ANNOTATED PROPOSED PROFESSIONAL INFORMATION

1.5.5.3 ANNOTATED PROPOSED PROFESSIONAL INFORMATION FOR DISPRIN® CARDIOCARE

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

DISPRIN® CARDIOCARE 100 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 mg Aspirin per tablet.

Sugar free

Contains sweetener: Saccharin 0,3 mg per tablet

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

A white matte circular, flat tablet, with bevelled edges embossed on one side with sword motif and having a lemon odour.

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 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

Use the lowest effective dose for the shortest possible duration of treatment

Adults:

100 to 300 mg (1 to 3 tablets) to be taken every day, preferably at the same time each day.

Method of administration

For oral administration

DISPRIN® CARDIOCARE disperses on the tongue without water. The tablets should preferably be taken after food to reduce gastrointestinal irritation.

Special populations

Paediatric patients:

DISPRIN CARDIOCARE is not recommended for use in paediatric patients, below 16 years (See section 4.3 and section 4.4).

Elderly:

DISPRIN® CARDIOCARE should be used with caution in elderly patients as they are more prone to the potential adverse events associated with NSAID treatment.

Patients with renal impairment:

DISPRIN CARDIOCARE is contraindicated in patients with severe renal impairment (see section 4.3). DISPRIN CARDIOCARE should be used with caution in patients with impaired renal function (see section 4.4).

Patients with hepatic impairment:

DISPRIN CARDIOCARE is contraindicated in patients with severe hepatic failure (see section 4.3).

4.3 Contraindications

DISPRIN® CARDIOCARE is contraindicated:

- in patients with hypersensitivity to aspirin or to any excipients listed under "COMPOSITION" or to other NSAIDs
- in patients with peptic ulcers,
- in patients with haemophilia,
- in patients with severe renal impairment (eGFR < 30 mL/minute,
- in patients with hepatic impairment (Child-Pugh C)
- in patients receiving oral anti-coagulant therapy,
- during the first and third trimesters of pregnancy and during lactation (see section 4.6).
- in patients with a history of gastrointestinal bleeding or perforation (PUB'S) related to previous NSAIDs including DISPRIN® CARDIOCARE,
- in patients with active or history of recurrent ulcer/haemorrhage/perforations,
- in patients with heart failure (NYHA grade III or IV),
- in patients with nasal polyps associated with asthma

- 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 at doses of 15 mg/week or more

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 DISPRIN® CARDIOCARE.

Caution is required inpatients with a history of hypertension and/ or heart failure as fluid retention and oedema have been reported in association with DISPRIN® CARDIOCARE therapy. In view of the DISPRIN® CARDIOCARE'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 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 DISPRIN® CARDIOCARE, treatment should be stopped.

DISPRIN® CARDIOCARE 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.

Gastrointestinal bleeding, ulceration or perforation which can be fatal, has been reported with all NSAIDs including DISPRIN® CARDIOCARE 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 DISPRIN® CARDIOCARE, 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. DISPRIN® CARDIOCARE 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 DISPRIN® CARDIOCARE 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.

DISPRIN® CARDIOCARE 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 DISPRIN® CARDIOCARE for indications related to the inhibition of platelet aggregation unless directed by a doctor.

DISPRIN® CARDIOCARE 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-re-uptake inhibitors, or anti-platelet agents such as clopidogrel and ticlopidine (see section 4.5).

Other NSAIDs:

The concomitant use of DISPRIN® CARDIOCARE 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:

DISPRIN® CARDIOCARE should be stopped several days before scheduled surgical procedures due to increased bleeding time.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) :

Drug Reaction with Eossinophillia and Systemic Symptoms (DRESS) has been reportd in patients taking NSAIDs such as DISPRIN® CARDIOCARE. Some of these events have been fatal or life-threatening. DRESS typically, althought not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. The clinical manifestations may include hepatitis, nephritis, haematologocal abnormalities, myocarditis, or myosiditis. Somestimes symptoms of DRESS mayresemble 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 DISPRIN® CARDIOCARE 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.

DISPRIN® CARDIOCARE should be withdrawn one week before surgery because of the possibility of increasing the bleeding times.

Respiratory effects:

DISPRIN® CARDIOCARE may cause allergic reactions, more commonly in asthmatics. Some persons especially asthmatics, exhibit notable sensitivity to aspirin which may provoke various hypersensitivity reactions which may include skin eruptions, urticaria, angioedema, paroxysmal bronchospasm, and dyspnoea.

