SCHEDULING STATUS

S2

1 NAME OF MEDICINE
TRINPRIN (Gastro-resistant Tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each gastro-resistant tablet contains 100 mg acetylsalicylic acid (aspirin).

Excipient with known effect:
Each tablet contains 60 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Gastro-resistant tablets.
White coloured gastro-resistant coated tablets, round and biconvex, without break-score.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
TRINPRIN is indicated for the following cardiovascular uses:
- 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 patients 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.
- For reducing the risk of myocardial ischaemic events in people with cardiovascular risk factors.

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 according to the individual needs of the patient, as determined by the medical practitioner.

Special populations
Paediatric patients
The safety and efficacy of TRINPRIN in children below 18 years of age has not been established. No data are available. Therefore, TRINPRIN is not recommended for use in paediatric patients, below 18 years.

Patients with hepatic impairment
TRINPRIN is contraindicated in patients with severe hepatic failure (see section 4.3). TRINPRIN should be used with particular caution in patients with impaired hepatic function (see section 4.4).

Patients with renal impairment
TRINPRIN is contraindicated in patients with severe renal failure (see section 4.3). TRINPRIN should be used with particular caution in patients with impaired renal function since acetylsalicylic acid may further increase the risk of renal impairment and acute renal failure (see section 4.4).

Method of administration
Oral route.
The tablets should be swallowed whole. Do not chew, break or crush the tablets as this will destroy the protective effect of the gastro-resistant coating.

4.3 Contraindications
TRINPRIN is contraindicated in:
- Patients with known hypersensitivity to acetylsalicylic acid, to other salicylates, or to any of the excipients (see section 6.1).
- A history of asthma induced by the administration of salicylates or substances with a similar action, notably non-steroidal anti-inflammatory medicines.;
- History of gastrointestinal perforation, ulceration or bleeding (peptic ulcer bleedings-PUBs) related to previous NSAIDs including TRINPRIN;
- Acute gastrointestinal ulcers;
- Haemorrhagic diathesis;
- Severe renal impairment (eGFR < 30 mL/minute);
- Severe hepatic impairment (Child-Pugh C);
- Severe cardiac failure (NYHA grade III or IV);
- Combination with methotrexate at doses of 15 mg/week or more (see section 4.5);
- Third trimester of pregnancy due to the risks of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use
Limit prescribing Non-steroidal Anti-inflammatory Drugs (NSAIDs), including TRINPRIN, between 20 to 30 weeks of pregnancy and avoid prescribing them during the third trimester of pregnancy. If NSAID treatment is determined necessary, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if NSAID treatment extends beyond 48 hours and discontinue the NSAID if oligohydramnios is found. Complications of prolonged oligohydramnios may include neonatal renal impairment, premature closure of the foetal ductus arteriosus, limb contractures and delayed lung maturation (see section 4.3 and 4.6).

TRINPRIN should be used with particular caution in the following cases:
- Hypersensitivity to analgesics, anti-inflammatory medicines, antirheumatic medicinal products and in the presence of other allergies.
- History of gastrointestinal ulcers including chronic or recurrent ulcer disease or history of gastrointestinal bleedings.
  The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal (see section 4.8)
  The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of TRINPRIN, in patients with a history of ulcers and the elderly.
  When gastrointestinal bleeding or ulceration occurs in patients receiving TRINPRIN, treatment with TRINPRIN should be stopped.
  TRINPRIN 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.
- With concomitant treatment with anticoagulants (see section 4.5).
  Impaired renal function or 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.
  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 TRINPRIN therapy.
  In patients suffering from severe glucose-6-phosphate dehydrogenase (G6PD) deficiency, TRINPRIN may induce haemolysis or haemolytic anaemia. Factors that may increase the risk of haemolysis are e.g., high dosage, fever or acute infections.
- Impaired hepatic function.
  Metamizide and some NSAIDs, such as ibuprofen and naproxen may attenuate acetylsalicylic acid's inhibitory effect on platelet aggregation. Patients should be advised to talk to their doctor if they are on a TRINPRIN regimen and plan to take metamizole or NSAIDs for pain (see section 4.5).
  Ibuprofen may interfere with the acetylsalicylic acid's inhibitory effect on platelet aggregation. Patients should tell their doctor if they are on a TRINPRIN regimen and take ibuprofen for pain.
  Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. TRINPRIN should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

TRINPRIN 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.

Due to its inhibitory effect on platelet aggregation which persists for several days after administration, TRINPRIN may lead to an increased bleeding tendency during and after surgical operations (including minor surgeries, e.g., dental extractions).

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 and hypoperfusion.

