PROFESSIONAL INFORMATION

CLOPIDOGREL 75 mg PD

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CLOPIDOGREL 75 mg PD film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains clopidogrel hydrogen sulphate equivalent to clopidogrel 75 mg.

Each tablet contains sugar (lactose – 108,125 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

Pink, round, biconvex, film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLOPIDOGREL 75 mg PD is indicated for the following:

- 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
- for patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave myocardial infarction [MI]) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG (coronary artery bypass graft), CLOPIDOGREL 75 mg PD in combination with

acetylsalicylic acid (aspirin) ASA has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), stroke or refractory ischaemia

- for patients with ST-segment elevation acute myocardial infarction, CLOPIDOGREL 75 mg PD in combination with ASA has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke.

4.2 Posology and method of administration

Posology

Adults:

Recent Myocardial Infarction (MI), Recent Stroke, or Established Peripheral Arterial Disease:

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

Acute Coronary Syndrome:

For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI), CLOPIDOGREL 75 mg PD should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg - 325 mg once daily) should be initiated and continued in combination with CLOPIDOGREL 75 mg PD.

For patients with ST-segment elevation acute myocardial infarction, the recommended dose of CLOPIDOGREL 75 mg PD is one tablet, once daily, administered in combination with aspirin, with or without thrombolytics. CLOPIDOGREL 75 mg PD may be initiated with or without a loading dose.

Special populations

Elderly:

No dosage adjustment is necessary for elderly patients.

Renal disease:

No dosage adjustment is necessary for patients with renal disease.

Pharmacogenetics:

CYP2C19 poor metaboliser status is associated with diminished antiplatelet response to clopidogrel. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Paediatric population

CLOPIDOGREL 75 mg PD should not be used in children below the age of 18 years because of efficacy concerns.

Method of administration

For oral use.

CLOPIDOGREL 75 mg PD can be taken with or without food.

Missed dose:

Medical practitioners should advise patients who forget to take CLOPIDOGREL 75 mg PD to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

CLOPIDOGREL 75 mg PD is contraindicated in:

- hypersensitivity to clopidogrel or to any of the ingredients of CLOPIDOGREL 75 mg PD (see section 6.1)
- active bleeding such as peptic ulcer and intracranial haemorrhage
- safety and efficacy in patients below the age of 18 have not been established
- pregnancy and lactation
- severe liver impairment
- thrombocytopenia
- platelet dysfunction

- haemophilia, congenital or acquired, or history of acquired haemophilia related to clopidogrel.

4.4 Special warnings and precautions for use

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH CLOPIDOGREL 75 mg PD 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 (TTP).

Thrombotic Thrombocytopenic Purpura (TTP):

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 fatal outcome, in the event of suspected thrombotic thrombocytopenic purpura, CLOPIDOGREL 75 mg PD should be stopped. The management of a patient with thrombotic thrombocytopenic purpura is complex. Early treatment with plasmapheresis is indicated in TTP.

Recent ischemic stroke:

In patients with recent transient ischaemic attack (TIA) or stroke, who are at high risk of recurrent ischaemic events, the combination of aspirin and CLOPIDOGREL 75 mg PD has not been shown to be more effective than CLOPIDOGREL 75 mg PD alone, but the combination has been shown to increase major bleeding. It is therefore recommended that such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

In view of the lack of data, CLOPIDOGREL 75 mg PD cannot be recommended in acute ischaemic

stroke (less than 7 days).

