



For Medical Professional only

Ogrel[®] Tablets

(Clopidogrel)

اوگرل ٹیبلٹس
(کلونڈوگرل)

DESCRIPTION:

Ogrel (clopidogrel bisulfate) is a thienopyridine class inhibitor of P2Y₁₂ ADP platelet receptors. Chemically it is methyl (+)-(S)- α -(2-chlorophenyl)-6,7-dihydro-thieno[3,2-c]pyridine-5(4H)- acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is C₁₆H₁₆ClNO₂S₂H₂SO₄ and its molecular weight is 419.9.

COMPOSITION:

Each film coated tablet contains:

Clopidogrel.....75mg as Clopidogrel Bisulfate U.S.P.

(Product Specs.: U.S.P.)

CLINICAL PHARMACOLOGY:

Pharmacodynamic Properties:

Pharmacotherapeutic group: platelet aggregation inhibitors excl. heparin, ATC Code: B01AC-04.

Mechanism of Action:

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y₁₂ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting 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 a 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.

Pharmacokinetic Properties

Absorption:

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2-2.5 ng/ml after a single 75 mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Distribution:

Clopidogrel and the main circulating (inactive) 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.

Metabolism:

Clopidogrel is extensively metabolised by the liver. In vitro and in vivo, clopidogrel is metabolised according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

Elimination:

Following an oral dose of ¹⁴C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. 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.

SPECIFIC POPULATIONS

Renal impairment:

After repeated doses of 75 mg clopidogrel per day in subjects with severe renal disease (creatinine clearance from 5 to 15 ml/min), inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy subjects, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel per day. In addition, clinical tolerance was good in all patients.

Hepatic impairment:

After repeated doses of 75 mg clopidogrel per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects. The mean bleeding time prolongation was also similar in the two groups.

THERAPEUTIC 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 or minor IS 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.

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 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.

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.

Adult patients with moderate to high-risk TIA or minor IS:

Adult patients with moderate to high-risk TIA or minor IS 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:

Safety and effectiveness in pediatric populations have not been established.

Elderly:

Patients with Renal Impairment:

Therapeutic experience is limited in patients with renal impairment.

Patients with Renal 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.

CONTRAINDICATIONS:

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

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. 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 ASA, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors, or selective serotonin reuptake inhibitors (SSRIs), or CYP2C19 strong inducers or other medicinal products associated with bleeding risk such as pentoxifylline. 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 oral anticoagulants is not recommended 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.

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.

Acquired haemophilia

Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Recent ischemic stroke

Initiation of therapy

- In acute minor IS or moderate to high-risk TIA patients, dual antiplatelet therapy (clopidogrel and ASA) should be started no later than 24 hours after the event onset.
- There is no data regarding the benefit-risk of short term dual antiplatelet therapy in acute minor IS or moderate to high-risk TIA patients, with a history of (non-traumatic) intracranial hemorrhage.
- In non-minor IS patients, clopidogrel monotherapy should be started only after the first 7 days of the event.

Non-minor IS patients

In view of the lack of data, use of dual antiplatelet therapy is not recommended.

Recent minor IS or moderate to high-risk TIA in patients for whom intervention is indicated or planned.

There is no data to support the use of dual antiplatelet therapy in patients for whom treatment with carotid endarterectomy or intravascular thrombectomy is

indicated, or in patients planned for thrombolysis or anticoagulant therapy. Dual antiplatelet therapy is not recommended in these situations.

Cytochrome P450 2C19 (CYP2C19)

Pharmacogenetics: In patients who are poor CYP2C19 metabolisers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype.

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged.

CYP2C8 substrates

Caution is required in patients treated concomitantly with clopidogrel and CYP2C8 substrate medicinal products.

Cross-reactions among thienopyridines

Patients should be evaluated for history of hypersensitivity to thienopyridines (such as clopidogrel, ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported. Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopenia and neutropenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

Renal impairment

Therapeutic experience with clopidogrel is limited in patients with renal impairment. Therefore clopidogrel should be used with caution in these patients.

Hepatic impairment

Experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population.

DRUG INTERACTIONS:

Medicinal products associated with bleeding risk:

There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of medicinal products associated with bleeding risk should be undertaken with caution.

Oral anticoagulants:

The concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings. Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin or International Normalised Ratio (INR) in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

Glycoprotein IIb/IIIa inhibitors:

Clopidogrel should be used with caution in patients who receive concomitant glycoprotein IIb/IIIa inhibitors.

Acetylsalicylic acid (ASA):

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.

Heparin:

Clopidogrel did not necessitate modification of the heparin dose or alter the effect

of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. A pharmacodynamic interaction between clopidogrel and heparin is possible, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution.

Thrombolytics:

The safety of the concomitant administration of clopidogrel, fibrin or non-fibrin specific thrombolytic agents and heparins was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytic agents and heparin are co-administered with ASA.

NSAIDs:

The concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs including Cox-2 inhibitors and clopidogrel should be co-administered with caution.

