PROPOSED PACKAGE INSERT (CLEAN) for

CLOPIDOGREL UNICORN 75

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

CLOPIDOGREL UNICORN 75 film coated tablet

COMPOSITION:

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

Inactive ingredients: Anhydrous lactose, castor oil (hydrogenated), hypromellose, iron oxide red, macrogol 6000, microcrystalline cellulose pH102, pregelatinised starch, propylene glycol, purified talc, titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

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/llla 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). 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.

Pharmacokinetics

After oral doses, clopidogrel is rapidly absorbed. Absorption is at least 50 %. Clopidogrel is extensively 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 the plasma. Clopidogrel and the main metabolite bind, *in vitro,* reversibly to human plasma proteins (98 % and 94 % respectively).

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 %).

INDICATIONS:

CLOPIDOGREL UNICORN 75 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.

CONTRA-INDICATIONS:

CLOPIDOGREL UNICORN 75 is contra-indicated in:

- Hypersensitivity to clopidogrel or any component of the product.
- 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.

WARNINGS:

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) HAS BEEN REPORTED TO OCCUR WITH **CLOPIDOGREL UNICORN 75** DURING POST-MARKETING EXPERIENCE. MOST CASES WERE REPORTED IN THE FIRST TWO WEEKS OF TREATMENT. IN ADDITION, PRESCRIBERS SHOULD WARN PATIENTS ABOUT THE SIGNS AND SYMPTOMS OF 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 UNICORN 75** should be stopped. The management of a patient with thrombotic thrombocytopenic purpura is complex. Early treatment with plasmapharesis is indicated in TTP.

- Risk of increased blood loss during dental and surgical procedures.
- Active bleeding such as peptic ulcer and intracranial haemorrhage.
- Use with caution in patients receiving other medicines that increase the risk of bleeding (anticoagulants, NSAIDs and other anticoagulants).

INTERACTIONS:

Acetylsalicylic acid (aspirin):

CLOPIDOGREL UNICORN 75 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. The safety of the chronic concomitant administration of acetylsalicylic acid (aspirin) and **CLOPIDOGREL UNICORN 75** has not been established (see **Special Precautions**).

Heparin:

The safety of this combination has not been established and concomitant use should be undertaken with caution. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding.

Thrombolytics:

The safety of the concomitant administration of **CLOPIDOGREL UNICORN 75** with other thrombolytic agents has not been established and should be undertaken with caution.

Warfarin:

The safety of the co-administration of **CLOPIDOGREL UNICORN 75** with warfarin has not been established. Consequently, concomitant administration of these two agents should be undertaken with caution.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including aspirin:

There is a potential risk of gastrointestinal bleeding and NSAIDs, including aspirin, and **CLOPIDOGREL UNICORN 75** should be co-administered with caution (see **Special Precautions**). NSAIDs, including COX-2 inhibitors, and clopidogrel should be co-administered with caution.

Glycoprotein IIb/IIIa inhibitors:

CLOPIDOGREL UNICORN 75 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.

Other concomitant therapy:

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

oestrogen. The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of **CLOPIDOGREL UNICORN 75** inhibits the activity of cytochrome P_{450} 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.

An interaction has been observed between clopidogrel and omeprazole /esomeprazole, resulting in decreasing antiplatelet activity. Concomitant use of **CLOPIDOGREL UNICORN 75** and omeprazole / esomeprazole is not recommended.

PREGNANCY AND LACTATION:

The use of **CLOPIDOGREL UNICORN 75** during pregnancy and lactation is not recommended as safety and efficacy have not been established (see **CONTRA-INDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE:

Adults:

CLOPIDOGREL UNICORN 75 should be given as a single daily dose of 75 mg, with or without food.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side- effects:

Blood and lymphatic system disorders:

Frequent: Purpura, haematoma.

Less frequent: Epistaxis, gastrointestinal haemorrhage, intracranial haemorrhage, severe neutropenia (including agranulocytosis), severe

thrombocytopenia (including thrombotic thrombocytopenic purpura)

The following has been reported but the frequency is 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, serum sickness.

Gastro-intestinal disorders:

Frequent: Abdominal pain, dyspepsia.

Less frequent: Gastrointestinal haemorrhage, diarrhoea, nausea, constipation, vomiting, peptic, gastric or duodenal ulcer.

The following has been reported but the frequency is unknown: Flatulence, gastritis.

