## 1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

**SCHEDULING STATUS**

**S2**

### 1. NAME OF THE MEDICINE

**CANCARD** 81 mg enteric coated tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric-coated tablet contains 81 mg aspirin (acetyl salicylic acid).

Sugar free.

For full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Enteric-coated tablets.

CANCARD is a white to off white enteric-coated, round, biconvex tablet, plain on both sides.

### 4. CLINICAL PARTICULARS

#### 4.1. Therapeutic indications

CANCARD is indicated in adults for indications related to inhibition of platelet aggregation:

- 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**

*Adults*

**For inhibition of platelet aggregation:**

One to three tablets as directed by your doctor to be taken every day, preferably at the same time each day.

The optimal dose for inhibition of platelet aggregation in humans is not known. CANCARD should not be used for indications related to the inhibition of platelet aggregation unless directed by a doctor.

**Paediatric population**

CANCARD should not be administered to children and adolescents younger than 16 years.

**Method of administration**

For oral administration.

CANCARD should be swallowed whole. Do not chew, break or crush the tablet as this will destroy the protective effect of the enteric coating.

## 4.3. Contraindications

CANCARD is contraindicated in:

- Patients with hypersensitivity to aspirin (acetyl salicylic acid), salicylic acid compounds, prostaglandin synthetase inhibitors (especially aspirin-sensitive asthmatics) or to any excipients in CANCARD, see listed in section 6.1,
- a history of asthma induced by the administration of salicylates or medicines with a similar action, notably non-steroidal anti-inflammatory medicines,

- active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage/perforations or other kinds of bleeding such as cerebrovascular haemorrhages,
- history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including aspirin, as contained in CANCARD,
- patients with haemorrhagic disorders such as haemorrhagic diathesis, coagulation disorders such as haemophilia and thrombocytopenia,
- severe hepatic impairment,
- severe renal impairment,
- patients with gout,
- pregnancy and lactation (see section 4.6),
- heart failure,
- patients taking methotrexate at doses > 15 mg/week (see section 4.5).

## 4.4. Special warnings and precautions for use

*Drug reaction with eosinophilia and systemic symptoms*

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs such as CANCARD. 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. 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 CANCARD and evaluate the patient immediately.

Aspirin, as contained in CANCARD, has been implicated in Reye's Syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza. A doctor should be consulted before CANCARD is used in such patients (see section 4.2).

Some persons, especially asthmatics exhibit notable sensitivity to aspirin, as contained in CANCARD, which may provoke various hypersensitivity reactions (see section 4.8).

Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with the use of aspirin, such as in CANCARD (see section 4.8). CANCARD should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Aspirin, as contained in CANCARD, increases the bleeding time and in large doses may cause hypoprothrombinaemia.

Patients should report any unusual bleeding symptoms to their doctor. If gastrointestinal bleeding or ulceration occurs the CANCARD treatment should be stopped.

There is an increased risk of haemorrhage particularly during or after operative procedures (even in cases of minor procedures, e.g. tooth extraction). Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary. CANCARD should be discontinued one week before scheduled surgical procedures.

CANCARD is not recommended during menorrhagia where it may increase menstrual bleeding.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including aspirin, as in CANCARD, especially gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

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

CANCARD 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.

CANCARD may cause hepatotoxicity particularly in patients with juvenile arthritis and other connective tissue disorders.
Use with caution in patients with impaired hepatic function.

Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

CANCARD should be administered with caution to patients with impaired renal function, dyspepsia, anaemia and when the patient is dehydrated since the use of NSAIDs, such as CANCARD, may result in deterioration of renal function (see section 4.3).

CANCARD is to be used with caution in cases of hypertension and/or heart failure as fluid retention and oedema have been reported in association with aspirin, as in CANCARD, therapy. In view of CANCARD's inherent potential to cause fluid retention, heart failure may be precipitated in compromised patients (see section 4.3).

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with aspirin, as contained in CANCARD taken at over dosage (see section 4.5).

Concomitant treatment with CANCARD and other medicines that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet medicines, anti-inflammatory medicines and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage (see section 4.5). If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox (see section 4.5).

Aspirin, as contained in CANCARD, in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks (see section 4.5).

*Use in pregnancy*

CANCARD is contraindicated and should not be used in pregnancy (see sections 4.3 and 4.6)

**Paediatric population**

The safety and efficacy of CANCARD in children has not yet been established. Aspirin, as contained in CANCARD, may be a contributory factor in the causation of Reye's Syndrome in some children (see section 4.2), a very rare but possibly life threatening illness requiring immediate medical attention.

In certain viral illnesses. especially influenzae A, influenzae Band varicella, there is a risk of Reye's syndrome. The risk may be increased when CANCARD is given concomitantly. Should persistent vomiting occur with such diseases, this may be a sign of Reye's syndrome (see section 4.2).