Bleeding and haematological disorders:

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

CLOPIDOGREL 75 mg PD should be used with caution in patients who may be at risk of increased bleeding including active bleeding such as peptic ulcer and inter-cranial haemorrhage and from trauma, dental and surgical procedures or other pathological conditions and in patients receiving treatment with acetylsalicylic acid (aspirin), nonsteroidal anti-inflammatory drugs (NSAIDs) (including COX-2 inhibitors), and anticoagulants such as heparin or glycoprotein IIb/IIIa inhibitors, selective serotonin reuptake inhibitors (SSRIs) or thrombolytics or CYP2C19 strong inducers (see section 4.5). Due to the increased risk of haemorrhage, triple antiplatelet therapy (clopidogrel + ASA + dipyridamole) for stroke secondary prevention is not recommended in patients with acute non-cardioembolic ischemic stroke or transient ischaemic attack (TIA) (see sections 4.5 and 4.8).

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, CLOPIDOGREL 75 mg PD should be discontinued 7 days prior to surgery.
Spinal and epidural anaesthesia should not be administered to a patient taking clopidogrel or for 7 days thereafter. No lumber puncture should be done during these 7 days due to risk of haematoma formation following lumber puncture or spinal and epidural anaesthesia.

Patients should be monitored carefully for any signs of bleeding, including occult bleeding, especially but not limited to during the first week of treatment and/or after invasive cardiac procedures or

surgery. The concomitant administration of CLOPIDOGREL 75 mg PD with warfarin is not recommended since it may increase the intensity of bleedings.

CLOPIDOGREL 75 mg PD prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed such as gastrointestinal ulcers and intra-ocular bleeding. Medicines that might induce lesions (such as acetylsalicylic acid and NSAIDs) should be used with caution in patients taking CLOPIDOGREL 75 mg PD.

Patients should be told that it may take longer than usual to stop bleeding when they take CLOPIDOGREL 75 mg PD, and that they should report any unusual bleeding to their medical practitioner. Patients should inform medical practitioners and dentists that they are taking CLOPIDOGREL 75 mg PD before any surgery is scheduled and before any new medicine is taken. In view of the possible increased risk of bleeding, the concomitant administration of CLOPIDOGREL 75 mg PD with acetylsalicylic acid, heparin, warfarin or thrombolytics should be undertaken with caution (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 75 mg PD should be discontinued (see section 4.3).

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; these tests can be used as an aid in determining therapeutic strategy (see section 4.2 - Pharmacogenetics).

Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than patients with normal CYP2C19 function (see section 5.2).

Use of medicines that induce the activity of CYP2C19 would be expected to result in increased medicine levels of the active metabolite of clopidogrel and might potentiate the bleeding risk. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.5).

CYP2C8 substrates

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

Acute myocardial infarction

In patients with acute myocardial infarction, CLOPIDOGREL 75 mg PD therapy should not be initiated within the first few days following myocardial infarction. In view of the lack of data, CLOPIDOGREL 75 mg PD cannot be recommended in coronary artery bypass graft (CABG) and acute ischaemic stroke (less than 7 days). Clinical experience is limited in patients with renal impairment and moderate hepatic disease with bleeding diatheses, CLOPIDOGREL 75 mg PD should be used with caution in these patients.

Cross-reactivity among thienopyridines:

Thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia have been reported in patients taking CLOPIDOGREL 75 mg PD (see section 4.8).

Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as 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 reactions such as thrombocytopenia and neutropenia. 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 cross-reactivity is advised.

Insulin autoimmune syndrome (IAS)

Insulin autoimmune syndrome (IAS) is characterized by hyperinsulinemic hypoglycaemia with elevated anti-insulin antibodies. The sulfhydryl group of clopidogrel metabolite could induce insulin autoimmune syndrome (IAS) as a rare side effect. Asians, most commonly observed in the Japanese population, have a genetic predisposition for IAS carrying HLA-DRB1*04:06, HLA-DQA1*03:01 and HLA-DQB1*03:02 haplotypes, and are more likely to develop IAS. Clopidogrel-induced-IAS may also cause hypoglycaemia in Caucasian populations, with the HLADRB1*04:03 haplotypes.

Hepatic impairment:

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. CLOPIDOGREL 75 mg PD should therefore be used with caution in this population.

