PROFESSIONAL INFORMATION FOR CLOPIDOGREL 75 MG TABLETS

SCHEDULING STATUS **S3**

1. NAME OF THE MEDICINE

AVIOLIX 75 (film-coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AVIOLIX 75

Each film-coated tablet contains

Clopidogrel hydrogen sulphate (molar equivalent of 75 mg of clopidogrel base)

AVIOLIX 75 Contains sugar (191,375 mg of lactose monohydrate).

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

AVIOLIX 75:

Pink coloured, circular, biconvex, film-coated tablet debossed “L11” on one side of the tablet and plain on other surface.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVIOLIX 75 is indicated for the following:

Recent myocardial infarction (MI), recent stroke or established peripheral arterial disease:

Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days until less than 35 days) or established peripheral arterial disease.

This indication is based on the results of the CAPRIE study comparing clopidogrel with acetyl salicylic acid (ASA). The slight but statistically significant difference of clopidogrel over ASA was mainly related to patients enrolled due to peripheral arterial disease.

4.2 Posology and method of administration

Posology:

Clopidogrel should be given as a single daily dose of 75 mg with or without food.

If a dose is missed:

- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.
- For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.

Special populations

Renal impairment

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore, clopidogrel should be used with caution in these patients (see section 4.4).

Hepatic impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population (see section 4.4).

Paediatric population

Safely in patients below the age of 18 years have not been established.

Method of administration:

Oral

4.3 Contraindications

AVIOLIX 75 is contraindicated in:

- Hypersensitivity to clopidogrel or to any of the excipients listed in 6.1.
- Active pathological bleeding such as peptic ulcer and intracranial haemorrhage.

- Safety and efficacy in patients below the age of 18 years have not been established.
- Safety and efficacy in pregnancy and lactation have not been established (see section 4.6).
- Severe liver impairment.
- Thrombocytopenia and platelet dysfunction.

4.4 Special warnings and precautions for use

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH CLOPIDOGREL. DURING POSTMARKETING EXPERIENCE, MOST CASES WERE REPORTED IN THE FIRST 2 WEEKS OF TREATMENT. PRESCRIBERS SHOULD ALSO WARN PATIENTS ABOUT THE SIGNS AND SYMPTOMS OF THROMBOTIC THROMBOCYTOPENIC PURPURA.

Thrombotic thrombocytopenic purpura

TTP is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with other neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis. Due to the risk of fatal outcome, in the event of suspected TTP, **AVIOLIX** 75 should be stopped.

Bleeding and haematological disorders

Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment (see section 4.8).

As with other antiplatelet medicines, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with acetylsalicylic acid (aspirin), heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), or other medicines associated with bleeding risk such as pentoxifylline (see section 4.5).

Patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery.

The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see INTERACTIONS).

Clopidogrel produces irreversible inhibition of platelet aggregation for the life of the platelet, which is 7-10 days. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, **AVIOLIX 75** should be discontinued 7 days prior to surgery.

Patients should be told it may take longer than usual to stop bleeding when they take **AVIOLIX 75** and that they should report any unusual bleeding to their medical practitioner. Patients should inform medical practitioners and dentists that they are taking **AVIOLIX 75** before any surgery schedule and before any new medicine is taken.

AVIOLIX 75 prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intra-ocular) such as ulcer. Medicines that might induce such lesions (such as acetylsalicylic acid [aspirin] and non-steroidal anti-inflammatory drugs) should be used with caution in patients taking **AVIOLIX 75**.

Neuraxial procedures

AVIOLIX must be discontinued for 7 days before a neuraxial procedure. The medicine may be restarted 2 hours after the neuraxial procedure or epidural catheter removal.

If a neuraxial procedure administration of **AVIOLIX** may be associated with the formation of a hematoma in the spinal or an epidural space, which may compromise neurological function of the spinal cord. Neurological monitoring should be carried out for 24 hours after the neuraxial procedure.

Recent ischaemic stroke

In view of the lack of data, **AVIOLIX 75** cannot be recommended in acute ischaemic stroke (less than 7 days).

In patients with acute myocardial infarction, **AVIOLIX** therapy should not be initiated within the first few days following myocardial infarction. In view of the lack of data, **AVIOLIX** cannot be recommended in unstable angina PTCA (stenting) and CABG.

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicines that inhibit the activity of this enzyme would be expected to result in reduced medicine levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged (see section 4.5).

CYP2C8 substrates

Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products (see section 4.5).

Acquired haemophilia

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Cross-reactions among thienopyridines

Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported. Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of

developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

Hepatic impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses; clopidogrel should therefore be used with caution in this population.

Renal impairment

Therapeutic experience with clopidogrel is limited in patients with renal impairment and therefore should be used with caution in these patients.

Lactose intolerance:

Contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **AVIOLIX 75.**

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Medicines associated with bleeding risk:

There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicines associated with bleeding risk should be undertaken with caution.

