1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Name of Product : CLOP 75 (Clopidogrel Tablets USP 75 mg)

1.1 (Trade) Name of Product : CLOP 75

1.2 Strength (formula) : Clopidogrel Bisulfate USP
Eq to Clopidogrel 75 mg

1.3 Pharmaceutical Dosage Form : Film Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Clopidogrel Bisulfate USP

Eq to Clopidogrel 75 mg
Excipients q.s
Color: Approved Colour

Product composition:

Sr. No	Ingredients	Specifications	Label Claim	Overages	Qty / Tablet	Activity	Uses
Active							
1.	Clopidogrel Bisulfate equivalent to Clopidogrel	USP 43	75.0 mg	5.134 %	102.90 mg	Active	Antiplatelet agent.
2.	Lactose	BP 2021	---	---	90.00 mg	In-Active	Binder
For paste							
3.	Povidone (PVPK-30)	BP 2021	---	---	5.000 mg	In-Active	Binder
4.	Isopropyl alcohol	BP 2021	---	---	50.000 ml	In-Active	Solvent
Lubrication							
5.	Magnesium stearate	BP 2021	-----	---	35.00 mg	In-Active	Lubricant
6.	Colloidal Anhydrous Silica	BP 2021	---	---	5.000 mg	In-Active	Glidant
7.	Sodium starch glycolate	BP 2021	---	---	6.000 mg	In-Active	Dissolving agent
8.	Tartaric Acid	BP 2021	---	---	15.00 mg	In-Active	Acidifying agent
9.	Croscarmellose sodium	BP 2021	---	---	5.95 mg	In-Active	Emulsifier.
Coating							
10.	Methylene Dichloride	BP 2021	-----	---	60.00 ml	In-Active	Solvent
11.	Isopropyl alcohol	BP 2021	-----	---	139.00 ml	In-Active	Solvent
12.	HPMC 15 CPS	BP 2021	-----	---	10.00 mg	In-Active	Coating Agent
13.	Titanium dioxide	BP 2021	-----	---	8.00 mg	In-Active	Pigmenting Agent
14.	Purified talcum	BP 2021	-----	---	7.15 mg	In-Active	Lubricant
15.	Propylene glycol	BP 2021	-----	---	1.33 ml	In-Active	Solubilizing Agent

Average weight: 290.00 mg
Product Expiry: 36 Months
BP 2021= British Pharmacopeia
USP 43 = United states Pharmacopeia

Quantity Calculation for Clopidogrel Bisulfate

$$= \frac{\text{Molecular Weight of Clopidogrel Bisulfate}}{\text{Molecular Weight of Clopidogrel}}$$

$$= \frac{419.90}{321.82}$$

$$= 1.305$$

Qty. of Clopidogrel Bisulfate Req. per tablet,

= 1.305 x 75 mg (+5.134% Overages)

= 102.90 mg

3. PHARMACEUTICAL FORM

Film Coated Tablet

A white coloured, circular, biconvex film coated tablet having breakline on one side and plain on other.

4. Clinical particulars

4.1 Therapeutic indications

Secondary prevention of atherothrombotic events

Clopidogrel is indicated as Secondary prevention of atherothrombotic events in following condition :

• Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease.

• Adult patients suffering from acute coronary syndrome:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing a stent placement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).

- ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

In patients with moderate to high-risk Transient Ischemic Attack (TIA) or minor Ischemic Stroke (IS)

4.2 Posology and method of administration

Posology

• Adults and elderly

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

In patients suffering from acute coronary syndrome:

- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction): clopidogrel treatment should be initiated with a single 300 mg or 600mg loading dose. A 600 mg loading dose may be considered in patients <75 years of age when percutaneous coronary intervention is intended. Clopidogrel treatment should be continued at 75 mg once a day (with acetylsalicylic acid (ASA) 75 mg-325 mg daily). Since higher doses of ASA were associated with higher bleeding risk it is recommended that the dose of ASA should not be higher than 100 mg. The optimal duration of treatment has not been formally established. Clinical trial data support use up to 12 months, and the maximum benefit was seen at 3 months.

- ST segment elevation acute myocardial infarction: clopidogrel should be given as a single daily dose of 75 mg initiated with a 300 mg loading dose in combination with ASA and with or without thrombolytics. For medically treated patients over 75 years of age clopidogrel should be initiated without a loading dose. Combined therapy should be started as early as possible after symptoms start and continued for at least four weeks. The benefit of the combination of clopidogrel with ASA beyond four weeks has not been studied in this setting.

