starch
Purified talc
Saccharin sodium (sweetener)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

Foil strips should be kept in the outer carton until required for use.

6.5 Nature and contents of container

Foil strips consisting of plain aluminum foil and printed aluminum foil.

Myoprin 100 mg tablets are available in packs of 30 tablets (10 tablets per strip, with three strips inserted together with the package insert in an outer cardboard carton).

6.6 Special precautions for disposal and other handling

No special precautions.

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

MIDRAND, 1683, SOUTH AFRICA

8 REGISTRATION NUMBER

B/2.7/1117

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 June 1983

10 DATE OF REVISION OF THE TEXT

09 June 2022