SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PRODUCT

Clopivid Tablet 75 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIVE INGREDIENTS	PER TABLET (MG)
Clopidogrel Bisulphate	97.90 mg

Kindly refer to Section 6.1 for excipient.

3. PHARMACEUTICAL FORM

Pink, round and bevel-edged with shallow convex faces film-coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Clopidogrel is indicated for the prevention of atherothrombotic events: in 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

4.2 Posology and Method of administration

Route of administration is oral.

Adult and elderly

Clopidogrel should be given as a single daily dose of 75mg, with or without food. Safety and efficacy in subjects below the age of 18 have not been established.

Contraindication

- Hypersensitivity to the active substance or to any of the excipients of the medicinal product.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.
- Breast-feeding

4.4 Warnings and precautions

Due to the risk of bleeding and haematological undesirable effects, 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 acetylsalicylic acid (ASA), non-steroidal anti-inflammatory drugs, heparin, glycoprotein IIb/IIIa inhibitors or thrombolytics. 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 warfarin is not recommended since it may increase the intensity of bleedings.

Surgical and Dental: Because of the risk of surgical blood loss, clopidogrel should be discontinued 7 days prior to elective surgery if an antiplatelet effect is not desired.

During the first weeks of treatment and/or after invasive cardiac procedures or surgery, patients should be carefully monitored for any signs of bleeding.

Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular).

Therapeutic experience with clopidogrel is limited in patients with renal impairment and hepatic disease (who may have bleeding diatheses). Therefore clopidogrel should be used with caution in these patients.

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 hemolytic anemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

In view of the lack of data, clopidogrel cannot be recommended in acute ischemic stroke (less than 7 days).

Pharmacogenetics: Based on literature data, patients with genetically reduced CYP22C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higer cardiovascular event rates following myocdardial infarction than do patients with normal CYP2C19 function.

The effectiveness of this medicine is reduced in patients who are poor metabolizers of Clopidogrel.

Drug Interactions

Warfarin
The concomitant administration of clopidogrel with warfarin is not recommended since it may increase the intensity of bleedings.

Heparin
Concomitant use should be with caution as interaction between clopidogrel and heparin is possible, thus may increase risk of bleeding.

Glycoprotein IIb/IIIa inhibitors
Clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions that receive concomitant glycoprotein IIb/IIIa inhibitors.

Acetylsalicylic acid (ASA)
Caution shall be taken when using clopidogrel and ASA concomitantly. 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.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Concomitant administration of clopidogrel and naproxen has been found to increase occult gastrointestinal blood loss. However, it is unclear whether there is an increased risk of gastrointestinal bleeding with other NSAIDs, as there is an insufficient interaction study with other NSAIDs. Consequently, NSAIDs and clopidogrel should be co-administered with caution.

Thrombolytics
The safety of concomitant administration of clopidogrel with other thrombolytic agents has not been formally established and should be undertaken with caution.

Since clopidogrel is metabolized 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 cilinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g proton pump inhibitors) should be discouraged.

Other concomitant therapy
No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, phenobarbital, cimetidine, or estrogen. Co-administration of clopidogrel with antacids, digoxin or theophylline did not modify the pharmacokinetics of clopidogrel.

Clopidogrel inhibits hepatic cytochrome P450 enzyme activity at high concentrations in vitro, thus possibility exists that it could interfere with metabolism of these medications: fluvastatin, phenytoin, tamoxifen, tolbutamide, torsemide.
Caution is recommended.

Pregnancy and lactation
Clopidogrel should not be used during pregnancy as no clinical data on exposed pregnancies are available.

Use in lactation
Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. Decision shall be made whether to discontinue nursing or discontinue clopidogrel.

Effects on ability to drive and use machines
Not applicable.

Main Side/ Adverse Effects
Incidence more frequent (≥ 5%)
Chest pain; generalized pain; purpura; upper respiratory infection; abdominal or stomach pain; arthralgia; back pain; dizziness; dyspepsia; flu-like symptoms; headache.

