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CLOPIVID TABLET 75 mg

VICLO31-var (MY)3

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

COMPOSITION
Each tablet contains Clopidogrel Hydrogen Sulphate equivalent to Clopidogrel 75 mg/tablet

PHARMACODYNAMICS
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.

PHARMACOKINETICS
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.

INDICATIONS
Secondary prevention of atherothrombotic events
Clopidogrel is indicated in:
- 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)
Clopidogrel in combination with ASA is indicated in:
- Adult patients with moderate to high-risk TIA (ABCD21 score ≥4) or minor IS (NIHSS2 ≤3) within 24 hours of either the TIA or IS event.

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.

CONTRAINDICATIONS
- 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

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.

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PREGNANCY AND LACTATION

Use in pregnancy
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.

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.

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.

OVERDOSE AND TREATMENT

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.

DOSAGE AND 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 or 600-mg loading dose. A 600 mg loading dose may be considered in patients < 75 years of age when percutaneous coronary intervention is intended (see section 4.4). 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.

Note: The information given here is limited. For further information, kindly consult your doctor or pharmacist.

Storage: Store below 30°C. Protect from light and moisture.

Presentation / Packing: Blister pack of 1 x10's, 3 x 10's, 10 x10's

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