PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

DEPLATT (75 mg film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains: Clopidogrel hydrogen sulfate equivalent to 75 mg clopidogrel.

Excipients with known effect

Each film-coated tablet contains 10,240 mg lactose monohydrate.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

DEPLATT film-coated tablets are light pink coloured, round, beveled edge, biconvex, engraved film-coated tablets, plain on both the sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

DEPLATT should be given as a single daily dose of 75 mg.

Paediatric population

The safety and efficacy of DEPLATT in children below 18 years has not yet been established.

Method of administration

For oral use.

DEPLATT can be taken at any time of day, with or without food.

4.3 Contraindications

- Hypersensitivity to clopidogrel or to any of the excipients (see section 6.1)
- Active pathological bleeding such as peptic ulcer and intracranial haemorrhage.
- Safety and efficacy in subjects below the age of 18 have not been established.
- Pregnancy and lactation (see Section 4.6).
- Severe liver impairment.
- Thrombocytopenia, neutropenia and other haematopoietic or haemorrhagic disorders.

4.4 Special warnings and precautions for use

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH CLOPIDOGREL AS IN **DEPLATT** DURING POST-MARKETING EXPERIENCE. MOST CASES WERE REPORTED IN THE FIRST TWO WEEKS OF TREATMENT. PRESCRIBERS SHOULD WARN PATIENTS ABOUT THE SIGNS AND SYMPTOMS OF THROMBOTIC THROMBOCYTOPENIC PURPURA.

The clinical diagnosis of TTP is characterised by the presence of thrombocytopenia, haemolytic anaemia, neurological symptoms, renal dysfunction and fever. Due to the risk of a fatal outcome, **DEPLATT** should be discontinued in the event of suspected TTP. Early treatment with plasmapheresis is indicated in TTP.

Clopidogrel as in **DEPLATT** produces irreversible inhibition of platelet aggregation for the life of a platelet, i.e. for 7 - 10 days. Routine surgery is not recommended until a patient has been off **DEPLATT** for 7 days. Spinal and epidural anaesthesia should not be administered to a patient taking **DEPLATT** or for 7 days thereafter. No lumbar puncture should be done during these 7 days.

In patients with acute myocardial infarction, **DEPLATT** therapy should not be initiated within the first few days following myocardial infarction. In view of the lack of data, **DEPLATT** cannot be recommended in unstable angina, PTCA (stenting), CABG and acute ischaemic stroke (less than 7 days).

Patients should be monitored carefully for any signs of bleeding, including occult bleeding, especially during the first week of treatment and/or after invasive cardiac procedures or surgery. **DEPLATT** prolongs bleeding time. **DEPLATT** should be

used with caution in patients who have lesions with a propensity to bleed, particularly gastrointestinal and intraocular.

Patients should be told that it may take longer than usual to stop bleeding when they take **DEPLATT**, and that they should report any unusual bleeding to their physician. Patients should be advised to inform medical practitioners and dentists that they are taking **DEPLATT** before any surgery is scheduled and before any new medicine is taken.

Risk of haematoma formulation following lumbar puncture or spinal and epidural anaesthesia.

Risk of active bleeding such as bleeding peptic ulcer and intracranial haemorrhage.

Risk of increased blood loss during dental and surgical procedures.

DEPLATT should be used with caution in patients receiving other medicines that increase the risk of bleeding (see Section 4.5).

The concomitant administration of **DEPLATT** with warfarin is not recommended since it may increase the risk and intensity of bleedings (see Section 4.5).
In view of the possible increased risk of bleeding, the concomitant administration of **DEPLATT** with aspirin (ASA), heparin, or thrombolytics should be undertaken with caution (see section 4.5).

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore, **DEPLATT** should be used with caution in these patients.

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

Medicines that might induce gastrointestinal lesions (such as Non-Steroidal Anti-Inflammatory Agents) should be used with caution in patients taking **DEPLATT** (see Section 4.5).

In patients who are poor CYP2C19 metabolisers, clopidogrel at the recommended dose, forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function.

Since clopidogrel is metabolised to its active metabolite by CYP2C19, concomitant use of **DEPLATT** and strong or moderate CYP2C19 inhibitors is not recommended (see Section 4.5).

DEPLATT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **DEPLATT**.
DEPLATT contains mannitol, which may have a mild laxative effect.
It also contains hydrogenated castor oil which may cause stomach upset and diarrhoea (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Aspirin: Did not modify the clopidogrel mediated inhibition of ADP-induced platelet aggregation. Clopidogrel as in **DEPLATT**, potentiates the effect of aspirin (acetylsalicylic acid) on collagen-induced platelet aggregation. A

pharmacodynamic interaction between **DEPLATT** and aspirin is possible, leading to an increased risk of bleeding. Therefore, concomitant administration should be undertaken with caution. The safety of the chronic concomitant administration of aspirin and **DEPLATT** has not been established (see section 4.4).

Heparin: A pharmacodynamic interaction between **DEPLATT** and heparin is possible, leading to an increased risk of bleeding. As the safety of this combination has not been established, concomitant use should be undertaken with caution.

Thrombolytics: The safety of the concomitant administration of **DEPLATT** with other thrombolytic agents has not been established and should be undertaken with caution.

Warfarin: The safety of the co-administration of **DEPLATT** with warfarin has not been established. Consequently, concomitant administration of these two agents should be undertaken with caution.

Non-Steroidal Anti-Inflammatory Agents [NSAIDs]: Due to a potential risk of gastrointestinal bleeding, NSAIDs and **DEPLATT** should be co-administered with caution (see section 4.4).

Glycoprotein IIb/IIIa inhibitors: DEPLATT should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other conditions/disorders that may require concomitant glycoprotein IIb/IIIa inhibitors intake.