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

Acetylsalicylic acid containing products should not be used in children and adolescents for viral infections with or without fever when consulting a healthcare professional. In certain viral illnesses, especially influenzae A, influenzae B and varicella, there is a risk of Reye's syndrome, a very rare but possibly life- threatening illness requiring immediate medical action. The risk may be increased when TRINPRIN is given concomitantly.

Should persistent vomiting occur with such diseases, this may be a sign of Reye's syndrome.

TRINPRIN contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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).

Metamizole and NSAIDs
The concurrent (same day) administration of metamizole and some NSAIDs, such as ibuprofen and naproxen, attenuate the irreversible platelet inhibition induced by acetylsalicylic acid. The clinical relevance of these interactions is not known. Treatment with metamizole and some NSAIDs, such as ibuprofen and naproxen, in patients with increased cardiovascular risk may limit the cardiovascular protection of BAYER ASPIRIN CARDIO 100 (see section 4.4).

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

Anticoagulants, thrombolytics/other inhibitors of platelet aggregation/haemostasis
Increased risk of bleeding.

Other non-steroidal anti-inflammatory medicines with salicylates
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 acetylsalicylic acid 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 of salicylates by corticosteroids. Concurrent use may increase the incidence of gastrointestinal bleeding and ulceration.

Angiotensin converting enzyme inhibitors (ACE) in combination with acetylsalicylic acid 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 acetylsalicylic acid and alcohol.

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

4.6 Fertility, pregnancy and lactation
Pregnancy
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. 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 child, at the end of pregnancy, may be exposed 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, TRINPRIN is contraindicated during the third trimester of pregnancy (see section 4.3).

Breastfeeding
Salicylates and their metabolites pass into breastmilk in small quantities. Safety has not been established. When regular use of TRINPRIN is indicated, breastfeeding should be discontinued.

Fertility
Based on the limited published data available, the studies in humans showed no consistent effect of acetylsalicylic acid on impairment of fertility and there is no conclusive evidence from animal studies.

4.7 Effects on ability to drive and use machines
TRINPRIN has no or negligible influence on the ability to drive and use machines. However due to side effect such as dizziness, patients should check how they react to TRINPRIN before driving a vehicle or operating machinery.

4.8 Undesirable effects
a. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Gastrointestinal disorders	*Frequent*	Dyspepsia, gastrointestinal and abdominal pain, gastrointestinal inflammation, gastrointestinal tract haemorrhage.
	Less frequent	Gingival bleeding, gastrointestinal ulcer and erosion, gastrointestinal ulcer perforation.
	Frequency unknown	Intestinal diaphragm disease
Blood and lymphatic system disorders	*Less frequent*	Serious bleedings, such as gastrointestinal tract haemorrhage, cerebral haemorrhage (especially in patients with uncontrolled hypertension and/or on concomitant anti-haemostatic medicines
	Frequency unknown	Increased risk of bleeding such as perioperative haemorrhage, hematomas, epistaxis, urogenital bleedings, gingival bleedings, 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 with respective laboratory and clinical manifestations include asthma syndrome, mild to moderate reactions potentially affecting skin, respiratory tract, gastrointestinal tract, and cardiovascular system, including symptoms such as rash, urticaria, oedema, pruritus, rhinitis, nasal congestion cardiorespiratory distress, and very rarely severe reactions, including anaphylactic shock
Nervous system disorders	*Frequent*	Dizziness
	Less frequent	Cerebral and intracranial haemorrhage
Hepatobiliary disorders	*Less frequent*	Transient hepatic impairment with increase in liver transaminases, hepatic impairment
Vascular disorders	*Less frequent*	Haematoma, haemorrhage, muscle haemorrhage
	Frequency unknown	Procedural haemorrhage
Respiratory, thoracic and mediastinal disorders	*Frequent*	Epistaxis, rhinitis
	Less frequent	Nasal congestion
	Frequency unknown	Aspirin exacerbated respiratory disease
Skin and subcutaneous tissue disorders	*Frequent*	Rash, pruritus
	Less frequent	Urticaria
Renal and urinary disorders	*Frequent*	Urogenital tract haemorrhage
	Less frequent	Renal impairment, renal failure acute
Injury, poisoning and procedural complications	*Frequent*	See overdose section

b. 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. Health care 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 (therapeutic overdose or frequent accidental poisoning) in whom it may be fatal.

Salicylate toxicity (> 100 mg/kg/day over 2 days may produce 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 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. Tinnitus can occur at plasma concentrations of 150 to 300 microgrammes/mL. More serious adverse events occur at concentrations above 300 microgrammes/mL.

The principal feature of acute intoxication is severe disturbance of the acid-base balance, which may vary with age and severity of intoxication. The most common presentation for a child is metabolic acidosis. 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 acetylsalicylic acid intoxication is determined by its extent, stage and clinical symptoms and according to standard poisoning management techniques. Predominant measures should be the accelerated excretion of the drug as well as the restoration of the electrolyte and acid-base metabolism.

