

## PROFESSIONAL INFORMATION

### 1 SCHEDULING STATUS

2 S3

3

### 4 1 NAME OF THE MEDICINE

5 DEPLATT (75 mg film-coated tablets)

6

### 7 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

9

#### 10 Excipients with known effect

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

12

13 For full list of excipients, see section 6.1

14

### 15 3 PHARMACEUTICAL FORM

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

18

### 19 4 CLINICAL PARTICULARS

#### 20 4.1 Therapeutic indications

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

25

#### 26 4.2 Posology and method of administration

##### 27 Posology

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

29 **Paediatric population**

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

31

32 **Method of administration**

33 For oral use.

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

35

36 **4.3 Contraindications**

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

43

44 **4.4 Special warnings and precautions for use**

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

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

54

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

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

62  
63 Patients should be monitored carefully for any signs of bleeding, including occult bleeding, especially  
64 during the first week of treatment and/or after invasive cardiac procedures or surgery. **DEPLATT**  
65 prolongs bleeding time. **DEPLATT** should be used with caution in patients who have lesions with a  
66 propensity to bleed, particularly gastrointestinal and intraocular.

67  
68 Patients should be told that it may take longer than usual to stop bleeding when they take **DEPLATT**,  
69 and that they should report any unusual bleeding to their physician. Patients should be advised to  
70 inform medical practitioners and dentists that they are taking **DEPLATT** before any surgery is  
71 scheduled and before any new medicine is taken.

72  
73 Risk of haematoma formation following lumbar puncture or spinal and epidural anaesthesia.

74  
75 Risk of active bleeding such as bleeding peptic ulcer and intracranial haemorrhage.

76  
77 Risk of increased blood loss during dental and surgical procedures.

78  
79 **DEPLATT** should be used with caution in patients receiving other medicines that increase the risk of  
80 bleeding (see Section 4.5).

81  
82 The concomitant administration of **DEPLATT** with warfarin is not recommended since it may increase  
83 the risk and intensity of bleedings (see Section 4.5).

84 In view of the possible increased risk of bleeding, the concomitant administration of **DEPLATT** with  
85 aspirin (ASA), heparin, or thrombolytics should be undertaken with caution (see section 4.5).

86  
87 Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore,  
88 **DEPLATT** should be used with caution in these patients.

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

91

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

94

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

97

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

100

101 **DEPLATT** contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp  
102 lactase deficiency or glucose-galactose malabsorption should not take **DEPLATT**.

103

104 **DEPLATT** contains mannitol, which may have a mild laxative effect.

105 It also contains hydrogenated castor oil which may cause stomach upset and diarrhoea (see section  
106 4.8).

107

#### 108 **4.5 Interaction with other medicines and other forms of interaction**

109 **Aspirin:** Did not modify the clopidogrel mediated inhibition of ADP-induced platelet aggregation.  
110 Clopidogrel as in **DEPLATT**, potentiates the effect of aspirin (acetylsalicylic acid) on collagen-induced  
111 platelet aggregation. A pharmacodynamic interaction between **DEPLATT** and aspirin is possible,  
112 leading to an increased risk of bleeding. Therefore, concomitant administration should be undertaken  
113 with caution. The safety of the chronic concomitant administration of aspirin and **DEPLATT** has not  
114 been established (see section 4.4).

115

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

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

121

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

124

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

127

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

131

132 **CYP2C19:** Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of  
133 medicines that inhibit the activity of this enzyme would be expected to result in reduced levels of the  
134 active metabolite of clopidogrel resulting in decreased antiplatelet activity. As a precaution, concomitant  
135 use of strong or moderate CYP2C19 inhibitors and **DEPLATT** is not recommended (see section 4.4).

136

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

140

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

147

148 **DEPLATT** inhibits the activity of one of the Cytochrome P450 (CYP) enzymes (CYP 2C9). This could

149 lead to increased plasma levels of medicines such as phenytoin, tolbutamide, warfarin, tamoxifen,  
 150 fluvastatin and NSAIDs which are metabolised by CYP 2C9.

151

152 **4.6 Fertility, pregnancy and lactation**

153 **Pregnancy**

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

155

156 **Breastfeeding**

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

158

159 **4.7 Effects on ability to drive and use machines**

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

162

163 **4.8 Undesirable effects**

164 **Tabulated summary of adverse reactions**

164.1 MedDRA system organ class	164.2 Frequency	164.3 Adverse reactions
164.2 Blood and lymphatic system disorders	164.2 Less frequent:	164.2 Thrombocytopenia; leucopenia; eosinophilia; neutropenia, including severe neutropenia; thrombotic thrombocytopenic purpura (TTP); aplastic anaemia; pancytopenia; agranulocytosis; severe thrombocytopenia; acquired haemophilia A; granulocytopenia; anaemia.
164.3 Immune system disorders	164.3 Frequency unknown:	164.3 Serum sickness; anaphylactoid reactions; cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel); angioedema, insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population).

