1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

Enclosed

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CLOPACT-75 (Clopidogrel Tablets 75mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Clopidogrel USP……75 mg

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutical Indications

Clopidogrel is indicated for the reduction of atherothrombotic events as follows:

- For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease
- For patients with acute coronary syndrome (unstable angina/non-Q-wave 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.

4.2 Contraindications

The use of clopidogrel is contraindicated in the following conditions:

- Hypersensitivity to the drug substance or any component of the product.
- Active pathological bleeding such as peptic ulcer, intracranial hemorrhage etc.

4.3 Special warnings and precautions for use

WARNINGS

Thrombotic thrombocytopenic purpura (TTP): TTP has been reported rarely following use of clopidogrel, sometimes after a short exposure (<2 weeks). TTP is a serious condition requiring prompt treatment. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented

RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. In world-wide postmarketing experience, however, TTP has been reported at a rate of about four cases per million patients exposed, or about 11 cases per million patient-years.

Precautions

Clopidogrel prolongs the bleeding time and therefore should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (particularly gastrointestinal and intraocular). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, the drug should be discontinued 5 days prior to surgery.

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

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel has not been shown to be more effective than clopidogrel alone, but the combination has been shown to increase major bleeding.

Clopidogrel should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking clopidogrel.

Experience of clopidogrel is limited in patients with severe hepatic disease, who may have bleeding diatheses. Hence clopidogrel should be used with caution in this population.

Experience of clopidogrel is limited in patients with severe renal impairment. Clopidogrel should be used with caution in this population.

Patients should be told that they may bleed more easily and it may take them longer than usual to stop bleeding when they take clopidogrel or clopidogrel combined with aspirin and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.

Effect on ability to drive and use machines – No impairment of driving or psychometric performance was observed following clopidogrel administration.

Usage in pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Clopidogrel should be used during pregnancy only if clearly needed.

It is not known whether clopidogrel is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

Usage in paediatrics

Safety and effectiveness in the paediatric population have not been established.

Usage in geriatrics

Plasma concentrations of the main circulating metabolite are significantly higher in elderly (>75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Drug interactions

- **Aspirin**: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500mg twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by

clopidogrel. Clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. Clopidogrel and aspirin have been administered together for up to one year.

- **Heparin:** In a study in healthy volunteers, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by clopidogrel.

- **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):** In healthy volunteers receiving naproxen, concomitant administration of clopidogrel was associated with increased occult gastrointestinal blood loss. NSAIDs and clopidogrel should be coadministered with caution.

- **Warfarin**: Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution.

- **Thrombolytics:** The safety of the concomitant administration of clopidogrel, rt-PA and heparin was assessed in patients with recent myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when rt-PA and heparin are coadministered with ASA. The safety of concomitant administration of clopidogrel with other thrombolytic agents has not been established and should be undertaken with caution.

- **Other concomitant therapy**: No clinically significant pharmacodynamic interactions were observed when clopidogrel was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of clopidogrel was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen.

  The pharmacokinetics of digoxin or theophylline was not modified by the coadministration of clopidogrel.

Clopidogrel may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with clopidogrel.

Patients entered into clinical trials with clopidogrel received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, hormone replacement therapy, heparins (unfractionated and LMWH) and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Adverse drug reactions

The clinically important adverse events observed with clopidogrel are haemorrhage (gastrointestinal and intracranial), neutropenia/agranulocytosis, gastrointestinal effects (e.g. abdominal pain, dyspepsia, gastritis and constipation, peptic, gastric or duodenal ulcers, diarrhoea), rash and other skin disorders and purpura.

Although the risk of myelotoxicity with clopidogrel appears to be quite low, this possibility should be considered when a patient receiving clopidogrel demonstrates fever or other sign of infection.

Other adverse events reported in 1% to more than 2.5% patients in clinical trials include:

Body as a Whole - Chest Pain, accidental/inflicted injury, influenza-like symptoms, pain, fatigue, asthenia, fever, hernia

Cardiovascular disorders – Edema, hypertension, cardiac failure

Central & peripheral nervous system disorders – Headache, dizziness, cramps in legs, hypoaesthesia, neuralgia, paraesthesia, vertigo

Autonomic nervous system disorders - Syncope, palpitation

Gastrointestinal system disorders - Abdominal pain, dyspepsia, diarrhea, nausea, constipation, vomiting

Metabolic & nutritional disorders – Hypercholesterolemia, gout, hyperuricemia, non-protein nitrogen (NPN) increased.

Musculo-skeletal system disorders – Arthralgia, back pain, arthritis, arthrosis.

Platelet, bleeding, & clotting disorders - Purpura/bruise, epistaxis, GI hemorrhage, hematoma, platelets decreased

Psychiatric disorders – Depression, anxiety, insomnia

Respiratory system disorders - Upper respiratory tract infection, dyspnea, rhinitis, bronchitis, coughing, pneumonia, sinusitis.

Skin & appendage disorders – Rash, pruritus, eczema, skin ulceration.

Urinary system disorders - Urinary tract infection, cystitis.

Heart rate and rhythm disorders - Atrial fibrillation.

Liver and biliary system disorders - Hepatic enzymes increased.

Red blood cell disorders - Anemia.

Vision disorders - Cataract, conjunctivitis.

4.4 Overdose

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

A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

One case of deliberate overdosage with clopidogrel was reported in the large CAPRIE, controlled clinical study. A 34-year old woman took a single, 1050mg dose of clopidogrel (equivalent to 14 standard 75-mg tablets). There were no associated adverse events. No special therapy was instituted and she recovered without sequelae.

No adverse events were reported after single oral administration of 600mg (equivalent to 8 standard 75-mg tablets) of clopidogrel in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75mg of clopidogrel per day.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Clopidogrel, a thienopyridine derivative, is an inhibitor of platelet aggregation. It selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel. Repeated doses of 75 mg clopidogrel per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg clopidogrel per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

5.2 Pharmacokinetic Properties

Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (~3 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing.

Administration of clopidogrel with meals did not significantly modify the bioavailability of clopidogrel. Clopidogrel and the main circulating metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively).

Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, and it too has no effect on platelet aggregation. Following an oral dose of clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.

5.3 Preclinical Safety Data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Lactose Monohydrate BP/EP
- Microcrystalline Cellulose BP/EP
- Colloidal Unhydrous Silica BP/EP
- Poly Vinyl Pyrolidone BP/EP
- Purified Water BP/EP
- Isopropyl Alcohol BP/EP
- Crospovidone BP/EP
- Purified Talc BP/EP
- Hydrogenated Castor oil IP
- Magnesium Stearate BP/EP
- Hypromellose BP/EP
- Titanium Dioxide BP/EP
- Ferric Oxide Red USP-NF
- Microgol 6000 BP/EP
- Methylene Chloride EP

6.2 Incompatability

None known

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^0C, in a dry place.

Keep out of reach of children

6.5 NATURE AND CONTENTS OF CONTAINER

Blister strip of 10 tablets. 3 such strip packed in a printed showbox along with leaflet.

6.6 Special precautions for disposal

None.

7. MARKETING AUTHORISATION HOLDER

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India