Important information. Please read carefully.

VITRAQ™

CLOPIDOGREL 75MG
Film-Coated Tablet

COMPOSITION

Each film-coated tablet contains 75mg Clopidogrel (as Clopidogrel Bisulfate).

PHARMACODYNAMICS

Clopidogrel is a prodrug that inhibits platelet aggregation after metabolized by the enzyme, CYP 450 to produce the active metabolite. The active metabolite of clopidogrel selectively and irreversibly inhibits the adenosine diphosphate (ADP) from binding to the $P2Y_{12}$ platelet receptor, and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thus inhibits 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 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.

PHARMACOKINETICS

Clopidogrel is rapidly but incompletely absorbed after oral doses, absorption appears to be at least 50%.

It is a prodrug and is extensively metabolized in the liver, mainly to the inactive carboxylic acid derivatives. Metabolism is mediated by the CYP 450 isoenzymes including CYP 3A4, CYP 2B6 and to a lesser extent by CYP 1A2, CYP 1A1, and CYP 2C19.

The active metabolite appears to be a thiol derivative, which has been identified *in vitro* but appears to be too unstable to be isolated from plasma.

Clopidogrel and the carboxylic acid derivative are highly protein bound. Clopidogrel and its metabolites are excreted in the urine and faeces. About 50% of an oral dose is recovered from the urine and about 46% from the faeces.

INDICATIONS

For the prevention of atherothrombotic events in:

- Peripheral arterial disease, myocardial infarction, ischemic stroke.
- Acute coronary syndrome
  - Non-ST segment elevation (unstable angina or non-Q-wave myocardial infarction) that 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.

DOSAGE AND ADMINISTRATION

Adults and elderly

VITRAQ Film-Coated Tablet 75mg is given as a single daily dose of 75mg with or without food.

- Non-ST segment elevation acute coronary syndrome
  Clopidogrel is used with aspirin as an adjunct to either medical or interventional treatment, including coronary stenting. A single loading dose of 300 mg is given, followed by 75 mg once daily.

- ST segment elevation acute myocardial infarction
  Clopidogrel is used with aspirin as an adjunct in medically treated patients. It is given in a dose of 75 mg once daily; patients under 75 years of age may be given a loading dose of 300 mg. Treatment should be continued for at least 4 weeks.

Children and adolescents (below 18 years old)

- The safety and efficacy of clopidogrel in this age group have not been established.

CONTRAINDICATIONS

- Hypersensitivity to the active ingredient or any of the excipients.
- Severe liver impairment.
- Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS AND PRECAUTIONS

Bleeding and hematological disorders

- Use with caution in the patients who may be at the risk of increased bleeding from trauma, surgery or other pathological conditions like lesions, particularly in gastrointestinal and intraocular, as well as in the patients who undergoing treatment with ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors.
- Patients should notice carefully any signs of bleeding including the occult bleeding, especially during the first week of treatment and/or after invasive cardiac procedures or surgery.
- Patients who going to undergo surgery and the anti-platelet effect is not preferred, thus clopidogrel should discontinue 7 days prior to surgery.
- Patients should inform their physicians, dentists, or respective healthcare provider that they are taking clopidogrel before any surgery is scheduled and before any new medicinal product is taken.
- It is not recommended to consume the clopidogrel together with the oral anti-coagulant because this may increase the intensity of bleedings.

Thrombotic Thrombocytopenic Purpura (TTP)

- TTP occur rarely after the used of clopidogrel and sometimes after a short exposure.
- It is characterized by thrombocytopenia, microangiopathic haemolytic anemia associated with either neurological findings, renal dysfunction or fever.
- A potentially fatal condition requires prompt treatment including plasmapheresis.

Cytochrome P450 2C19 (CYP2C19)

- Avoid taking clopidogrel with other medicinal products that are stronger or moderate CYP2C19 inhibitors as would expected to result in reduced levels of the active metabolite of clopidogrel.

Pharmacogenetics :

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

Recent ischaemic stroke

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

Renal impairment

Clopidogrel should use with caution in the patients with renal impairment as the therapeutic experience with clopidogrel is limited.

Liver impairment

Clopidogrel should use with caution in the patients with liver impairment because patients with moderate hepatic disease have limited experience and may have bleeding diatheses.

DRUG INTERACTIONS

Oral anticoagulants

Administration of clopidogrel with oral anticoagulants may increase the intensity of bleedings. This is caused by the independent effects on homeostasis, although clopidogrel did not alter the pharmacokinetics of S-warfarin or International Normalized Ratio (INR) in patients receiving long-term warfarin therapy.

Glycoprotein IIb/IIIa inhibitors

Clopidogrel must be used with caution in the patients who may be at higher risk of increased bleeding from trauma, surgery or other pathological conditions that given together with glycoprotein IIb/IIIa inhibitors.

Acetylsalicylic acid (ASA)

The pharmacodynamic interaction between clopidogrel and ASA could lead to increase risk of bleeding, although 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. Concomitant use should be undertaken with caution.

Heparin

Administration of clopidogrel with heparin would increase the risk of bleeding due to the pharmacodynamic interaction, even though clopidogrel did not modify the heparin dose or alter the effect of heparin on coagulation.

Thrombolytics

Concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparin results in clinically significant bleeding.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Administration of clopidogrel with NSAIDs may increase the risk of gastrointestinal bleeding.

CYP2C19 inhibitors

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 clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g. proton pump inhibitors) should be discouraged.

Medicinal products that inhibit CYP2C19 include omeprazole, esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

PREGNANCY AND LACTATION

Use during pregnancy

No clinical data supports that clopidogrel can be used during pregnancies. It is preferable not to be used during pregnancy as a precautionary measure.

Use during breastfeeding

Animal studies in rat have shown that clopidogrel is excreted in the breast milk. However, it is still unknown whether clopidogrel is excreted in human breast milk. It is preferable not to continue treatment with clopidogrel during breastfeeding.

SIDE EFFECTS

Common: dyspepsia, abdominal pain, diarrhoea, bleeding disorders (including gastrointestinal and intracranial).

Less common: nausea, vomiting, gastritis, flatulence, constipation, gastric and duodenal ulcers, headache, dizziness, paraesthesia, leucopenia, decreased platelets, eosinophilia, rash and pruritus.

Rare: vertigo

Very rare: colitis, pancreatitis, hepatitis, acute liver failure, vasculitis, confusion, hallucinations, taste disturbance, stomatitis, bronchospasm, interstitial pneumonitis, blood disorders (including thrombocytopenic purpura, agranulocytosis and pancytopenia), and hypersensitivity reactions (including fever, glomerulonephritis, arthralgia, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus).

SYMPTOMS AND TREATMENT FOR OVERDOSAGE

Clopidogrel irreversibly inhibits the platelet aggregation until the end of the platelet's life. Overdose of clopidogrel may lead to prolonged bleeding time and following bleeding complications.

No antidote had been found to overcome the over dosage of clopidogrel. If immediate correction of prolonged bleeding time is require, platelet transfusion may restore clotting ability.

STORAGE CONDITION

Store below 30°C.

SHELF LIFE

The expiry date is indicated on the packaging.

PRODUCT DESCRIPTION

Pink, round, normal convex film- coatedtablet.
Available as blister strips of 10's in packing of 30, 90 and 100 tablets per box.

KEEP OUT OF REACH OF CHILDREN / JAUHI DARI KANAK-KANAK

For further information, please consult your pharmacist or physician.

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