Renal effects:

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

Paediatric use:

DISPRIN® CARDIOCARE 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, DISPRIN® CARDIOCARE 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 salicylates 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.

Anti-coagulants:

DISPRIN® CARDIOCARE 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 DISPRIN®

CARDIOCARE may result in further deterioration of renal function, including acute renal failure. These interactions should be considered in patients taking DISPRIN® CARDIOCARE 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 DISPRIN® CARDIOCARE.

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

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

Uricosurics:

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

Sedatives:

Barbiturates and other sedatives may mask the respiratory symptoms of DISPRIN® CARDIOCARE 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 DISPRIN® CARDIOCARE may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma digoxin levels.

Varicella vaccine:

Avoid use of aspirin 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 aspirin on platelet aggregation when they are dosed concomitantly.

Ciclosporin:

There is increased risk of nephrotoxicity with DISPRIN® CARDIOCARE.

Tacrolimus:

There is a possible increased risk of nephrotoxicity when DISPRIN® CARDIOCARE are given with tacrolimus.

Zidovudine:

There is an increased risk of haematological toxicity when DISPRIN® CARDIOCARE are given with zidovudine.

Metoclopramide and domperidone:

Metoclopramide and domperidone may increase the rate of absorption of DISPRIN® CARDIOCARE**.**

Valproate:

DISPRIN® CARDIOCARE may increase valproate levels resulting in valproate toxicity.

Quinolone antibiotics:

Animal data indicate that DISPRIN® CARDIOCARE can increase the risk of convulsions associated with quinolone antibiotics. Patients taking DISPRIN® CARDIOCARE and quinolones may have an increased risk of developing convulsions.

Mifepristone:

DISPRIN® CARDIOCARE can reduce the effect of mifepristone.

Antidiabetic Medicines, e.g. insulin, sulphonylureas:

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

Alcohol:

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

Interference with laboratory tests:

Salicylates may produce falsely increased results for blood creatinine, urate (low dose aspirin) and urea. Falsely decreased results may be obtained for blood thyroxine and urate (>4g/day aspirin) 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: aspirin may cause a false negative test in the presence of glycosuria.

4.6 Fertility, pregnancy and lactation

Pregnancy:

DISPRIN® CARDIOCARE 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.

Lactation:

DISPRIN® CARDIOCARE should not be taken during lactation.

Fertility:

Medicines such as DISPRIN® CARDIOCARE which inhibit cyclo-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

DISPRIN® CARDIOCARE has none to 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 DISPRIN® CARDIOCARE before drivinga vehicle or operating 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, and oedema
Metabolism and Nutrition Disorders	Frequency not known	Sodium retention and fluid retention
Nervous System Disorders	Frequency not known	Meningitis, Headache and 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, and rhinitis
Gastrointestinal Disorders	Frequent	Gastrointestinal disturbances including nausea, vomiting and dyspepsia. Gastrointestinal haemorrhage melaena, haematemesis, gastritis, diarrhoea, constipation, flatulence, peptic ulcer, and mouth ulceration (ulcerative stomatitis).
Hepato-biliary 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 and pruritus

	Frequency not known	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 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 Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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

Aspirin has analgesic, anti-pyretic and anti-inflammatory actions.

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

Following oral administration, acetylsalicylic acid is well absorbed from the gastro-intestinal 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.

5.3 Preclinical safety data

The preclinical safety profile of acetylsalicylic acid is well documented. In animal studies, salicylates caused kidney damage at high dosages. Acetylsalicylic acid has been extensively studied in vitro and in vivo for mutagenicity; no relevant evidence of a mutagenic potential was found. The same applies to carcinogenicity studies. Salicylates have exhibited teratogenic effects in animal studies and a number of different species. Implantation disorders, embryotoxic and fetotoxic effects and impairment of learning ability in the offspring after prenatal exposure have been described.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine

Maize starch

Microcrystalline cellulose

Purified talc

Lemon flavour 51124

Saccharin (sweetener)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Packs of 30 tablets in foil

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Reckitt Benckiser Pharmaceuticals (Pty) Ltd

8 Jet Park Road

Elandsfontein

1601

8. REGISTRATION NUMBER

31/2.8/0071

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date on the registration certificate of DISPRIN® CARDIOCARE: 16 January 1997

10. DATE OF REVISION OF THE TEXT

Date of the most recently revised package insert as approved by council: 17 April 2024

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