SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of the medicinal product

Brand Name: **CLOPA**

INN Name: **Clopidogrel Tablets USP 75 mg**

2. Qualitative and quantitative composition

Each film coated tablet contains:

Clopidogrel bisulfate USP equivalent to Clopidogrel……	75 mg
Excipients.....	q.s.

For full list of excipients, see section 6.1.

3. Pharmaceutical form :

White coloured, round shaped, biconvex, film coated tablets plain on both sides.

4. Clinical Particulars

4.1. Therapeutic indications

Prevention of atherothrombotic events

Clopidogrel is indicated in:

Adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic 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.

ST segment elevation acute myocardial infarction, in combination with acetylsalicylate acid (ASA) in medically treated patients eligible for thrombolytic therapy.

Prevention of atherothrombotic and thromboembolic events in atrial fibrillation

In adult patients with atrial fibrillation who have at least one risk factor for vascular events, are not suitable for treatment with Vitamin K antagonists (VKA) and who have a low bleeding risk,

clopidogrel is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

4.2 Posology and method of administration

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 loading dose and then 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 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.

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.

Mode of Administration:

For oral use. It may be given with or without food.

4.3 Contraindications

Hypersensitivity to clopidogrel or to any of the excipients
Severe hepatic impairment.
Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

4.4 Special warnings and precautions for use

Bleeding and haematological 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 other medicinal products associated with bleeding risk such as pentoxifylline Patients should be followed carefully for any signs of bleeding including occult bleeding, especially duringthe 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.
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 characterised 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 ischaemic stroke

In view of the lack of data, clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.

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 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

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 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 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

Clopidogrel contains hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Clopidogrel should be used with caution in patients receiving other drugs that increase the risk of bleeding, including anticoagulants, other antiplatelets, and NSAIDs.

Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g proton pump inhibitors) should be discouraged.

Concurrent use of clopidogrel and the following may result in an increased risk of bleeding:

Alteplase, Recombinant, Aspirin, Celecoxib, Citalopram, Dabigatran Etexilate, Desvenlafaxine, Diclofenac, Dipyridamole, Duloxetine,Enoxaparin
Escitalopram, Etoricoxib,Fluoxetine ,Heparin,Fondaparinux, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic Acid, Meloxicam
Milnacipran, Naproxen, Parecoxib, Paroxetine, Pentoxifylline, Piroxicam, Rivaroxaban, Sertraline, Tinzaparin,Venlafaxine,Warfarin,
Concurrent use of clopidogrel and amiodarone may result in an ineffective inhibition of platelet aggregation.
Concurrent use of clopidogrel and the following may result in decreased antiplatelet effect and increased risk of thrombotic events
Amlodipine, □ Diltiazem, □ Felodipine, □ Nicardipine, □ Nimodipine, □ Verapamil. Concurrent use of clopidogrel and the following may result in a reduction in clinical efficacy of clopidogrel:
Chloramphenicol ,□ Cimetidine, □ Fluconazole, □ Fluoxetine, □ Ketoconazole, □ Omeprazole, □ Ticlopidine, □ Voriconazole.
Concurrent use of clopidogrel and fluvoxamine may result in contradictory effects of a reduction in clinical efficacy of clopidogrel and also an increased risk of bleeding.
Concurrent use of clopidogrel and isoniazid may result in reduced antiplatelet activity of clopidogrel.
Concurrent use of clopidogrel and the following may result in an increased risk for thrombosis: □
Esomeprazole, Omeprazole, Rabeprazole Concurrent use of clopidogrel and tamoxifen may result in an increased risk of tamoxifen toxicity (nausea, vomiting, dizziness, hyperreflexia, QT prolongation, increase in liver function tests).
No clinically significant pharmacodynamic interactions were observed when clopidogrel was co administered with atenolol, nifedipine, or both atenolol and nifedipine.

