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NØCLOT®
(CLOPIDOGREL)
75 mg Tablet

NØCLOT-LD300®
(CLOPIDOGREL)
300 mg Tablet

نوکلوٹ

نوکلوٹ-ایل ڈی ۳۰۰

COMPOSITION:

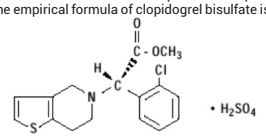
Noclot Tablet 75 mg:
Each film coated tablet contains:
Clopidogrel Bisulfate USP equivalent to
Clopidogrel..... 75 mg.

Product Specs.: USP

Noclot-LD Tablet 300 mg:
Each film coated tablet contains:
Clopidogrel Bisulfate USP equivalent to
Clopidogrel ..... 300 mg.

Product Specs.: USP

DESCRIPTION:
NOCLOT (clopidogrel bisulfate) is a thienopyridine class inhibitor of P2Y12 ADP platelet receptors. Chemically it is methyl (+)-(S)-α-(2-chlorophenyl)-6,7-dihydrothieno[3,2-c] pyridine-5(4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ and its molecular weight is 419.9. The structural formula is as follows:



CLINICAL PHARMACOLOGY:
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.
Pharmacokinetics:
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. Metabolism results in formation of the active metabolite, a thiol derivative of clopidogrel, which binds rapidly and irreversibly to platelet receptors, inhibiting platelet aggregation. Cmax occurs approximately 30 to 60 minutes after dosing. 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.
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.
Pharmacokinetics in Special 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 is lower (25%) than healthy individuals, however, the prolongation of bleeding time was similar to that seen in healthy subjects receiving 75 mg of clopidogrel/day.
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.

INDICATIONS AND USAGE:
Clopidogrel is indicated in:
Secondary prevention of atherothrombotic events:
- 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, in combination with acetylsalicylic acid (ASA).
  - ST segment elevation acute myocardial infarction, in combination with 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.

DOSAGE AND ADMINISTRATION:
NOCLOT 75 mg, should be given as a single daily dose of 75 mg.
NOCLOT-LD 300 mg, is intended for use as a loading dose.
- ***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.

ADMINISTRATION:
For oral use: It may be given with or without food.
Dose Modification Recommendations:
Paediatric population: Clopidogrel should not be used in children because of efficacy concerns.

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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.

CONTRAINDICATIONS:
- Hypersensitivity to the active substance.
- 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. 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. If antiplatelet effect is temporarily not desirable, clopidogrel should be discontinued 7 days prior to elective surgery. Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular). 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): 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: 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, clopidogrel should be discontinued.
Recent ischaemic stroke: clopidogrel cannot be recommended during the first 7 days after acute ischaemic stroke.
Cytochrome P450 2C19 (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. 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: such as (clopidogrel, ticlopidine, prasugrel) may cause mild to severe allergic reactions such as rash, angioedema, or haematological cross-reactions such as thrombocytopaenia and neutropaenia. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.
Renal impairment: 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:
Oral anticoagulants: the concomitant administration of clopidogrel with oral anticoagulants is not recommended since it may increase the intensity of bleedings. co-administration 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. However, concomitant administration of 500 mg of ASA twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. A pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible. Therefore, concomitant use should be undertaken with caution.
Heparin: 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 incidence of clinically significant bleeding is similar to that observed when thrombolytic agents and heparin are co-administered with ASA.
NSAIDs: 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.
Other concomitant therapy: Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of medicinal products that inhibit (such as omeprazole and esomeprazole, fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, carbamazepine, and efavirenz) the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

USE IN SPECIFIC POPULATIONS:
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.
Nursing Mothers:
It is unknown whether clopidogrel is excreted in human breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with NOCLOT.

ADVERSE REACTIONS:
The drug is generally well tolerated. Side effects that have been reported include abdominal pain, dyspepsia, gastritis, diarrhea, nausea, vomiting, constipation, gastrointestinal hemorrhage, ulceration, neutropenia, rash, palpitation, syncope, drowsiness, asthenia, neuralgia, paresthesia and vertigo.

OVERDOSAGE:
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.

INSTRUCTIONS:
Store below 30°C. Protect from heat, sunlight & moisture. Keep out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
Noclot Tablet 75 mg : Pack of 2 x 10 tablets.
Noclot-LD Tablet 300 mg : Pack of 1 x 1 tablet.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATIONS PLEASE CONTACT:

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