SCHEDULING STATUS: S2

1 NAME OF THE MEDICINE

CARDASA 100 mg enteric-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric-coated tablet contains 100 mg acetylsalicylic acid.

Excipient with known effect

Contains sugar: Lactose monohydrate 60 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Enteric-coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CARDASA 100 mg is indicated in adults 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 at increased cardiovascular risk.

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

Patients with hepatic impairment

CARDASA 100 mg tablets is contraindicated in patients with severe hepatic failure (see section 4.3). CARDASA 100 mg tablets should be used with particular caution in patients with impaired hepatic function (see section 4.4).

Patients with renal impairment

CARDASA 100 mg tablets is contraindicated in patients with severe renal failure (see section 4.3). CARDASA 100 mg tablets 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).

Paediatric population

The safety and efficacy of CARDASA 100 mg tablets in children below 18 years of age has not been established. No data are available. Therefore, CARDASA 100 mg tablets is not recommended for use in paediatric patients below 18 years.

Method of administration

For oral use.

The tablets should preferably be taken at least 30 minutes before meals, with plenty of water. They should not be crushed, broken or chewed to ensure a release in the alkaline milieu of the intestine and to not destroy the protective effect of the enteric coating.

4.3 Contraindications

- Hypersensitivity to acetylsalicylic acid, other salicylates or to any of the excipients (listed in section 6.1).
- History of asthma caused by salicylates or other substances with a similar mechanism of action, particularly non-steroidal anti-inflammatory drugs (NSAIDs).
- Acute gastric and intestinal ulcers.
- History of gastrointestinal bleeding or perforation related to previous NSAIDs therapy.
- Active, or history of, recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven

ulceration or bleeding).

- Patients with haemophilia.
- In patients receiving oral anticoagulant therapy.
- Severe renal (eGFR < 30 mL/minute) and hepatic insufficiency.
- Patients with heart failure.
- Haemorrhagic diathesis.
- During the first and last trimester of pregnancy and during lactation (see section 4.6).
- In children under the age of 16, due to a possible risk of Reye's syndrome, unless specifically indicated (see section 4.4).
- Combination with methotrexate.

4.4 Special warnings and precautions for use

Cardiovascular effects

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 NSAIDs therapy like CARDASA 100 mg tablets.

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 CARDASA 100 mg tablets. In view of the CARDASA 100 mg tablets 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 diclofenac after careful consideration.

Gastrointestinal (GI) effects

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing dosages of NSAIDs in patients with a history of ulcers and the elderly.

These patients should commence treatment on the lowest dose available.

When gastrointestinal bleeding or ulceration occurs in patients receiving CARDASA 100 mg tablets, treatment should be stopped.

CARDASA 100 mg tablets should be given with caution to patients with a history of gastrointestinal

disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastroesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.

Gastrointestinal bleeding, ulceration or perforation which can be fatal, has been reported with all NSAIDs including CARDASA 100 mg tablets at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs including CARDASA 100 mg tablets, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of the treatment.

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. CARDASA 100 mg tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Pregnancy

Regular use of NSAIDs such as CARDASA 100 mg tablets 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 newborn. The onset of labour may be delayed, and its duration increased.

CARDASA 100 mg tablets may cause impaired female fertility (see section 4.6)

The optimal dose for inhibition of platelet aggregation in humans is not known. Do not use CARDASA 100 mg tablets for indications related to the inhibition of platelet aggregation unless directed by a doctor.

CARDASA 100 mg tablets decreases platelet adhesiveness and increases bleeding time. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors, or anti-platelet agents such as clopidogrel and ticlopidine (see section 4.5).

Other NSAIDs

The concomitant use of CARDASA 100 mg tablets with NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Gout

The product should not be given to patients with gout as serum urate may be increased and acute gout attacks may be precipitated unless recommended by a healthcare professional.

Surgical procedures

CARDASA 100 mg tablets should be stopped several days before scheduled surgical procedures due to increased bleeding time.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as CARDASA 100 mg tablets. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. The 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 CARDASA 100 mg tablets and evaluate the patient immediately.

Foetal renal dysfunction

The use of NSAIDS around 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. CARDASA 100 mg tablets should be withdrawn one week before surgery because of the possibility of increasing the bleeding times.

Respiratory effects

CARDASA 100 mg tablets may cause allergic reactions, more commonly in asthmatics. Some persons especially asthmatics, exhibit notable sensitivity to acetylsalicylic acid which may provoke various hypersensitivity reactions which may include skin eruptions, urticaria, angioedema, paroxysmal bronchospasm, and dyspnoea.