Due to the complex pathophysiologic effects of salicylate poisoning, signs and symptoms/investigational findings may include:

Signs and Symptoms	Investigational findings	Therapeutic measures
Mild to moderate intoxication		**Repeated administration of activated charcoal, forced alkaline diuresis**
Tachypnoea, hyperventilation, respiratory alkalosis	Alkalaemia, alkaluria	Fluid and electrolyte management
Diaphoresis		
Nausea, vomiting		
Moderate to-severe intoxication		**Repeated administration of activated charcoal, forced alkaline diuresis, hemodialysis in severe cases**
Respiratory alkalosis with compensatory metabolic acidosis,	Acidaemia, aciduria	Fluid and electrolyte management
Hyperpyrexia		Fluid and electrolyte management
Respiratory: ranging from hyperventilation, non-cardiogenic pulmonary edema to respiratory arrest, asphyxiation		
Cardiovascular: ranging from dysrhythmias, hypotension to cardiovascular arrest	e.g., Blood pressure, ECG alteration	
Fluid and electrolyte loss: dehydration, oliguria to renal failure	e.g., Hypokalaemia, hypernatraemia, hyponatraemia, altered renal function	Fluid and electrolyte management
Impaired glucose metabolism, ketosis	Hyperglycaemia, hypoglycaemia (especially in children) Increased ketone levels	
Tinnitus, deafness		
Gastrointestinal: GI bleeding		
Haematologic: ranging from platelet inhibition to coagulopathy	e.g., PT prolongation, hypoprothrombinaemia	
Neurologic: Toxic encephalopathy and CNS depression with manifestations ranging from lethargy, confusion to coma and seizures		

Emergency management
Immediate transfer to hospital specialist unit, gastric lavage, administration of activated charcoal, check of acid-base balance, alkaline diuresis so as to obtain a urine pH between 7.5 and 8, forced alkaline diuresis should be considered when the plasma salicylate concentration is greater than: 500 mg/litre (3,6 mmol/litre) in adults or 300 mg/litre (2,2 mmol/litre) in children, possibility of haemodialysis in severe poisoning, fluid losses should be replaced, symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
A. B Medicines acting on the blood and haemopoietic system
Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin
ATC code- N02BA01

Acetylsalicylic acid inhibits platelet aggregation by inactivation of platelet cyclo-oxygenase, the enzymethat produces the cyclic endoperoxide precursor of thromboxane A2. Its mechanism of action is based on irreversible inhibition of cyclo- oxygenase (COX-1). This inhibitory effect is especially pronounced in platelets because platelets are unable to resynthesize this enzyme.

Platelet aggregation is inhibited for the lifespan of the platelet, 8-10 days. Acetylsalicylic acid is also thought to have other inhibitory effects on platelets. Acetylsalicylic acid belongs to the group of acidic nonsteroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory properties.

5.2 Pharmacokinetic properties
Absorption
Following oral administration, acetylsalicylic acid is well absorbed from the gastrointestinal tract. During and after absorption acetylsalicylic acid is converted into its main metabolite, salicylic acid. Due to the principle of the acid-resistant formulation of TRINPRIN tablets, acetylsalicylic acid is not released in the stomach but in the alkaline milieu of the intestine. Therefore, C_{max} of acetylsalicylic acid is reached 2-7 hours after the administration of TRINPRIN in comparison to plain tablets.

Simultaneous ingestion of food leads to a delayed but complete absorption of acetylsalicylic acid, implying that its rate of absorption, but not the extent of absorption, is altered by food. Due to the mechanistic relationship between the total plasma exposure of acetylsalicylic acid and its inhibitory effect on platelet aggregation, the delay of absorption for TRINPRIN is not considered relevant for the chronic therapy with low dose TRINPRIN in order to accomplish adequate inhibition of platelet aggregation. Nevertheless, in order to assure the beneficial gastro-resistance of the formulation, TRINPRIN tablets should be taken preferably (30 minutes or more) before meals, with plenty of liquid (see section 4.2)

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 (see section 4.6).

Metabolism/Biotransformation
The parent drug 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. The main metabolite, salicylic acid is eliminated predominantly by hepatic metabolism. 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
Lactose monohydrate
Microcrystalline cellulose
Colloidal anhydrous silica
Potato starch
Talc
Triacetin
Methacrylic acid-ethylacrylate copolymer (1:1)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at or below 30 °C.

6.5 Nature and contents of container
PVC/Aluminium Blisters.
Pack sizes available in 10, 20, 28, 30, 50, 56, 60, 90 or 100 gastro-resistant tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION
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