Renal impairment:

Therapeutic experience with clopidogrel is limited in patients with severe renal impairment. Therefore, CLOPIDOGREL 75 mg PD should be used with caution in these patients.

Information on excipients of CLOPIDOGREL 75 mg PD:

CLOPIDOGREL 75 mg PD contains lactose. Patients with rare hereditary problems of fructose intolerance, galactose intolerance, galactosaemia or glucose-galactose malabsorption should not takeCLOPIDOGREL 75 mg PD.

CLOPIDOGREL 75 mg PD contains hydrogenated castor oil which may cause stomach upset or diarrhoea.

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.

Acetylsalicylic acid (aspirin):

Acetylsalicylic acid (ASA) did not modify the clopidogrel-mediated inhibition of adenosine diphosphate (ADP)-induced platelet aggregation. Concomitant administration of 500 mg of acetylsalicylic acid twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake.

CLOPIDOGREL 75 mg PD potentiates the effects of acetylsalicylic acid on collagen-induced platelet aggregation. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid (aspirin) is possible, leading to increased risk of bleeding.

Therefore, concomitant use should be undertaken with caution.

However, clopidogrel and ASA (75 - 325 mg once daily) have been administered together for up to one year.

Heparin:

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, concomitant use should be undertaken with caution.

Thrombolytics:

The safety of the concomitant administration of clopidogrel, as in CLOPIDOGREL 75 mg PD, 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 heparins are co-administered with acetylsalicylic acid. However, the concomitant use of CLOPIDOGREL 75 mg PD with thrombolytic medicines should be undertaken with caution.

Warfarin:

The concomitant administration of clopidogrel with oral anticoagulants, including warfarin, is not recommended since it may increase the intensity of bleedings (see section 4.4).

The safety of the co-administration of CLOPIDOGREL 75 mg PD with warfarin has not been established.

Consequently, concomitant administration of these two medicines should be undertaken with caution.

Nonsteroidal anti-inflammatory medicines (NSAIDs) including aspirin:

There is a potential risk of gastrointestinal bleeding, and NSAIDs, including aspirin, and CLOPIDOGREL 75 mg PD should be co-administered with caution (see section 4.4). 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.

NSAIDs, including COX-2 inhibitors, and CLOPIDOGREL 75 mg PD should be co-administered with caution.

Glycoprotein IIb/IIIa inhibitors:

CLOPIDOGREL 75 mg PD 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.

Selective serotonin reuptake inhibitors (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:

No clinically significant pharmacodynamic interactions were observed when CLOPIDOGREL 75 mg PD was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of CLOPIDOGREL 75 mg PD was not significantly influenced by the co-administration of phenobarbital, cimetidine, or oestrogen.

CLOPIDOGREL 75 mg PD inhibits the activity of cytochrome P450 enzyme: CYP2C9. This leads to increased plasma levels of medicines such as phenytoin, tolbutamide, warfarin, tamoxifen, fluvastatin and many NSAIDs which are metabolised by CYP2C9.

Inducers of CYP2C19:

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicines that induce the activity of this enzyme would be expected to result in increased medicine levels of the active metabolite of clopidogrel.

Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged (see section 4.4).

Inhibitors of CYP2C19:

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicine that inhibit the activity of this enzyme would be expected to result in reduced medicine levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, carbamazepine, and efavirenz) should be discouraged (see sections 4.2 and 4.4 – Pharmacogenetics). If a proton pump inhibitor is to be used concomitantly with CLOPIDOGREL 75 mg PD, consider using one with less CYP2C19 inhibitory activity.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel, as in CLOPIDOGREL 75 mg PD. Antacids did not modify the extent of clopidogrel absorption.

CYP2C8 substrate medicines:

Due to the risk of increased plasma concentrations, concomitant administration of CLOPIDOGREL 75 mg PD and medicines primarily cleared by CYP2C8 metabolism (e.g. repaglinide, paclitaxel) should be undertaken with caution.