Renal effects

CARDASA 100 mg tablets should be administered with caution to patients with impaired renal function, dyspepsia, anaemia and when the patient is dehydrated.

Paediatric use

CARDASA 100 mg tablets has been implicated in Reye's Syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza, which affects the brain and the liver, and can be fatal. For this reason, CARDASA 100 mg tablets should not be given to children under the age 16 unless specifically indicated.

Prolonged use of high doses my lead to anaemia, blood dyscrasia, perforation or gastrointestinal haemorrhage, peptic ulceration (sometimes fatal), and renal papillary necrosis.

SLE and mixed connective tissue disease

Systemic lupus erythematosus and mixed connective tissue disease, due to increased risk of aseptic meningitis (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Other NSAIDS or other salicylate including cyclo-oxygenase-2 selective inhibitors

Concomitant therapy with other gastric irritants, such as non-steroidal anti-inflammatory agents may result in an increase of side effects.

NSAIDs

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

Anticoagulants

CARDASA 100 mg tablets may enhance the activity of coumarin anticoagulants, such as warfarin. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as anticoagulants such as warfarin, antiplatelet agents such as clopidogrel and ticlopidine.

Methotrexate

NSAIDs can lead to decreased elimination of methotrexate and increased methotrexate side effects.

Anti-hypertensives (ACE inhibitors and angiotensin II antagonists and renin antagonists such as aliskiren) and diuretics

NSAIDs may reduce the effect of diuretics and decrease the blood pressure lowering effect of anti-hypertensive medicines.

In patients with compromised renal function and dehydrated patients or elderly patients the co-

administration of an ACE inhibitor or angiotensin II antagonist and CARDASA 100 mg tablets may result in further deterioration of renal function, including acute renal failure. These interactions should be considered in patients taking CARDASA 100 mg tablets concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter. Diuretics can increase the risk of nephrotoxicity of CARDASA 100 mg tablets.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs)

SSRI may lead to an increased risk of bleeding including gastrointestinal bleeding.

Uricosuric medicines

Acetylsalicylic acid diminishes the effects of anti-gout preparations such as probenecid and sulphinpyrazone.

Sedatives

Barbiturates and other sedatives may mask the respiratory symptoms of CARDASA 100 mg tablets and have been reported to enhance its toxicity.

Corticosteroids

Increased risk of gastrointestinal ulceration or bleeding (PUBs).

Calcium channel blockers

Reduced hypotensive effects, increased anti-platelet effects rarely resulting in prolonged bleeding time.

Cardiac glycosides such as digoxin

NSAIDs including CARDASA 100 mg tablets may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma digoxin levels.

Varicella vaccine

Avoid use of acetylsalicylic acid in varicella vaccine recipients due to a possible association with Reye's syndrome.

Ibuprofen

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

Ciclosporin

There is increased risk of nephrotoxicity with CARDASA 100 mg tablets.

Tacrolimus

There is a possible increased risk of nephrotoxicity when CARDASA 100 mg tablets are given with tacrolimus.

Zidovudine

There is an increased risk of haematological toxicity when CARDASA 100 mg tablets are given with zidovudine.

Metoclopramide and domperidone

Metoclopramide and domperidone may increase the rate of absorption of CARDASA 100 mg tablets.

Valproate

CARDASA 100 mg tablets may increase valproate levels resulting in valproate toxicity.

Quinolone antibiotics

CARDASA 100 mg tablets can increase the risk of convulsions associated with quinolone antibiotics. Patients taking CARDASA 100 mg tablets and quinolones may have an increased risk of developing convulsions.

Mifepristone

CARDASA 100 mg tablets can reduce the effect of mifepristone.

Antidiabetic medicines e.g. insulin, sulphonylureas

Increased hypoglycaemic effect by high doses of CARDASA 100 mg tablets via hypoglycaemic action of CARDASA 100 mg tablets and displacement of sulphonylurea from its plasma protein binding sites.

Alcohol

Increased damage to gastrointestinal mucosa and prolonged bleeding time due to additive effects of CARDASA 100 mg tablets and alcohol.

Interference with laboratory tests

Salicylates may produce falsely increased results for blood creatinine, urate (low-dose acetylsalicylic acid) and urea. Falsely decreased results may be obtained for blood thyroxine and urate (> 4g/day acetylsalicylic acid) and for urinary 5-HIAA (with nitroso-naphthol method). Urinary VMA (HMMA) levels may be falsely increased or decreased depending on the method of analysis. Urinary glucose oxidase: acetylsalicylic acid may cause a false negative test in the presence of glycosuria.

