Final approved PI as per SAHPRA email dated 22/02/2021: submitted 26/02/2021

FINAL PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CLOVEXA (Film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 97,875 mg clopidogrel hydrogen sulfate (equivalent to 75 mg clopidogrel).

Contains lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

Pink coloured, round, biconvex, film coated tablet, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLOVEXA is indicated for the reduction of artherothrombotic events as follows:

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

The recommended daily dose of CLOVEXA is 75 mg once daily 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

The safety and efficacy of CLOVEXA in children below the age of 18 years has not been established.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, clopidogrel, or to any of the excipients listed in section 6.1.
- Active pathological bleeding such as peptic ulcer and intracranial haemorrhage.
- Safety and efficacy in children below the age of 18 years has not been established.
- Safety and efficacy in pregnancy and lactation have not been established.
- CLOVEXA is contraindicated in severe liver impairment.

4.4 Special warnings and precautions for use

Thrombotic thrombocytopenic purpura (TTP) has been reported to occur with clopidogrel during post-marketing experience. Most cases were reported in the first two weeks of treatment. Prescribers should also warn patients about the signs and symptoms of thrombotic thrombocytopenic purpura.

Thrombotic thrombocytopenic purpura

Thrombotic Thrombocytopenic Purpura (TTP) has been reported following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

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). 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 (ASA), heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), or other medicinal products 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 section 4.5).

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform medical practitioners and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Neuraxial procedures

CLOVEXA 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 is to be performed in a patient on CLOVEXA before 7 days of discontinuation, a residual antiplatelet activity test should be performed.

After a neuraxial procedure, administration of CLOVEXA may be associated with the formation of a haematoma 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.

Patients should be told that it might take longer than usual to stop bleeding when they take clopidogrel (alone or in combination with ASA), and that they should report any unusual bleeding (site or duration) to their medical pratitioner.

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.

Recent ischaemic stroke

In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

In patients with acute myocardial infarction, CLOVEXA therapy should not be initiated within the first few days following myocardial infarction.
In view of the lack of data, CLOVEXA 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 medicinal products 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 for a list of CYP2C19 inhibitors, see also section 5.2).

CYP2C8 substrates

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

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 (see section 4.8). 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.

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 4.2).

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 4.2).

Excipients

CLOVEXA contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, total lactase deficiency, glucose-galactose malabsorption should not take CLOVEXA.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products associated with bleeding risk

There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution (see section 4.4).

Oral anticoagulants

The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.4). 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, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on haemostasis.

Glycoprotein IIb/IIIa inhibitors

Clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

Acetylsalicylic acid (ASA)

ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of ASA on collagen-induced platelet aggregation. However, concomitant administration of 500 mg of 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

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 clopidogrel should be undertaken with caution.

Other concomitant therapy

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products 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 sections 4.4 and 5.2).

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

Proton Pump Inhibitors (PPI):

Omeprazole 80 mg once 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 or 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.

Other medicinal products

A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbitone or oestrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids 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.

CYP2C8 substrate medicinal products

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 (see section 4.4).

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, ACEI, 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 medicines in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

4.6 Fertility, pregnancy and lactation

Safety and efficacy of CLOVEXA 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 CLOVEXA.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

CLOVEXA 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

Summary of the safety profile

The most commonly reported adverse reaction is bleeding, especially during the first month of treatment.

Tabulated list of adverse reactions

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
Blood and the lymphatic system disorders	Less frequent	Thrombocytopenia, leukopenia, eosinophilia Neutropenia, including severe neutropenia Thrombotic thrombocytopenic purpura (TTP) (see section 4.4), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia
Immune system disorders	Less frequent	Serum sickness, anaphylactoid reactions, cross-reactive medicine hypersensitivity among thienopyridines (such as ticlopidine,

		prasugrel) (see section 4.4), insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)*
Psychiatric disorders	Less frequent	Hallucinations, confusion
Nervous system disorders	Less frequent	Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness Taste disturbances, ageusia
Eye disorders	Frequency unknown	Eye bleeding (conjunctival, ocular, retinal)
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Kounis syndrome (vasospastic allergicangina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel*
Vascular disorders	Frequent	Haematoma
	Less frequent	Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxis
	Less frequent	Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia

Gastrointestinal disorders	Frequent	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia
	Less frequent	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence Retroperitoneal haemorrhage Gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepatobiliary disorders	Less frequent	Acute liver failure, hepatitis, abnormal liver function test
Skin and subcutaneous tissue disorders	Frequent	Bruising
	Less frequent	Rash, pruritus, skin bleeding (purpura) Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, medicine-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus
Musculoskeletal, connective tissue and bone disorders	Less frequent	Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia

Renal and urinary disorders	Less frequent	Haematuria Glomerulonephritis, blood creatinine increased
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Frequent	Bleeding at puncture site
	Less frequent	Fever
Investigations	Less frequent	Bleeding time prolonged, neutrophil count decreased, platelet count decreased

*Information related to clopidogrel with frequency "not known".

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 professionals 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

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.

No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 8.2 Anticoagulants

Pharmacotherapeutic group: platelet aggregation inhibitors Excl. Heparin

ATC code: B01AC-04

Mechanism of action

Clopidogrel is a specific and potent inhibitor of platelet aggregation.

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet $P2Y_{12}$ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other medicinal products, not all patients will have adequate platelet inhibition.

Pharmacodynamic effects

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40 % and 60 %. Platelet

aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

Paediatric population

In a dose escalation study, the dose of 0,2 mg/kg achieved the mean percent inhibition of 49,3 % (5 µM ADP-induced platelet aggregation) which was comparable to that of adults taking clopidogrel 75 mg/day.

The CLARINET and the PICOLO trials were conducted using a constituted solution of clopidogrel. In a relative bioavailability study in adults, the constituted solution of clopidogrel showed a similar extent and slightly higher rate of absorption of the main circulating (inactive) metabolite compared to the authorised tablet.

5.2 Pharmacokinetic properties

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 3 mg/L after a single 75 mg oral dose) occurred approximately 1 hour after dosing. Absorption is at least 50 %, based on urinary excretion of clopidogrel metabolites.

Distribution

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

Biotransformation

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. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated *in vitro*, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The C_{max} of the active metabolite is twice as high following a single 300-mg clopidogrel loading dose as it is after four days of 75-mg maintenance dose. C_{max} occurs approximately 30 to 60 minutes after dosing.

Elimination

Following an oral dose of ^{14}C-labelled clopidogrel in man, approximately 50 % was excreted in the urine and approximately 46 % in the faeces in the 120-hour interval 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 was 8 hours after single and repeated administration.

Special populations

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* platelet aggregation assays, differ according to CYP2C19 genotype.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomised, controlled trials. There have been a number of retrospective analyses, however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping result. None of these analyses were adequately sized to detect differences in outcome in poor metabolisers.

Renal impairment:

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25 %) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

Hepatic impairment:

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

5.3 Preclinical safety data

During non-clinical studies in rats and baboons, 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 rats and baboons.

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

Anhydrous lactose

Low substituted hydroxypropyl cellulose

Hydroxypropyl cellulose

Microcrystalline cellulose

Hydrogenated castor oil

Colloidal anhydrous silica

Film coating

Opadry II Pink

Opadry white

Lactose monohydrate

Hypromellose

Titanium dioxide

Glycerol triacetate

Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

CLOVEXA is packed in Alu-Alu blister packs comprising aluminium foil (hard tempered) with HSL coating on bright side. The forming material is cold formable Alu-Alu triple laminated foil. The blisters are further packed in a cardboard carton in pack sizes of 7, 14, 28, 30, 50, 84, 90 and 100 tablets per pack. (Not all pack sizes will be marketed).

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Building 2, Tuscany Office Park,

6 Coombe Place

Rivonia

Johannesburg

South Africa

8. REGISTRATION NUMBER(S)

47/8.2/0395

FINAL PROFESSIONAL INFORMATION

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 March 2021

10. DATE OF REVISION OF THE TEXT

9 March 2021