Adult patients with moderate to high-risk TIA or minor IS:

Adult patients with moderate to high-risk TIA (ABCD2 score ≥4) or minor IS (NIHSS ≤3) should be given a loading dose of clopidogrel 300 mg followed by clopidogrel 75 mg once daily and ASA (75 mg -100 mg once daily). Treatment with clopidogrel and ASA should be started within 24 hours of the event and be continued for 21 days followed by single antiplatelet therapy.

In patients with atrial fibrillation, clopidogrel should be given as a single daily dose of 75 mg. ASA (75-100 mg daily) should be initiated and continued in combination with Clopidogrel.

If a dose is missed:

- Within less than 12 hours after regular scheduled time: patients should take the dose immediately and then take the next dose at the regular scheduled time.

- For more than 12 hours: patients should take the next dose at the regular scheduled time and should not double the dose.

• Paediatric population

Clopidogrel should not be used in children because of efficacy concerns.

• Renal impairment

Therapeutic experience is limited in patients with renal impairment.

• Hepatic impairment

Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses.

Method of administration

For oral use

It may be given with or without food.

4.3 Contraindications

Clop 75 is contra-indicated in: -

- Hypersensitivity to any of the active or auxiliary substances of the drug.
- Severe hepatic insufficiency (more than 9 on the Child-Pugh scale).
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.4 Special warnings and precautions for use

Special instructions

Bleeding and blood disorders

Due to the risk of bleeding and haematological adverse reactions, blood cell count determination and/or other appropriate testing should be promptly considered whenever clinical symptoms suggestive of bleeding arise during the course of treatment. As with other antiplatelet agents, clopidogrel 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-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers or other medicinal products associated with bleeding risk such as pentoxifylline. 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. The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings.

If a patient is to undergo elective surgery and antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to surgery. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken. Clopidogrel prolongs bleeding time and should be used with caution in

patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

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

The use of clopidogrel 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, sometimes after a short exposure. It is characterized by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. 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 hemorrhage.
◦ In non-minor IS patients, clopidogrel monotherapy should be started only after the 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.
• 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 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.

Since clopidogrel is metabolized to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels

of the 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.

Use of medicinal products that induce the activity of CYP2C19 would be expected to result in increased drug 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.

CYP2C8 substrates
Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products.

Cross-reactions among thienopyridines
Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported. Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia 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 of 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 should be used with caution in these patients.

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

Excipients
Clop 75 contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products associated with bleeding risk There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution.

Oral anticoagulants The concomitant administration of Clopidogrel/Acetylsalicylic acid with oral anticoagulants is not recommended since it may increase the intensity of bleeding. Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

Glycoprotein IIb/IIIa inhibitors: clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors

Acetylsalicylic acid (ASA): ASA did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but 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. However, clopidogrel and ASA have been administered together for up to one year.

Thrombolytics
The safety of the combined use of clopidogrel, fibrin-specific or non-fibrin-specific thrombolytic agents, and heparin 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

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 use should be undertaken with caution

NSAIDs In a clinical study conducted 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. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution

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:

Inducers of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products 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.

Inhibitors of CYP2C19

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the 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.

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

Proton Pump Inhibitors (PPI):

Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs 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.

Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole.

The plasma concentrations 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 medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with 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 medicinal products: A number of other clinical studies have been conducted with clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen.

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 medicinal products: 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 the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.

Apart from the specific medicinal product interaction information described above, interaction studies with clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

As with other oral P2Y12 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.

4.6 Pregnancy and Lactation

Pregnancy

As no clinical data on exposure to clopidogrel during pregnancy are available, it is preferable not to use clopidogrel during pregnancy as a precautionary measure.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Breast-feeding

It is unknown whether clopidogrel is excreted in human breast milk. Animal studies have shown excretion of clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clop 75.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that CLOP 75 (Clopidogrel Tablets USP 75 mg) may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

The following adverse reactions have been identified during post-approval use of Clop 75. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP)
- Gastrointestinal disorders: Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis
- General disorders and administration site condition: Fever, hemorrhage of operative wound
- Hepato-biliary disorders: Acute liver failure, hepatitis (non-infectious), abnormal liver function test
- Immune system disorders: Hypersensitivity reactions, anaphylactoid reactions, serum sickness