Oral anticoagulants:

The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings. Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, co-administration of clopidogrel with warfarin increases the risk of bleeding because of independent effects of haemostasis.

Glycoprotein IIb/IIIa inhibitors

Clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors.

Acetylsalicylic Acid (aspirin):

ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation but clopidogrel potentiates the effect of ASA (aspirin) on collagen-induced platelet aggregation. However, concomitant administration of 500 mg ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4). However, clopidogrel and ASA have been administered together for up to one year (see section 5.1).

Heparin (anticoagulants):

In a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution (see section 4.4).

Thrombolytics:

The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic medicines and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic medicines and heparin are co-administered with ASA (see section 4.8).

NSAIDs:

In a clinical study conducted in healthy volunteers the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding

with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution (see section 4.4).

SSRIs:

Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with **AVIOLIX 75** should be undertaken with caution.

CYP2C8 substrate medicines:

Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. *In vitro* studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations concomitant administration of clopidogrel and medicines primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.

Other concomitant therapy:

Since clopidogrel is metabolised to its active metabolite partly by CYP 2C19 use of medicines that inhibit the activity of this enzyme, would be expected to result in reduced levels of the active metabolite and a reduction in clinical efficacy. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g. omeprazole and esomeprazole) should be discouraged.

Medicinal products that are strong or moderate CYP2C19 that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine and efavirenz.

Protein Pump Inhibitors (PPI):

Omeprazole 80 mg one daily administered either at the same time as clopidogrel or with 12 hours between administration of the two medicines, decreased the exposure of the active metabolite. The decrease was associated with a reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and

clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged (see section 4.4).

Less pronounced reductions of metabolite exposure have been observed with pantoprazole and lansoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine or both atenolol and nifedipine. The pharmacodynamic activity of clopidogrel was not significantly influenced by the coadministration of phenobarbitone, cimetidine or oestrogen.

The pharmacokinetics of digoxin or theophylline was not modified by the coadministration of clopidogrel. Antacids and H_2 antihistamines did not modify the extent of clopidogrel absorption.

Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta-blockers, AECI, calcium antagonists, cholesterol lowering medicines, coronary vasodilators, antidiabetic medicines (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

As with other oral P2Y12 inhibitors co-administration of opioid agonists has the potential to delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying. The clinical

relevance is unknown. Consider the use of a parenteral antiplatelet medicine in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

4.6 Fertility, pregnancy and lactation

Safety and efficacy of **AVIOLIX 75** in pregnancy and lactation have not been established.

Pregnancy

As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Breastfeeding

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast- feeding should not be continued during treatment with **AVIOLIX 75**.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

AVIOLIX 75 has no or negligible influence on the ability to drive and use machines. However, it may cause dizziness and vertigo and patients must therefore be advised not to drive or operate machinery if they experience these symptoms.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Less frequent: Severe neutropenia, severe thrombocytopenia (including thrombotic thrombocytopenic purpura, TTP), leukopenia, eosinophilia.

Frequency not known: Aplastic anaemia, pancytopenia, agranulocytosis, granulocytopenia, anaemia, acquired haemophilia A.

Immune system disorders:

Frequency not known: Serum sickness, angioedema, anaphylactoid reactions, cross-reactive hypersensitivity among thienopyridines, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS).

Psychiatric disorders:

Frequency not known: Hallucinations, confusion.

Nervous system disorders:

Less frequent: Headache, paraesthesia, dizziness, intracranial bleeding.

Frequency not known: Taste disturbances.

Eye disorders:

Less frequent: Eye bleeding (conjunctival, ocular, retinal).

Ear and labyrinth disorders:

Less frequent: Vertigo.

Cardiac disorders

Frequency not known: Kounis syndrome (vasospastic allergic angina/allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel.

Vascular disorders:

Frequent: Haematoma.

Frequency not known: Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Epistaxis.

Frequency not known: Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia.

Gastro-intestinal disorders:

Frequent: Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia.

Less frequent: Gastric and duodenal ulcer, gastritis, nausea, constipation, vomiting, flatulence.

Frequency not known: Retroperitoneal haemorrhage, gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis.

Reproductive systems and breast disorders:

Less frequent: Gynaecomastia.

Hepatobiliary disorders:

Frequency not known: Abnormal liver function tests, hepatitis, acute liver failure.

Skin and subcutaneous tissue disorders:

Frequent: Bruising.

Less frequent: Rash, pruritus, skin bleeding (purpura).

Frequency not known: Bullous dermatitis (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), acute generalised exanthematous pustulosis (AGEP), rash erythematous, lichen planus, urticaria, eczema.

Musculoskeletal, connective tissue and bone disorders:

Frequency not known: Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia.

Renal and urinary disorders:

Less frequent: Haematuria.