Skin and subcutaneous tissue disorders:

Less frequent: Rash, severe skin reactions (including bullous eruption)

The following has been reported but the frequency is unknown: Pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus, urticaria, eczema

Nervous system disorders:

Frequent: Headache, dizziness.

Less frequent: Paraesthesia, intracranial bleeding, syncope, anxiety, hypoaesthesia, insomnia, mental depression.

The following has been reported but the frequency is unknown: Vertigo, confusion, hallucinations, taste disorders.

Cardiac disorders:

Frequent: Chest pain.

Less frequent: Atrial fibrillation or palpitations, oedema.

Vascular Disorders:

The following has been reported but the frequency is unknown: Hypotension, vasculitis, hypertension.

Respiratory, thoracic and mediastinal disorders:

Frequent: Upper respiratory tract infections.

Less frequent: Bronchitis, dyspnoea, cough, rhinitis.

The following has been reported but the frequency is unknown: Interstitial pneumonitis.

Hepatobiliary disorders:

The following has been reported but the frequency is unknown: Abnormal liver function tests, hepatitis, acute liver failure.

Renal and urinary disorders:

Less frequent: Urinary tract infection.

The following has been reported but the frequency is unknown: Glomerulopathy, increased creatinine levels.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Arthralgia, back pain.

Less frequent: Gout, leg cramps.

The following has been reported but the frequency is unknown: Myalgia, arthritis.

General disorders and administration site conditions:

Frequent: Generalised pain, flu-like symptoms

Less frequent: Fatigue, asthenia, oedema, itching, tooth disorder.

Immune system disorders

The following has been reported but the frequency is unknown: Hypersensitivity reactions such as bronchospasm, angioedema or anaphylactoid reactions.

Special Precautions:

CLOPIDOGREL UNICORN 75 should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions and in patients receiving treatment with acetylsalicylic acid (aspirin), NSAIDs (including COX-2 inhibitors), heparin or glycoprotein llb/llla inhibitors.

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. The concomitant administration of clopidogrel with warfarin is not recommended since it may increase the intensity of bleedings. If a patient is to undergo elective surgery and an anti-platelet effect is not desired, **CLOPIDOGREL UNICORN 75** should be discontinued 7 days prior to surgery.

CLOPIDOGREL UNICORN 75 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 UNICORN 75.**

Patients should be told that it may take longer than usual to stop bleeding when they take **CLOPIDOGREL UNICORN 75** and that they should report any unusual bleeding to their medical practitioner. Patients should inform medical practitioners and dentists that they are taking **CLOPIDOGREL UNICORN 75** 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 UNICORN 75** with acetylsalicylic acid, heparin, warfarin or thrombolytics should be undertaken with caution (see **INTERACTIONS**).

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 UNICORN 75** has not been shown to be more effective than **CLOPIDOGREL UNICORN 75** alone, but the combination has been shown to increase major bleeding. It is therefore recommended that such addition should be undertaken with caution. In patients with acute myocardial infarction, **CLOPIDOGREL UNICORN 75** therapy should not be initiated within the first few days following myocardial infarction. In view of the lack of data, **CLOPIDOGREL UNICORN 75** 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 UNICORN 75** should be used with caution in these patients.

Thrombocytopenia, neutropenia, aplastic anaemia and pancytopenia have been reported in patients taking clopidogrel (see **SIDE-EFFECTS**).

CLOPIDOGREL UNICORN 75 contains lactose and should not be given to patients with rare hereditary problems or a history of galactose intolerance, Lapp-lactase deficiency or glucose galactose malabsorption.

Effects on ability to drive and use machines:

No impairment of driving or psychometric performance was observed following **CLOPIDOGREL UNICORN 75** administration.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See SIDE-EFFECTS AND SPECIAL PRECAUTIONS)

Overdose following **CLOPIDOGREL UNICORN 75** administration may lead to prolonged bleeding time and subsequent bleeding complications. Treatment is symptomatic and supportive.

IDENTIFICATION:

Pink, round, slightly biconvex, film-coated tablets.

PRESENTATION:

CLOPIDOGREL UNICORN 75 tablets are packed in OPA/AL/PVC film and heat sealing aluminium blister strips. Each strip contains ten tablets. The blister strips are packed in an outer carton in packs of 30s.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER:

42/8.2/0250

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

Unicorn Pharmaceuticals (Pty) Ltd.

Corner Searle and Pontac Streets

Cape Town

8001

DATE OF PUBLICATION OF THIS PACKAGE INSERT

Date of registration: 31 July 2014

Date of revision: *To be included on approval of change in proprietary name.*