Approved Professional Information for Medicines for Human Use

CLOPIDOGREL 75 mg AUSTELL film-coated tablets

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CLOPIDOGREL 75 mg AUSTELL film-coated tablets

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

CLOPIDOGREL 75 mg AUSTELL film-coated tablets

Each film-coated tablet contains 97,86 mg of clopidogrel bisulphate (Form I) corresponding to 75,0 mg of clopidogrel base.

Contains sugar: lactose anhydrous 78,14 mg

3. PHARMACEUTICAL FORM

Film-coated tablets

Pink, round, biconvex, film-coated tablets with an “I” engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

CLOPIDOGREL AUSTELL 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 patient 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 AUSTELL in combination with ASA has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischaemia.
- for patients with ST-segment elevation acute myocardial infarction, CLOPIDOGREL AUSTELL 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

Adults:

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

CLOPIDOGREL AUSTELL 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 AUSTELL should be initiated with a single 300 mg loading dose and then continued at 75 mg daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with CLOPIDOGREL AUSTELL.

For patients with ST-segment elevation acute myocardial infarction, the recommended dose at CLOPIDOGREL AUSTELL is one tablet, once daily administered in combination with aspirin, with or without thrombolytics. CLOPIDOGREL AUSTELL 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 AUSTELL should not be used in children below the age of 18 years because of efficacy concerns.

Method of administration

CLOPIDOGREL AUSTELL is for oral use, with or without food.

4.3 Contraindications

- hypersensitivity to the clopidogrel or to any of the excipients listed in 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 uses

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH CLOPIDOGREL AUSTELL 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.

Bleeding and haematological disorders

Due to the risk of bleeding and haematological adverse reactions, blood cell count deteremination and/or other appropriate testing should be promptly considerered whenever clincial symptoms suggestive of bleeding arise during the course of treatment (see section 4.8). As with other antiplatelet CLOPIDOGREL AUSTELL 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 ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steriodal anti-infalmmatory drugs (NSAIDs) including COX-2 inhibitors, or selective serotonin reuptake inhibotors (SSRIs), or CYP2C19 strong inducers or other medicines associated with bleeding risk sich 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.

If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform medical practitoners and dentists that they are taking CLOPIDOGREL AUSTELL before any surgery is scheduled and before any new medicines is taken. CLOPIDOGREL AUSTELL prolongs bleeding time and should be used with caution in patient who have lesions with a propensity to bleed (particularly gastrointestinal and intra-ocular).

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

The use of CLOPIDOGREL AUSTELL 600 mg loading dose is not recommended in patients with non-ST segment elevation acute coronary syndrome and ≥ 75 years of age due to increased bleeding risk in this population.

Thrombotic Thrombocytopenic Purpura (TTP)

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

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 ischemic stroke

- Initiation of therapy
- In acute minor IS or moderate to high-risk TIA patients, dual antiplatelet therapy (clopidogrel and ASA) should be started no later than 24 hours after the event onset.
- There is no data regarding the benefit-risk of short term dual antiplatelet therapy in acute minor IS or moderate to high-risk TIA patients, with a history of (non-traumatic) intracranial haemorrhage.
- In non-minor IS patients, clopidogrel monotherapy should be started only after first 7 days of the event.
- Non-minor IS patients (NIHSS> 4)

In view of the lack of data, use of dual antiplatelet therapy is not recommended (see section 4.1).

- Recent minor IS or moderate to high-risk TIA in patients for whom intervention is indicated or planned.

There is no data to support the use of dual antiplatelet therapy in patients for whom treatment with carotid endarterectomy or intravascular thrombectomy is indicated, or in patients planned for thrombolysis or anticoagulant therapy. Dual antiplatelet therapy is not recommended in these situations.

Cytochrome P450 2C19 (CYP2C19)

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

Since CLOPIDOGREL AUSTELL 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 drug levels of the active metabolite of CLOPIDOGREL AUSTELL. 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).

Use of medicine that induce the activity of CYP2C19 would be expected to result in increased drug levels of the active metabolite of CLOPIDOGREL AUSTELL 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 AUSTELL and CYP2C8 substrate medicines (see section 4.5).

Cross-reactions among thienopyridines

Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine and 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 thrombocytopenia 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 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 AUSTELL 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 AUSTELL should be used with caution in this population (see section 4.2).

Excipient lactose

CLOPIDOGREL AUSTELL tablets contain lactose.
Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take CLOPIDOGREL AUSTELL.

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 (see section 4.4).

Oral anticoagulants

The concomitant administration of CLOPIDOGREL AUSTELL with oral anticoagulants is not recommended since it may increase the intensity of bleedings (see section 4.4). Although the administration of CLOPIDOGREL AUSTELL/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of CLOPIDOGREL AUSTELL with warfarin increases the risk of bleeding because of independent effects on hemostasis.

NSAIDs

In a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastro-intestinal bleeding with all NSAIDs. Consequentlly, NSAIDs including cox-2 inhibitors and clopidogrel should be co-administered with caution (see section 4.

Acetylsalicylic acid (ASA)

ASA did not modify the clopidogrel - mediated inhibition of ADP-induced platelet aggregation, 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).

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 usage should be undertaken with caution (see section 4.4).

Thrombolytics

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

Glycoprotein IIb/IIIa inhibitors

Caution is advised when clopidogrel is used in patients who receive concomitant glycoprotein IIb/IIIa inhibitors (see section 4.4).

Selective serotonin reuptake inhibitors (SSRIs)

Concomitant administration of SSRIs with clopidogrel should be undertaken with caution as SSRIs affect platelet activation and increase the risk of bleeding.