Frequency not known: Glomerulonephritis, increased blood creatinine levels.

General disorders:

Frequent: Bleeding at puncture site.

Frequency not known: Fever.

Investigations:

Less frequent: Prolonged bleeding time, decreased neutrophil count, decreased platelet count.

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

Symptoms of overdosage: prolonged bleeding time and subsequent bleeding complications

Treatment is symptomatic and supportive. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of **AVIOLIX 75**.

5. PHARMACOLOGICAL PROPERTIES

Pharmaceutical groups: A 8.2 Anticoagulants

ATC Code: B01AC-04

5.1 Pharmacodynamic properties

Clopidogrel is a specific and potent inhibitor of platelet aggregation. It acts by irreversibly modifying the platelet ADP-receptors.

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.

Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of platelet activation by released ADP.

Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate consistent with platelet turnover (approximately 7 days).

Dose-dependent inhibition of platelet aggregation was noted 2 hours after single oral doses of clopidogrel.

Repeated doses of 75 mg per day may produce inhibition of ADP-induced platelet aggregation from the first day; this may increase progressively and reach steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day may be between 40 % and 60 %. Platelet aggregation and bleeding time gradually returns to baseline values, generally within 7 days after treatment has been discontinued.

5.2 Pharmacokinetic properties

Absorption

After repeated oral doses of 75 mg per day, clopidogrel is well absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2,2-2,5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50 % based on urinary excretion of clopidogrel metabolites.

Distribution

Clopidogrel and the main circulating (inactive) metabolite bind reversibly to human plasma proteins (98 % and 94 % respectively). The binding is non-saturable *in vitro* over a wide concentration range.

Metabolism

Clopidogrel is extensively metabolised by the liver. *In vitro* and *in vivo*, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85 % of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. *In vitro*, this metabolic pathway is mediated by

CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversible to platelet receptors, thus inhibiting platelet aggregation.

Elimination

Following an oral dose of ^{14}C-labelled clopidogrel in man, approximately 50 % is excreted in the urine and approximately 46 % in the faeces in 120-hour intervals after dosing. After a single oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite is 8 hours after single and repeated administration.

Pharmacogenetics

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* aggregation assays, differ according to CYP2C19 genotype. The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in White (85 %) and Asian (99 %) poor metabolisers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metaboliser genotypes are approximately 2 % for Whites, 4 % for Blacks and 14 % for Chinese. Tests are available to determine a patient's CYP2C19 genotype.
No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71 % compared to extensive metabolisers.

At steady state, platelet aggregation inhibition (5 µM ADP) was decreased in poor metabolisers with mean IPA of 37 % compared to 58 % in the extensive metabolisers and 60 % in the intermediate metabolisers. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

In a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28 % for intermediate metabolisers, and 72 % for poor metabolisers while platelet aggregation inhibition (5 µM ADP) was decreased with differences in IPA of 5,9 % and 21.4 % respectively, when compared to extensive metabolisers.

There is some evidence that patients who are either intermediate or poor metablisers may have a higher rate of cardiovascular events (death, myocardial infarction, stroke or stent thrombosis) compared to extensive metabolisers.

Special populations

The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations:

Elderly:

In elderly (≥ 75 years) volunteers compared to young healthy volunteers, there were no differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renal impairment:

After repeated administration of 75 mg clopidogrel/day in subjects with severe renal impairment (creatinine clearance from 5 to 15 ml/min) ADP-induced platelet aggregation was lower (25 %) than that observed in healthy subjects, however, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg clopidogrel per day.

Ethnicity:

The prevalence of CYCP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to ethnicity (see Pharmacokinetic properties, Pharmacogenetics). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

5.3 Preclinical safety data

During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolising enzymes. No

effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day). Clopidogrel has been tested in a range of in vitro and in vivo genotoxicity studies, and showed no genotoxic activity. Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactose monohydrate, low substituted hydroxypropyl cellulose, silica colloidal anhydrous, castor oil hydrogenated, dimeticone, coating containing hypromellose 6cp, macrogol 400, titanium dioxide (CI No.: 77891) and iron oxide red (CI No.: 77491).

Contains sugar (191,375 mg of lactose monohydrate).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the manufacturing date for container pack and blister pack

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

1) Blister Pack:

Tablets are packed in cold form laminate OPA/AL/PVC as the forming material and 25 μ aluminium foil with 6-8 gsm heat seal lacquer as the lidding material.

Pack size: 28's, 30's

2) HDPE Container Pack:

Tablets are packed in white, round 40 ml HDPE container with 33 mm neck finish closed with 33 mm white closure with wad having induction sealing liner. Each container contains 30 tablets.

Pack size: 30's - One HDPE container contains 30 tablets.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

AVIOLIX 75: 47/8.2/0009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 February 2022

10. DATE OF REVISION OF THE TEXT

28 February 2022

PM0241-001