164.4	Psychiatric disorders	Less frequent:	Hallucinations; confusion.
164.5	Nervous system disorders	Less frequent:	Intracranial bleeding (some cases were reported with fatal outcome); headache; paraesthesia; dizziness; taste disturbances.
164.6	Eye disorders	Less frequent:	Eye bleeding (conjunctival, ocular, retinal).
164.7	Ear and labyrinth disorders	Less frequent:	Vertigo.
164.8	Vascular disorders	Frequent:	Haematoma.
		Less frequent:	Serious haemorrhage; haemorrhage of operative wound; vasculitis; hypotension.
164.9	Respiratory, thoracic and mediastinal disorders	Frequent:	Epistaxis.
		Less frequent:	Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage); bronchospasm; interstitial pneumonitis; eosinophilic pneumonia.
164.10	Gastrointestinal disorders	Frequent:	Gastrointestinal haemorrhage; diarrhoea; abdominal pain; dyspepsia.
164.11		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.
164.12	Hepato-biliary disorders	Less frequent:	Acute liver failure; hepatitis; abnormal liver function test.
164.13	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.
164.14	Musculoskeletal and connective tissue disorders	Less frequent: Musculo-skeletal bleeding (haemarthrosis); arthritis; arthralgia; myalgia.
164.15	Renal and urinary disorders	Less frequent: Haematuria; glomerulonephritis; increased blood creatinine.
164.16	General disorders and administration site conditions	Frequent: Bleeding at puncture site.
		Less frequent: Fever.
164.17	Investigations	Less frequent: Bleeding time prolonged; decreased neutrophil count; decreased platelet count.

165

#### 166 *Reporting of suspected adverse reactions*

167 Reporting suspected adverse reactions after authorisation of the medicine is important. It allows  
168 continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to  
169 report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting**  
170 **Form**”, found online under SAHPRA’s publications:

171 <https://www.sahpra.org.za/Publications/Index/8>

172

#### 173 **4.9 Overdose**

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

176 Treatment is symptomatic and supportive.

177

### 178 **5 PHARMACOLOGICAL PROPERTIES**

#### 179 **5.1 Pharmacodynamic properties**

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

181

182 A 8.2 Anticoagulants

183 Clopidogrel is a specific and potent inhibitor of platelet aggregation. Clopidogrel selectively inhibits the  
184 binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated  
185 activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Clopidogrel  
186 acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel  
187 are affected for the remainder of their lifespan and recovery of normal platelet function occurs at a rate  
188 consistent with platelet turnover (approximately 7 days).

189  
190 Clopidogrel also inhibits platelet aggregation induced by other agonists by blocking the amplification of  
191 platelet activation by released ADP. Biotransformation of clopidogrel is necessary to produce inhibition  
192 of platelet aggregation.

193  
194 Repeated doses of 75 mg per day produced inhibition of ADP-induced platelet aggregation from the  
195 first day; this may increase progressively and reach steady state between Day 3 and Day 7. At steady  
196 state, the average inhibition level observed with a dose of 75 mg per day was between 40 % and 60  
197 %. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 7 days  
198 after treatment was discontinued.

199  
200 **5.2 Pharmacokinetic properties**

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

204  
205 **Distribution**  
206 Clopidogrel and the main circulating metabolite bind *in vitro* reversibly to human plasma proteins (98  
207 % and 94 % respectively).

208  
209 **Biotransformation**  
210 Clopidogrel is metabolised by the liver and the main metabolite, which is inactive, is the carboxylic acid  
211 derivative which represents about 85 % of the circulating compound in plasma.

212 Plasma concentrations of the main circulating metabolite were significantly higher in elderly subjects (>  
213 75 years) as compared to young healthy volunteers. However, these higher plasma levels were not  
214 associated with differences in platelet aggregation and bleeding time.

215

216 After repeated administration of 75 mg/day, plasma levels of the main circulating metabolite were lower  
217 in subjects with severe renal impairment (creatinine clearance from 5 to 15 ml/min) compared to  
218 subjects with moderate renal impairment (creatinine clearance from 30 to 60 ml/min) and healthy  
219 subjects. Although inhibition of ADP-induced platelet aggregation was lower [25 %] than that observed  
220 in healthy subjects, the prolongation of bleeding was similar to that seen in healthy subjects receiving  
221 75 mg clopidogrel per day.

222

## 223 **Elimination**

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

227

## 228 **6 PHARMACEUTICAL PARTICULARS**

### 229 **6.1 List of excipients**

230 Tablet Core:

231 Colloidal anhydrous silica

232 Hydrogenated castor oil

233 Hydroxy propyl cellulose

234 Lactose

235 Magnesium stearate

236 Mannitol

237 Microcrystalline cellulose

238 Polyethylene glycol 6000

239

240 Film Coating:

241 Hypromellose 6 cps

242 Ferric oxide red

243 Titanium dioxide

244 Polyethylene glycol 6000

245

## 246 **6.2 Incompatibilities**

247 There are no incompatibilities

248

## 249 **6.3 Shelf life**

250 24 months.

251

## 252 **6.4 Special precautions for storage**

253 This medicine does not require any special storage conditions.

254 Store at or below 30 °C.

255 Keep out of reach of children.

256

## 257 **6.5 Nature and contents of container**

258 Printed cardboard cartons with silver coloured cold forming blister aluminium foil (OPA 25 µ / Aluminium

259 45 µ PVC 60 µ), sealed with aluminium foil (0,025 x 132 mm) with heat seal lacquer coating blisters

260 containing 10, 30 or 100 tablets. Each blister strip contains 10 tablets.

261

## 262 **6.6 Special precautions for disposal and other handling**

263 No special requirements

264

## 265 **7 HOLDER OF CERTIFICATE OF REGISTRATION**

266 Trinity Pharma (Pty) Ltd.

267 106, 16<sup>th</sup> Road

268 Building 2, Midrand

269 Johannesburg, 1686

270 South Africa

271 **8 REGISTRATION NUMBER(S)**

272 45/8.2/1031

273

274 **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

275 23 November 2017

276

277 **10 DATE OF REVISION OF THE TEXT**

278 19 December 2023