Results of additional clinical studies in which patients received a variety of concomitant medications including diuretics, beta-blocking medicines, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering medicines, coronary vasodilators, antidiabetic medicines, anti-epileptic medicines and hormone replacement therapy, showed no evidence of clinically significant adverse interactions.

Opioid agonists:

Co-administration of opioid agonists has the potential to delay and reduce the absorption of an oral $P2Y_{12}$ antagonist such as 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.

Rosuvastatin:

Clopidogrel has been shown to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1,3-fold (C_{max}) after administration of a 300 mg clopidogrel dose and by 1,4-fold (AUC) without effect on C_{max}, after repeated administration of a CLOPIDOGREL 75 mg PD dose.

Boosted antiretroviral therapy (ART):

Human immunodeficiency virus (HIV) patients treated with boosted antiretroviral therapies (ART) are

at high-risk of vascular events.

A significantly reduced platelet inhibition has been shown in HIV patients treated with ritonavir-or cobicistat-boosted ART. Although the clinical relevance of these findings is uncertain, there have been spontaneous reports of HIV-infected patients treated with ritonavir boosted ART, who have experienced re-occlusive events after de-obstruction or have suffered thrombotic events under a clopidogrel loading treatment schedule. Average platelet inhibition can be decreased with concomitant use of clopidogrel and ritonavir. Therefore, concomitant use of clopidogrel with ART boosted therapies should be discouraged.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of CLOPIDOGREL 75 mg PD during pregnancy is not recommended as safety and efficacy have not been established (see section 4.3).

Breastfeeding

The use of CLOPIDOGREL 75 mg PD during lactation is not recommended as safety and efficacy have not been established (see section 4.3).

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether clopidogrel is excreted in human breast milk.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

No impairment of driving or psychometric performance was observed following CLOPIDOGREL 75 mg PD administration.

CLOPIDOGREL 75 mg PD has no, or negligible, effect on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

Bleeding is the most common reaction reported both in clinical studies where frequencies varied from common to very common, as well as in post-marketing experience.

b. Tabulated list of adverse effects

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequent	Purpura, haematoma
	Less frequent	Severe neutropenia (including agranulocytosis), severe thrombocytopenia (including thrombotic thrombocytopenic purpura), increased bleeding time, eosinophilia, leucopenia
	Frequency unknown	Bruising, haematuria*, ocular bleeding* (mainly conjunctival, but also ocular and retinal), respiratory tract bleeding* and aplastic anaemia (pancytopenia), musculoskeletal bleeding (including haemathrosis), haemorrhagic ulcer, haemothorax, haemorrhage of operative wound* and retroperitoneal haemorrhage* with fatal outcome, serum sickness, gastrointestinal haemorrhage*, intracranial haemorrhage*

Immune system disorders	Frequency unknown	Hypersensitivity reactions such as bronchospasm, angioedema or anaphylactoid reactions, insulin autoimmune syndrome, which can lead to severe hypoglycaemia, particularly in patients with human leukocyte antigen (HLA) DRA4 subtype (more frequent in the Japanese population), serum sickness, cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see section 4.4)
Psychiatric disorders	Less frequent Frequency unknown	Mental depression Confusion, hallucinations
Nervous system disorders	Frequent Less frequent Frequency unknown	Headache, dizziness Paraesthesia, intracranial bleeding, syncope, anxiety, hypoaesthesia, insomnia, intracranial bleeding (fatal outcome in some cases) Taste disorders, ageusia*
Eye disorders	Less frequent	Eye bleeding (conjunctival, ocular, retinal)
Ear and labyrinth disorders	Frequency unknown	Vertigo*

