PACKAGE INSERT TEMPLATE FOR CLOPIDOGREL TABLET

Brand or Product Name
[Product name] Tablet 75mg
[Product name] Tablet 300mg

Name and Strength of Active Substance(s)
Clopidogrel hydrogen sulphate/ bisulfate …mg equivalent to 75mg clopidogrel
Clopidogrel hydrogen sulphate/ bisulfate …mg equivalent to 300mg clopidogrel

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge tablets marked '75' on one side]

Pharmacodynamics
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.

Pharmacokinetics
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.

Indication

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.

Recommended Dosage

- Adults and elderly

Clopidogrel should be given as a single daily dose of 75 mg.

**The 300 mg tablet of clopidogrel is intended for use as a loading dose in patients suffering from acute coronary syndrome.*

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

Contraindications
- hypersensitivity to clopidogrel or to any of the excipients
- severe hepatic impairment.
- active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

Warnings and Precautions

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.
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. Patients should be monitored carefully for any signs of bleeding including occult bleeding, especially during the first week of treatment and/or after invasive cardiac procedures or surgery. The concomitant administration of clopidogrel with oral anticoagulants should be avoided 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 advised 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.

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: 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 higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.
Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.
Concomitant use with the CYP2C19 inhibitors omeprazole and esomeprazole should be avoided.

Renal impairment: use with caution.

Hepatic impairment: used with caution

Premature discontinuation of therapy
May increase risk of cardiovascular events (ie, stent thrombosis, myocardial infarction, and death), particularly in patients undergoing percutaneous coronary intervention.

Lapses in therapy: increased risk of cardiovascular events; restart as soon as possible

Nasogastric administration in critically ill patients after cardiopulmonary resuscitation: increased risk of impaired clopidogrel bioavailability

**If formulation contains lactose or hydrogenated castor oil, kindly include necessary warnings and precautions.*

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

Interactions with Other Medicaments
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.

Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolised by CYP2C9 can be safely co-administered with clopidogrel.

Statement on Usage During 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.

Breastfeeding

It is unknown whether clopidogrel is excreted in human breast milk. In animal studies, clopidogrel and/or its metabolites have been shown to be excreted in breast milk. Because human data are lacking regarding the use of clopidogrel in nursing women, it is recommended that a decision be made to discontinue either the drug or nursing after considering the importance of the drug to the mother.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

Adverse Effects / 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

Overdose and Treatment
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.

Treatment
Antidote is not available. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size eg]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]