SSRIs:

Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Inducers of CYP2C19:

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that induce the activity of this enzyme would be expected to result in increased drug levels of the active metabolite of clopidogrel.

Rifampicin strongly induces CYP2C19, resulting in both an increased level of clopidogrel active metabolite and platelet inhibition, which in particular might potentiate the risk of bleeding. As a precaution, concomitant use of strong CYP2C19 inducers should be discouraged.

Inhibitors of CYP2C19:

Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. As a precaution concomitant use of strong or moderate CYP2C19 inhibitors should be discouraged.

Medicinal products that are strong or moderate CYP2C19 inhibitors include, for example, omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz.

Proton Pump Inhibitors (PPI):

Omeprazole 80 mg once daily administered either at the same time as clopidogrel or with 12 hours between the administrations of the two drugs decreased the exposure of the active metabolite by 45% (loading dose) and 40% (maintenance dose). The decrease was associated with a 39% (loading dose) and 21% (maintenance dose) reduction of inhibition of platelet aggregation. Esomeprazole is expected to give a similar interaction with clopidogrel. Less pronounced reductions of metabolite exposure has been observed with pantoprazole or lansoprazole. The plasma concentrations of the active metabolite was 20% reduced (loading dose) and 14% reduced (maintenance dose) during concomitant treatment with pantoprazole 80 mg once daily. This was associated with a reduction of the mean inhibition of platelet aggregation by 15% and 11%, respectively. There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of clopidogrel.

Boosted anti-retroviral therapy (ART):

HIV patients treated with boosted anti-retroviral therapies (ART) are at high risk of vascular events. A significantly reduced platelet inhibition has been shown in

HIV patients treated with ritonavir-or cobicistat-boosted ART. Average platelet inhibition can be decreased with concomitant use of clopidogrel and ritonavir. Therefore, concomitant use of clopidogrel with ART boosted therapies should be discouraged.

Rosuvastatin:

Clopidogrel has been shown to increase rosuvastatin exposure in patients by 2-fold (AUC) and 1.3-fold (Cmax) after administration of a 300 mg clopidogrel dose, and by 1.4 fold (AUC) without effect on Cmax after repeated administration of a 75 mg clopidogrel dose.

Other:

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

As with other oral P2Y12 inhibitors, co-administration of opioid agonists has the potential to delay and reduce the absorption of clopidogrel presumably because of slowed gastric emptying.

ADVERSE EFFECTS:

Common:

Haematoma, Epistaxis, Gastrointestinal hemorrhage, diarrhoea, abdominal pain, dyspepsia, Bruising, Bleeding at puncture site.

Uncommon:

Thrombocytopenia, leucopenia, eosinophilia, Intracranial bleeding, headache, paraesthesia, dizziness, Eye bleeding (conjunctival, ocular, retinal), Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence, Rash, pruritus, skin bleeding (purpura), Haematuria, Bleeding time prolonged, neutrophil count decreased, platelet count decreased.

Rare:

Neutropenia, including severe neutropenia, Vertigo, Retroperitoneal hemorrhage, Gynaecomastia.

Very Rare & Not Known:

Thrombotic thrombocytopenic purpura (TTP), aplastic anaemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia, Kounis syndrome (vasospastic allergic angina / allergic myocardial infarction) in the context of a hypersensitivity reaction due to clopidogrel, Serum sickness, anaphylactoid reactions, cross-reactive drug hypersensitivity among thienopyridines, insulin autoimmune syndrome, which can lead to severe hypoglycemia, particularly in patients with HLA DRA4 subtype, Hallucinations, confusion, Hallucinations, confusion, Serious hemorrhage, hemorrhage of operative wound, vasculitis, hypotension, Respiratory tract bleeding (haemoptysis, pulmonary hemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia, Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis, Acute liver failure, hepatitis, abnormal liver function test, Bullous dermatitis (toxic epidermal necrolysis, Stevens Johnson Syndrome, erythema multiforme, acute generalised exanthematous pustulosis (AGEP), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus, Musculo-skeletal bleeding (haemarthrosis), arthritis, arthralgia, myalgia, Glomerulonephritis, blood creatinine increased, fever.

USE IN 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.

Lactation:

It is unknown whether clopidogrel is excreted in human breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Ogrel.

OVERDOSE:

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleedings are observed.

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.

SHELF LIFE:

3 years

STORAGE:

Protect from heat, sunlight & moisture, store below 30°C.

The expiration date refer to the product correctly stored at the required condition. Keep out of the reach of children.

Patients and healthcare professionals can also report suspected adverse drug reaction at ade@bosch-pharma.com.

To be sold on prescription of a registered medical practitioner only.

PRESENTATION:

Ogrel (Clopidogrel) is available in Cold form Cold seal pack of 10's tablets.

پیداہیات:

دسویں، گرمی اور نی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخے پر فروخت کے لئے۔



Manufactured by:

Bosch PHARMACEUTICALS (Pvt) Ltd.

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