## 4.5. Interaction with other medicines and other forms of interaction

*Methotrexate*

The combined medicines, methotrexate and CANCARD enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by anti-inflammatory medicines in general, and displacement of methotrexate from its plasma protein binding by salicylates.

***At doses > 15 mg/week:*** The concomitant use of methotrexate with CANCARD is contraindicated (see section 4.3).

***At doses < 15 mg/week:*** This combination should be used with caution. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

*Uricosuric medicines*

Aspirin as contained in CANCARD diminishes the effects of uricosuric medicines such as probenecid, benzbromarone and sulfinpyrazone. (competition of renal tubular uric acid elimination). The combination should be avoided (see section 4.4).

*Anticoagulants e.g. coumarin, heparin, warfarin*

Aspirin, as contained in CANCARD, may enhance the activity of coumarin anticoagulants such as warfarin.

Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored (see section 4.4).

*Anti-platelet medicines (e.g. clopidogrel and dipyridamole) and selective serotonin reuptake inhibitors (SSRIs; such as sertraline or paroxetine)*

Increased risk of gastrointestinal bleeding due to possibly synergistic effect (see section 4.4).

*Antidiabetics e.g. insulin, sulfonylureas*

Salicylates, such as CANCARD, may increase the hypoglycaemic effect of sulfonylureas (see section 4.4). Increased hypoglycaemic effect by high doses of acetylsalicylic acid via hypoglycaemic action of acetylsalicylic acid and displacement of sulfonylurea from its plasma protein binding.

*Digoxin and lithium*

Aspirin, as contained in CANCARD, impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium

is recommended when initiating and terminating treatment with CANCARD. Dose adjustment may be necessary.

*Antihypertensives and diuretics*

NSAIDs, such as aspirin as contained in CANCARD, may decrease the antihypertensive effects of diuretics and other antihypertensive medicines. Concomitant administration of aspirin at higher doses with ACE-inhibitors increases the risk of acute renal insufficiency.

*Diuretics in combination with aspirin in high doses*

Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

*Carbonic anhydrase inhibitors (acetazolamide)*

May result in severe acidosis and increased central nervous system toxicity.

*Systemic corticosteroids*

The risk of gastrointestinal perforation, ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered (see section 4.4).

*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.

*Other NSAIDs*

Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects. Use of two or more NSAIDs concomitantly could result in an increase in side effects.

*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 CANCARD.

*Metamizole*

Metamizole may reduce the effect of aspirin as contained in CANCARD on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose CANCARD for cardioprotection.

*Ciclosporin, tacrolimus*

Concomitant use of NSAIDs, such as CANCARD, and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these medicines and CANCARD.

*Antacids*

The excretion of aspirin, as contained in CANCARD, is increased by alkaline urine, which can occur with some antacids.

*Alcohol*

Concomitant administration of alcohol and aspirin as contained in CANCARD increases damage to gastrointestinal mucosa, increases the risk of gastrointestinal bleeding and prolongs bleeding time due to additive effects of aspirin and alcohol.

*Phenytoin, valproic acid*

Aspirin as contained in CANCARD may enhance the activity of phenytoin and valproic acid.

Increased toxicity of valproic acid due to displacement from protein binding sites.
High-dose aspirin can cause protein-binding displacement of phenytoin. Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead 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.

## 4.6. Fertility, pregnancy and lactation

The use of CANCARD is contraindicated in pregnancy and during lactation (see section 4.3).

**Women of childbearing potential**

If aspirin as contained in CANCARD is used by a woman attempting to conceive, the dose should be kept as low and duration of treatment as short as possible.

**Pregnancy**

Regular use of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin may result in:

*First trimester*

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various

malformations including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

*Second and Third trimester*

During the third trimester of pregnancy, 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 oligo-hydroamniosis. At the end of pregnancy, the mother and the neonate may be exposed to: possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses; inhibition of uterine contractions resulting in delayed or prolonged labour.

**Breastfeeding**

Low quantities of salicylates and of their metabolites are excreted into the breast milk. Aspirin is secreted into breast milk in low concentration and should, therefore, be avoided during lactation because of the possible risk of Reye's Syndrome and the fact that high doses could potentially impair platelet function.

**Fertility**

There are no fertility data.

## 4.7. Effects on ability to drive and use machines

CANCARD may cause dizziness. Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that CANCARD does not adversely affect their ability to do so safely (see section 4.8).