4.6 Fertility, 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 clopidogrel.

Fertility
Clopidogrel was not shown to alter fertility in animal studies.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

- Blood and the lymphatic system disorders: Thrombocytopenia, leucopenia, eosinophilia, neutropenia, including severe neutropenia, thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, granulocytopenia, anaemia
- Immune system disorders: Serum sickness, anaphylactoid reactions
- Psychiatric disorders: Hallucinations, confusion
- Nervous system disorders: Intracranial bleeding, headache, paraesthesia, dizziness, taste disturbances
- Eye disorders: Eye bleeding (conjunctival, ocular, retinal)
- Ear and labyrinth disorders: Vertigo
- Vascular disorders: Haematoma, serious haemorrhage, haemorrhage of operative wound, vasculitis, hypotension
- Respiratory, thoracic and mediastinal disorders: epistaxis, respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis
- Gastrointestinal disorders: Gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia, gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence, retroperitoneal haemorrhage, gastrointestinal and retroperitoneal haemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
- 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), angioedema, rash erythematous, urticaria, eczema, lichen planus Musculoskeletal, connective tissue and bone disorders:
- Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia
- Renal and urinary disorders: Haematuria, glomerulonephritis, blood creatinine increased
- General disorders and administration site conditions: Bleeding at puncture site, fever
- Investigations: Bleeding time prolonged, neutrophil count decreased, platelet count decreased

4.9 Overdose

Bleeding associated with clopidogrel is common. Major bleeding complications are uncommon. Intentional overdose is rare. Symptoms In general, no clinical bleeding is expected in the absence of pre-existing bleeding pathology or trauma. Mild to moderate: Nausea and vomiting are likely

to be present after significant acute overdose. Ecchymosis, gum bleeding, and inhibited wound clotting is possible in overdose. Severe: Patients with associated trauma or gastrointestinal bleeding may have prolonged bleeding and large volume blood loss.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Clopidogrel is a prodrug that is metabolized by CYP450 enzymes to the active thiol derivative. The active thiol derivative, selectively and irreversibly binds to the adenosine diphosphate (ADP) P2Y12 receptor on platelets. This prevents ADP from binding and activating the glucoprotein GPIIb/IIIa complex, which is necessary for platelet aggregation. Additionally, other agonists are blocked from inducing platelet aggregation because they are dependent on platelet activation, which is mediated by ADP. The action is irreversible for the lifespan of the platelet (7 to 10 days).
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.

5.2 Pharmacokinetic properties

Absorption
Based on urinary excretion of metabolites, after single and multiple oral doses of clopidogrel 75 mg/day, absorption is rapid and is at least 50%(dose-limited). Food has no effect on the absorption of clopidogrel.

Distribution
Clopidogrel and the carboxylic acid derivative (metabolite) are highly protein bound.

Metabolism
Clopidogrel is extensively metabolised by the liver, mainly to the inactive carboxylic acid derivative (85% of circulating metabolites). Clopidogrel is a prodrug that is oxidized by the cytochrome P450 system into an intermediary metabolite, 2-oxo-clopidogrel, that is subsequently hydrolyzed to the active thiol metabolite.
The oxidative step is regulated primarily by Cytochrome P450 ISOENZYMES 2B6, 3A4, 1A1, 1A2 and 2C19.

Excretion
Clopidogrel and its metabolites are excreted in urine and in faeces; about 50% of an oral dose is recovered from the urine and about 46% from the faeces. 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 (inactive) metabolite was 8 hours after single and repeated administration.

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 metabolizing enzymes. No effect on hepatic metabolizing 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 upto 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 :

Corn Starch, Microcrystalline Cellulose, Lactose Monohydrate, Povidone K-30, Isopropyl Alcohol, Sodium Starch Glycolate, Talc, Magnesium Stearate, Colloidal Silicon Dioxide, Croscarmellose Sodium, Hypromellose, Titanium Dioxide, Polyethylene Glycol-6000, Methylene chloride.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life :

36 months

6.4 Special precautions for storage :

Store below 30^0C. Protect from light.

6.5 Nature and contents of container :

CLOPA (Clopidogrel Tablets USP 75 mg) are packed in Alu-Alu blister of 10 tablets. 3 such blisters are packed in a printed carton along with the pack insert.

6.6 Special precautions for disposal and other handling

Not Applicable

7. Marketing Authorisation holder and Manufacturing site Address

Pinnacle Life Science Pvt. Ltd.

Mahendra Industrial Estate, 3rd Floor

Plot no .109-D, Road no 29,

Sion (East), Mumbai 400 022, INDIA

Manufacturing site Address

PINNACLE LIFE SCIENCE PVT. LTD.

Khasra No. 1328-1330, Village -Manpura, Tehsil -Baddi

Dist . Solan, Himachal Pradesh (INDIA)

8. Marketing Authorisation number(s)

MNB/08/729
08419/09394/NMR/2021

9. Date of first Authorisation/renewal of the Authorisation

20-03-2009

10. Date of revision of the text

01-01-2021