Incidence less frequent (1 to < 5%)
Atrial fibrillation or palpitation; bronchitis; dyspnea; edema; epistaxis; gastrointestinal hemorrhage; gout; hypertension; syncope; urinary tract infection; anxiety; asthenia; constipation; cough; diarrhea; fatigue; hypoesthesia or paresthesia; insomnia; itching; leg cramps; mental depression; nausea; rhinitis; skin rash; vomiting.

Incidence rare (< 1%)
Intracranial hemorrhage; neutropenia including agranulocytosis; peptic, gastric or duodenal ulcer; severe skin reaction, thrombocytopenia.

Overdose

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

Pharmacodynamic properties

Clopidogrel acts by inhibiting platelet aggregation through selective inhibition of binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent ADP-mediated activation of the GPIIb/IIIa complex. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation.

Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of the platelet activation by released ADP. The action of Clopidogrel in modifying the platelet ADP receptor is irreversible. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

At steady state, which occurs within 3 to 7 days, 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.

Pharmacokinetic properties

Absorption
Clopidogrel is rapidly absorbed, after repeated doses of 75 mg per day. Absorption is at least 50%.

Distribution
Plasma concentrations of the parent compound are very low and below the quantification limit (0.00025 mg/l) beyond 2 hours.

Metabolism
Clopidogrel is extensively metabolized by the liver to its main metabolite, a carboxylic acid derivative. It represents about 85% of the circulating drug-related compounds and achieves peak plasma level approximately 1 hour after dosing. Neither the parent compound nor the carboxylic acid derivative has platelet inhibiting effect.

Clopidogrel is a prodrug. The active metabolite, a thiol derivative, is formed by oxidation of clopidogrel to 2-oxoclopidogrel and subsequent hydrolysis. The oxidative step is regulated primarily by Cytochrome P450 isoenzymes 2B6 and 3A4 and to a lesser extent by 1A1, 1A2 and 2C19. The active thiol metabolite, which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation. This metabolite has not been detected in plasma.

Clopidogrel and the main circulating 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.

Elimination
Approximately 50% was excreted in the urine and 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.

Preclinical Safety Data
NOT APPLICABLE

6. PHARMACEUTICAL PARTICULARS

List of excipients
Microcrystalline Cellulose
Sodium Starch Glycolate
Crospovidone
Colloidal Silicon Dioxide
Magnesium Stearate
Kollidon VA-64
Isopropyl Alcohol
Hydroxypropyl Methylcellulose E-5
Hydroxypropyl Methylcellulose E-15
Talc
Titanium Dioxide
Iron Oxide Red
Propylene Glycol

Incompatibilities
NOT APPLICABLE

Shelf life
3 years from date of manufacture

Special precaution for storage
Store below 25˚C. Protect from light and moisture.

Nature and contents of container

I. Immediate Container/Packaging
Blister Pack
Type: Push-through blister pack; the package consists of a transparent thermoformable plastic material (PVC) and a heat-sealable lacquered backing material aluminium foil.

Material: Thermoformable plastic material : Polyvinyl Chloride (PVC)
Backing Material : *Aluminium foil*

II. Secondary Packaging Components
a) Material description : Clopivid 75 mg Tablet (3 x 10) Unit Box
b) Material description : Plain carton for Clopivid 75 mg Tablet
c) Material description : Clopivid 75 mg Tablet

6.6 Instructions for use and handling <and disposal>

NOT APPLICABLE

7. MARKETING AUTHORISATION HOLDER

Name	:	HOVID Bhd.
Address	:	121, Jalan Tunku Abdul Rahman, (Jalan Kuala Kangsar) 30010 Ipoh, Perak, Malaysia

Manufacturer Name :

Name	:	HOVID Bhd.
Address	:	Lot 56442, 7 ½ Miles, Jalan Ipoh / Chemor, 31200 Chemor, Perak., Malaysia.

8. NUMBER (S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

05728/06668/REN/2018

9. DATE OF FIRST AUTHORISATION\

2018

10. DATE OF REVISION OF THE TEXT

May 2020