4.6 Fertility, pregnancy and lactation

Pregnancy

CARDASA 100 mg tablets should not be taken during the first and third trimesters of pregnancy and should be avoided during the second trimesters.

Regular use of non-steroidal anti-inflammatory drugs 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 newborn. The onset of labour may be delayed, and its duration increased. The use of NSAIDs around 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

Breastfeeding

CARDASA 100 mg tablets should not be taken during lactation.

Fertility

Medicines such as CARDASA 100 mg tablets which inhibit cycle-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect of ovulation. This is reversible on withdrawal of treatment.

4.7 Effects on ability to drive and use machines

CARDASA 100 mg tablets causes dizziness, which may affect the ability to drive a vehicle or operate machinery.

4.8 Undesirable effects

System Organ Class	Frequency	Adverse events
Blood and lymphatic system disorders	Frequency not known	Hypoprothrombinaemia, thrombocytopenia, aplastic anaemia, agranulocytosis, pancytopenia.
Immune system disorders	Frequency not known	Various skin eruptions, pyrexia, angioedema, oedema.
Metabolism and nutrition disorders	Frequency not known	Sodium retention and fluid retention.

Nervous system disorders	Frequency not known	Meningitis, headache, dizziness.
Cardiac disorders	Frequency not known	Hypertension, cardiac failure.
Vascular disorders	Frequency not known	Hypertension.
Respiratory, thoracic and mediastinal disorders	Frequency not known	Respiratory tract reactivity, bronchospasm, asthma, dyspnoea, rhinitis.
Gastrointestinal disorders	Frequent	Gastrointestinal disturbances including nausea, vomiting and dyspepsia. Gastrointestinal haemorrhage, melaena, haematemesis, gastritis, diarrhoea, constipation, flatulence, peptic ulcer, mouth ulceration (ulcerative stomatitis).
Hepatobiliary disorders	Frequency not known	Hepatotoxicity.
	Less frequent	Transaminases increased.
Skin and subcutaneous tissue disorders	Frequency not known	Stevens-Johnson syndrome, toxic epidermal necrolysis, rash, urticaria, pruritus. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4).
Renal and urinary disorders	Frequency not known	Increased blood uric acid.
Investigations	Frequency not known	Bleeding time prolonged, platelet adhesiveness decreased.

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 medicine. Healthcare professionals 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 the SAHPRA website.

4.9 Overdose

Symptoms of overdose

Common features include dizziness (vertigo), tinnitus, sweating, nausea, vomiting, fluid and electrolyte losses (dehydration), deafness, warm extremities with bounding pulses, increased respiratory rate, ketosis and hyperventilation.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH is usual in adults and children over the age of 4 years.

In children aged 4 years or less, (serious signs of overdosage may develop rapidly), a dominant metabolic acidosis is common.

Uncommon features include haematemesis, hyperpyrexia, altered glucose metabolism (hypoglycaemia), hypokalaemia, thrombocytopenia, increased international normalise/ prothrombin time ratio (INR/PTR), intravascular coagulation, renal failure, and non-cardiac pulmonary oedema.

Depression of central nervous system may lead to coma, (mental) confusion, disorientation, cardiovascular collapse, and respiratory failure. Convulsions are less common in adults than in children.

Treatment of overdose

In cases of overdosage, consult a doctor immediately. Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/ kg.

Forced alkaline diuresis, restoration of fluid, electrolyte and acid balance, dialysis and supportive therapy may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 8 Medicines acting on the blood and haemopoietic system

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin. ATC code: N02BA01.

Acetylsalicylic acid has analgesic, anti-pyretic and anti-inflammatory actions.

Acetylsalicylic acid 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 well absorbed from the gastrointestinal tract. During and after absorption, acetylsalicylic acid is converted into its main metabolite, salicylic acid.

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

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 half-life 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

Colloidal anhydrous silica

Lactose monohydrate

Methacrylic acid-ethylacrylate copolymer (1:1) dispersion 30 %

Microcrystalline cellulose

Potato starch

Talc

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

PVC/aluminium blister packs containing 30, 50 or 100 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Kempton Park

Gauteng, 1601

Tel. no.: +27 11 451 1300

8 MARKETING AUTHORISATION NUMBER(S)

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