Proton Pump Inhibitors (PPIs)

Omeprazole 80 mg once daily administered either concurrently with clopidogrel or with 12 hours between the administrations of the two medicines~~,~~ decreased the exposure of the active metabolite by 45 % (loading dose) and 40 % (maintenance dose). The decrease was associated with a 39 % (loading dose) and 21 % (maintenance dose) 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.

The plasma concentration of the active metabolite was 20 % reduced (loading dose) and 14 % reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15 % and 11 %, respectively. These results indicate that clopidogrel can be administered with pantoprazole.

There is no evidence that other medicines that reduce stomach acid such as H_2 blockers or antacids interfere with the antiplatelet activity of clopidogrel.

Boosted anti-retroviral therapy (ART)

HIV patients treated with boosted anti-retroviral 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.

Other concomitant therapy

Inducers of CYP2C19

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 drug 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 in particular 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

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 drug levels of 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 4.4 and 5.2).

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

Other medicines

Co-administration of clopidogrel with atenolol, nifedipine, or both atenolol and nifedipine showed no

clinically significant pharmacodynamic interactions.

Co-administration of clopidogrel with phenobarbitone, or oestrogen did not significantly influence the pharmacodynamic activity of clopidogrel.

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 medicines
Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. In vitro studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to 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 medicines interaction information described above, interaction studies with clopidogrel and some medicines commonly administered in patients with atherothrombotic disease have not been performed. However, patients received concomitant medicines including diuretics, beta-blocking medicines, angiotensin converting enzyme inhibitors (ACEI), calcium antagonists, cholesterol lowering medicines, coronary vasodilators, anti-diabetic medicines (including insulin), anti-epileptic medicines and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

As with other oral $P2Y_{12}$ 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 agent 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 (Cmax) after administration of a 300 mg clopidogrel dose, and by 1.4-fold (AUC) without effect on Cmax after repeated administration of a 75 mg clopidogrel dose.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

It is not known whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. CLOPIDOGREL AUSTELL is contraindicated in breastfeeding. Breastfeeding should not be continued during treatment with CLOPIDOGREL AUSTELL.

Fertility

CLOPIDOGREL AUSTELL was not shown to alter fertility in animal studies.

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4.7 Effects on ability to drive and use machines

CLOPIDOGREL AUSTELL has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile

The clinically relevant adverse reactions observed in the studies are discussed below. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with clopidogrel bisulphate.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**

Blood and the lymphatic system disorders		Thrombocytopenia, leucopenia, 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		Serum sickness, anaphylactoid reactions	Cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see section 4.4), insulin autoimmuno syndrome,

			which can lead to severe hypoglycemia, particularly in patients with HLA DRA4 subtype (more frequent in the Japanese population)
Psychiatric disorders		Hallucinations, confusion	
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness	Taste disturbances, ageusia
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)	

Ear and labyrinth disorders		Vertigo	
Cardiac disorders			Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel
Vascular disorders	Haematoma	Serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension	
Respiratory, thoracic and	Epistaxis	Respiratory tract bleeding (haemoptysis, pulmonary hemorrhage),	

mediastinal disorders		bronchospasm, interstitial pneumonitis, eosinophilic pneumonia	
Gastrointestinal disorders	Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastric, vomiting, nausea, constipation, flatulence, retroperitoneal haemorrhage, gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis	
Hepato-biliary disorders		Acute liver failure, hepatitis, abnormal liver function test	
Skin and subcutaneous tissue disorders	Bruising	Rash, pruritus, skin bleeding (purpura), bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson	

		Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP)), angioedema, 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		Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia	
Renal and urinary disorders		Haematuria, glomerulonephritis, blood creatinine increased	
Reproductive system and breast disorders		Gynaecomastia	

General disorders and administration site conditions	Bleeding at puncture site	Fever	
Investigations		Bleeding time prolonged, neutrophil count decreased, platelet count decreased	

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 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.

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za.

4.9 Overdose

Signs and symptoms

Overdose following CLOPIDOGREL AUSTELL administration may lead to prolonged bleeding time and subsequent bleeding complications.

Management

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

Treatment

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: 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. 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, and thereby inhibits 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. 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 well absorbed.

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

Distribution

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

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 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.

CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2CI9*3 allele 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.

Special populations

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

Elderly

In elderly (> 75 years) volunteers compared to young healthy volunteers, there were no differences in platelet aggregation and bleeding time.

Renal Impairment

After repeated administration of 75 mg clopidogrel/day in subjects with severe renal impairment (creatinine clearance from 5 to 15 ml/min) ADP-induced platelet aggregation was also 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 population are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose anhydrous

Cellulose, microcrystalline (PH 102)

Crospovidone (type A)

Glycerol Dibehenate

Talc

Film-coating

Opadry II Pink (85G34669) consisting of:

Polyvinyl alcohol

Talc

Titanium dioxide (E171)

Macrogol 3350

Lecithin (E332)

Iron oxide red (E172)

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

AIuminium-AIuminium blisters: 36 months

Polyethylene containers: 36 months

6.4 Special precautions for storage

AIuminium/AIuminium blister packs: Store at or below 30 °C.

Polyethylene tablet containers: Store at or below 25 °C.

6.5 Nature and contents of container

CLOPIDOGREL AUSTELL film-coated tablets are packed in Aluminium/Aluminium blister strips of 7 or 10 tablets, which are further packed in printed cartons in pack sizes of 7, 10, 14, 20, 28, 30, 50, 56, 60, 84, 90 or 100.

CLOPIDOGREL AUSTELL tablets are also packed in polyethylene tablet containers in pack sizes of 100 tablets.

Not all pack sizes and pack types are necessary marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd.

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8. REGISTRATION NUMBER

49/8.2/0442

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 June 2019

10. DATE OF REVISION OF THE TEXT

10 March 2025