• Musculoskeletal, connective tissue and bone disorders: Musculoskeletal bleeding, myalgia, arthralgia, arthritis
• Nervous system disorders: Taste disorders, fatal intracranial bleeding
• Eye disorders: Eye (conjunctival, ocular, retinal) bleeding
• Psychiatric disorders: Confusion, hallucinations
• Respiratory, thoracic and mediastinal disorders: Bronchospasm, interstitial pneumonitis, respiratory tract bleeding
• Renal and urinary disorders: Glomerulopathy, increased creatinine levels
• Skin and subcutaneous tissue disorders: Maculopapular or erythematous rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, erythema multiforme, skin bleeding, lichen planus
• Vascular disorders: Vasculitis, hypotension

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving Clop 75 (clopidogrel bisulfate) in the controlled clinical trials are listed below regardless of relationship to Clop 75. In general, the incidence of these events was similar to that in patients receiving aspirin (in CAPRIE) or placebo + aspirin (in the other clinical trials).

Autonomic Nervous System Disorders: Syncope, Palpitation.
Body as a Whole-general disorders: Asthenia, Fever, Hernia.
Cardiovascular disorders: Cardiac failure.
Central and peripheral nervous system disorders: Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo.
Gastrointestinal system disorders: Constipation, Vomiting.
Heart rate and rhythm disorders: Fibrillation atrial.
Liver and biliary system disorders: Hepatic enzymes increased.
Metabolic and nutritional disorders: Gout, hyperuricemia, non-protein nitrogen (NPN) increased.
Musculo-skeletal system disorders: Arthritis, Arthrosis.
Platelet, bleeding & clotting disorders: GI hemorrhage, hematoma, platelets decreased.
Psychiatric disorders: Anxiety, Insomnia.
Red blood cell disorders: Anemia.
Respiratory system disorders: Pneumonia, Sinusitis.
Skin and appendage disorders: Eczema, Skin ulceration.
Urinary system disorders: Cystitis. Vision disorders: Cataract, Conjunctivitis.

4.9 Overdose

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin,

ATC code: B01AC-04.

Mechanism of action

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

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

Pharmacodynamics effects

Repeated doses of 75 mg per day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

5.2 Pharmacokinetic properties

Clopidogrel is a prodrug and is metabolized to a pharmacologically active metabolite and inactive metabolites.

Absorption:
After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Distribution:
Clopidogrel and the main circulating (inactive) metabolite bind reversibly in vitro to human plasma proteins (98% and 94% respectively). The binding is non-saturable in vitro over a wide concentration range.

Biotransformation:
Clop 75 can be administered with or without food. In a study in healthy male subjects when Clop 75 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC0-24 was unchanged in the presence of food, while there was a 57% decrease in active metabolite Cmax. Similar results were observed when a Clop 75 300 mg loading dose was administered with a high-fat breakfast.

Metabolism:
Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. Cytochromes first oxidize clopidogrel 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. This metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6 and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet. The Cmax of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. Cmax occurs approximately 30 to 60 minutes after dosing. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: increasing the dose by a factor of four results in 2.0- and 2.7-fold increases in Cmax and AUC, respectively.

Elimination:
Following an oral dose of 14C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post-dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.

Special populations

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

Renal impairment

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

Hepatic impairment

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

Race

The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity (see 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

During non-clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans

receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolising enzymes. No effect on hepatic metabolising enzymes was observed in humans receiving clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of clopidogrel was also reported in rat and baboon.

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose	BP 2021
Povidone (PVPK-30)	BP 2021
Isopropyl alcohol	BP 2021
Magnesium stearate	BP 2021
Colloidal Anhydrous Silica	BP 2021
Sodium starch glycolate	BP 2021
Tartaric Acid	BP 2021
Croscarmellose sodium	BP 2021
Methylene Dichloride	BP 2021
Isopropyl alcohol	BP 2021
HPMC 15 CPS	BP 2021
Titanium dioxide	BP 2021
Purified talcum	BP 2021
Propylene glycol	BP 2021

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from moisture and light. Keep out of reach of children.

6.5 Nature and contents of container

10 Tablets packed in a Alu-Alu blister. Such 3 Alu-Alu blister packed in an inner carton. Such 10 mono cartons packed in a outer carton along with insert.

6.6 Special precautions for disposal <and other handling>

No special requirements

7 MARKETING AUTHORISATION HOLDER

VENUS INTERNATIONAL

Shree Krishna Commercial Centre,
6 Udyog Nagar, Office No. 310 (Part A),
Near Kamat Club, S.V. Road.
Goregaon (West)
Mumbai – 400 062.