Cardiac disorders	Frequent Less frequent Frequency unknown	Chest pain Atrial fibrillation or palpitations Kounis syndrome* (vasospastic allergic angina)
Vascular disorders	Less frequent Frequency unknown	Hypertension Hypotension, vasculitis, serious haemorrhage, haemorrhage of operative wound
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent Frequency unknown	Upper respiratory tract infections, epistaxis Bronchitis, dyspnoea, cough, rhinitis Interstitial pneumonitis*, bronchospasm*, eosinophilic pneumonia*, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage)
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Abdominal pain, dyspepsia, diarrhoea Gastrointestinal haemorrhage, nausea, constipation, vomiting, peptic, gastric or duodenal ulcer, flatulence, gastritis Colitis* (including ulcerative or lymphocytic colitis), pancreatitis*, stomatitis*
Hepatobiliary disorders	Frequency unknown	Abnormal liver function tests*, hepatitis*, acute liver failure*

Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Bruising Rash, pruritus, purpura Severe skin reactions (including bullous eruption)*, erythema multiforme*, Stevens-Johnson syndrome*, toxic epidermal necrolysis*, lichen planus*, urticaria*, eczema*, maculopapular, erythematous or exfoliative rash*, urticaria*, angioedema*, bullous dermatitis*, acute generalised exanthematous pustulosis (AGEP)*, drug-induced hypersensitivity syndrome*, drug rash with eosinophilia*, systemic symptoms (DRESS)*
Musculoskeletal, connective tissue and bone disorders	Frequent Less frequent Frequency unknown	Back pain Gout, leg cramps Myalgia*, arthritis*, arthralgia*
Renal and urinary disorders	Less frequent Frequency unknown	Urinary tract infection, haematuria Glomerulopathy*, increased creatinine levels*
Reproductive system and breast disorders	Frequency unknown	Gynaecomastia*
General disorders and administrative site conditions	Frequent Frequency unknown	Bleeding at injection site Fever*

Investigations	Less frequent	Bleeding time prolonged, neutrophil count decreased, platelet count decreased

*Post marketing.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Overdose following CLOPIDOGREL 75 mg PD administration may lead to prolonged bleeding time and subsequent bleeding complications.

Management of overdose:

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. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excl. heparin.

ATC code: B01AC 04

Pharmacological classification: A 8.2 Anticoagulants.

Mechanism of action

Clopidogrel is a specific and potent inhibitor of platelet aggregation. It acts by irreversibly modifying the platelet ADP receptors. It inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. 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 (of about 7 days).

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

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.

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

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 single and repeated oral doses, clopidogrel is rapidly absorbed. Absorption is at least 50 %.

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 metabolite bind, *in vitro*, reversibly 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 and is metabolised according to two main metabolic pathways: the main metabolite, which is inactive, is the carboxylic acid derivative which represents about 85 % of the circulating compound in the plasma 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 irreversibly to platelet receptors, thus inhibiting platelet aggregation.

Elimination:

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 metabolite is up to 8 hours after administration.

Clopidogrel and the main metabolite are excreted in urine (50 %) and faeces (46 %) in the 120-hour interval after dosing.

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 non-functional. 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 ultra-rapid, 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 metabolisers may have a higher rate of cardiovascular events (death, myocardial infarction, stroke or stent thrombosis) compared to extensive metabolisers.

Pharmacokinetics in special patient groups

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 - 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 CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to ethnicity (see section 5.2, 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

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Castor oil (hydrogenated)

Hypromellose

Iron oxide red

Macrogol

Microcrystalline cellulose

Pregelatinised starch

Propylene glycol

Talc

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

CLOPIDOGREL 75 mg PD tablets are packed in OPA/AL/PVC film and heat sealing aluminium blister strips. The blister strips are packed in an outer carton in packs of 28 or 30. Not all pack sizes are marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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8. REGISTRATION NUMBER(S)

A42/8.2/0128

9. DATE OF FIRST AUTHORISATION

Date of registration: 04 December 2009

10. DATE OF REVISION OF THE TEXT

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Manufactured by:

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8501, Novo Mesto, Slovenia