CYP2C19: 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 levels of the active metabolite of clopidogrel resulting

in decreased antiplatelet activity. As a precaution, concomitant use of strong or moderate CYP2C19 inhibitors and **DEPLATT** is not recommended (see section 4.4).

Medicine products that inhibit CYP2C19 include omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

Other concomitant therapy: No clinically significant pharmacodynamic interactions were observed when clopidogrel as in **DEPLATT** was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of **DEPLATT** was not significantly influenced by the co-administration of phenobarbitone, or oestrogen. The pharmacokinetics of digoxin or theophylline was not modified by the co-administration of **DEPLATT**. Antacids did not modify the extent of clopidogrel absorption.

DEPLATT inhibits the activity of one of the Cytochrome P450 (CYP) enzymes (CYP 2C9). This could lead to increased plasma levels of medicines such as phenytoin, tolbutamide, warfarin, tamoxifen, fluvastatin and NSAIDs which are metabolised by CYP 2C9.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of **DEPLATT** during pregnancy and breastfeeding is not recommended (see section 4.3)

Breastfeeding

It is unknown whether clopidogrel is excreted in human breast milk.

4.7 Effects on ability to drive and use machines

No impairment of driving or psychometric performance was observed following clopidogrel administration.

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent:	Thrombocytopenia; leucopenia; eosinophilia; neutropenia, including severe neutropenia; thrombotic thrombocytopenic purpura (TTP); aplastic anaemia; pancytopenia; agranulocytosis; severe thrombocytopenia; acquired haemophilia A; granulocytopenia; anaemia.
Immune system disorders	Frequency unknown:	Serum sickness; anaphylactoid reactions; cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel); angioedema.
Psychiatric disorders	Less frequent:	Hallucinations; confusion.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Nervous system disorders	Less frequent:	Intracranial bleeding (some cases were reported with fatal outcome); headache; paraesthesia; dizziness; taste disturbances.
Eye disorders	Less frequent:	Eye bleeding (conjunctival, ocular, retinal).
Ear and labyrinth disorders	Less frequent:	Vertigo.
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;

MedDRA system organ class	Frequency	Adverse reactions
		retroperitoneal haemorrhage; gastrointestinal and retroperitoneal haemorrhage with fatal outcome; pancreatitis; colitis (including ulcerative or lymphocytic colitis); stomatitis.
Hepato-biliary 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); drug-induced hypersensitivity syndrome; drug rash with eosinophilia and systemic symptoms (DRESS); rash erythematous or exfoliative; urticaria; eczema; lichen planus.
Musculoskeletal and connective tissue disorders	Less frequent:	Musculo-skeletal bleeding (haemarthrosis); arthritis; arthralgia; myalgia.
Renal and urinary disorders	Less frequent:	Haematuria; glomerulonephritis; increased blood creatinine.

MedDRA system organ class	Frequency	Adverse reactions
General disorders and administration site conditions	Frequent:	Bleeding at puncture site.
	Less frequent:	Fever.
Investigations	Less frequent:	Bleeding time prolonged; 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

An overdose of **DEPLATT** may lead to prolonged bleeding time and subsequent bleeding complications.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin ATC Code: B01AC-04.

A 8.2 Anticoagulants

Clopidogrel is a specific and potent inhibitor of platelet aggregation. 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. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. 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).

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

Repeated doses of 75 mg per day produced 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 was between 40 % and 60 %. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 7 days after treatment was discontinued.

5.2 Pharmacokinetic properties

Absorption

Clopidogrel is well absorbed after oral administration. Absorption is at least 50 %, based on urinary excretion of clopidogrel metabolites.

Distribution

Clopidogrel and the main circulating metabolite bind *in vitro* reversibly to human plasma proteins (98 % end 94 % respectively).

Biotransformation

Clopidogrel is metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid derivative which represents about 85 % of the circulating compound in plasma.

Plasma concentrations of the main circulating metabolite were significantly higher in elderly subjects (> 75 years) as compared to young healthy volunteers. However, these higher plasma levels were not associated with differences in platelet aggregation and bleeding time.

After repeated administration of 75 mg/day, plasma levels of the main circulating metabolite were lower in subjects with severe renal impairment (creatinine clearance from 5 to 15 ml/min) compared to subjects with moderate renal impairment (creatinine clearance from 30 to 60 ml/min) and healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower [25 %] than that observed in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving 75 mg clopidogrel per day.

Elimination

Following an oral dose of 14C-labelled clopidogrel in man, approximately 50 % was excreted in the urine and approximately 46 % in the faeces in the 120 hour interval after dosing. The elimination half-life of the main circulating metabolite may reach 8 hours after single and repeated administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Colloidal anhydrous silica

Hydrogenated castor oil

Hydroxy propyl cellulose

Lactose

Magnesium stearate

Mannitol

Microcrystalline cellulose

Polyethylene glycol 6000

Film Coating:

Hypromellose 6 cps

Ferric oxide red

Titanium dioxide

Polyethylene glycol 6000

6.2 Incompatibilities

There are no incompatibilities

6.3 Shelf life

24 months.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

Store at or below 30 °C.

Keep out of reach of children.

6.5 Nature and contents of container

Printed cardboard cartons with silver coloured cold forming blister aluminium foil (OPA 25 µ / Aluminium 45 µ PVC 60 µ), sealed with aluminium foil (0,025 x 132 mm) with heat seal lacquer coating blisters containing 10, 30 or 100 tablets. Each blister strip contains 10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

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8 REGISTRATION NUMBER(S)

A45/8.2/1031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 November 2017

10 DATE OF REVISION OF THE TEXT

2 September 2022