## 4.8. Undesirable effects

*a) Tabulated list of adverse reactions*

| System organ class | Frequent | Less frequent | Frequency unknown (cannot be estimated from the available data) |
|---|---|---|---|
| **Blood and the lymphatic system disorders** | Increased bleeding tendencies | Thrombocytopenia, granulocytosis, aplastic anaemia | Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding, perioperative haemorrhage, haematomas, epistaxis, urogenital bleedings and gingival bleedings, have been observed and in large doses may cause hypoprothrombinaemia. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses) |
| **Immune system disorders** | | Hypersensitivity reactions such as skin eruptions, urticaria, angio-edema, allergic oedema, anaphylactic reactions including shock | |
| **Metabolism and nutrition disorders** | | | Hyperuricemia |
| **Nervous system disorders** | | | Dizziness, |
| | | Intracranial haemorrhage | headache, vertigo |
| **Ear and labyrinth disorders** | | | Reduced hearing ability, tinnitus |
| **Cardiac disorders** | | | Oedema, hypertension, cardiac failure |
| **Vascular disorders** | | Haemorrhagic vasculitis | |
| **Respiratory, thoracic and mediastinal disorders** | | Rhinitis, dyspnoea, bronchospasm, asthma attacks | |

| | | | |
|---|---|---|---|
| **Gastrointestinal disorders** | Nausea, dyspepsia, vomiting, peptic ulcers, perforation or gastrointestinal bleeding, diarrhoea, flatulence, constipation, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis, Crohn's disease, gastritis | | Erosion |
| **Hepato-biliary disorders** | | Transient hepatic impairment with increase in liver transaminases has very rarely been reported | Hepatic insufficiency, hepatotoxicity (see section 4.4) |
| **Skin and subcutaneous tissue disorders** | | Urticaria, Stevens-Johnson syndrome, Lyell's syndrome, purpura, erythema nodosum, erythema multiforme | Toxic epidermal necrolysis, bullous reactions, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4). |
| **Renal and urinary disorders** | | | Impaired renal function, salt and water retention |
| **Reproductive system and breast disorders** | | Menorrhagia | |

*b) Description of selected adverse reactions*

**Blood and the lymphatic system disorders:** Symptoms of prolonged bleeding may persist for a period of 4 to 8 days after aspirin as contained in CANCARD discontinuation. As a result, there may be an increased risk of bleeding during surgical procedures.

*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

**Aspen Pharmacare:**

**E-mail:** Drugsafety@aspenpharma.com

**Tel:** 0800 118 088

### 4.9. Overdose

**Symptoms**

Mild chronic salicylate intoxication usually occurs only after repeated administration of large doses. Symptoms include dizziness, tinnitus, deafness, sweating, nausea, headache, vomiting and mental confusion.

Symptoms of more acute or severe intoxication following overdosage include hyperventilation, fever, restlessness, ketosis, respiratory alkalosis and metabolic acidosis.

Depression of the central nervous system may lead to coma, cardiovascular collapse, severe hypoglycaemia or respiratory failure.

In children drowsiness and metabolic acidosis commonly occur, hypoglycaemia may be severe.

Overdose may be harmful for elderly patients and particularly for small children (therapeutic overdose or frequent accidental intoxications may be fatal).

**Treatment**

In case 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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Category and Class: A 8 Medicines acting on the blood and haemopoietic system.

Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors excl. heparin

ATC code: B01AC06

*Mechanism of action*

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**

After oral administration, aspirin is rapidly absorbed from the gastrointestinal tract. However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process.

**Distribution**

Acetylsalicylic acid (aspirin), as well as the main metabolite salicylic acid, are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. Maximum plasma concentration is reached after 0,3 to 2 hours (total salicylate). The volume of distribution of aspirin is ca. 0,16 L/kg of body weight.

Salicylic acid passes into breast milk and crosses the placenta.

**Biotransformation**

Aspirin is rapidly metabolised to salicylic acid, with a half-life of 15 to 30 minutes. Salicylic acid is subsequently predominantly converted into glycine and glucuronic acid conjugates. Elimination kinetics of salicylic acid is dose-dependent, because the metabolism is limited by liver enzyme capacity. Thus, elimination half-time varies and is 2 to 3 hours after low doses (75 mg to 160 mg).

**Elimination**

Aspirin and its metabolites are predominantly excreted via the kidneys.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Colloidal anhydrous silica, hypromellose (E464), macrogol (E1521), methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 %, microcrystalline cellulose, pregelatinised starch, purified talc, stearic acid, titanium dioxide (E171), triethyl citrate.

### 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf life

24 months

### 6.4. Special precautions for storage

Store at or below 25 °C.

### 6.5. Nature and contents of container

30, 50 or 100 tablets are packed in a white round high density polyethylene (HDPE) bottle with a white round opaque HDPE screw cap with induction seal, together with a silica gel desiccant or silica gel-molecular sieve dessicant, and leaflet.

10 tablets are packed in a clear rigid polyvinylchloride, polyethylene and polyvinylidene chloride film sealed with an aluminium foil backing. 3 or 10 blister strips are packed into an outer cardboard carton together with a leaflet.

10 tablets are packed in a cold forming foil made of oriented polyamide (OPA), aluminium and polyvinylchloride. 3 or 10 blister strips are packed into an outer cardboard carton together with a leaflet.

### 6.6. Special precautions for disposal

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

## 8. REGISTRATION NUMBER

48/2.7/0609

## 9. DATE OF FIRST AUTHORISATION

23 January 2024

## 10. DATE OF REVISION OF TEXT

23 January 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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