SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DILOXOL (clopidogrel) 75mg Film Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film tablet contains: 97.875 mg Clopidogrel hydrogen sulfate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In patients with a history of symptomatic atherosclerotic disease (such as recent stroke, recent myocardial infarction (MI) or peripheral arterial disease), preventing vascular ischemic events (myocardial infarction, stroke, vascular death).

4.2 Posology and method of administration

Adults:

Diloxol® Film Tablet should be administered in single 75 mg dose once daily. No dosage adjustment is necessary for elderly patients or patients with renal disease (See pharmacokinetic properties).

Children and Youngsters:

The safety and efficacy has not been determined in patients less then 18 years of age.

Diloxol® Film Tablet can be administered once daily with or without food.

4.3 Contraindications

-Hypersensitivity to any component of the product.

-Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.4 Special warnings and precautions for use

Diloxol® should be used with caution, as with other antiaggregant agents, in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions. If a

patient is to undergo elective surgery and an antiplatelet effect is not desired, Diloxol® should be discontinued 7 days prior to surgery.

Diloxol® prolongs the bleeding time; therefore should be used with caution in patients who may be at risk of increased bleeding. Drugs that might induce such lesions (acetylsalicylic acid and nonsteroidal anti-inflammatory drugs) should be used with caution in patients taking Diloxol®.

Diloxol® should be used with caution in patients who have lesions with a propensity to bleed such as gastrointestinal ulcer.
Patients should be told that it may take them longer than usual to stop bleeding when they take Diloxol®, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking Diloxol® before any surgery is scheduled and before any new drug is taken.

Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Therefore Diloxol® should be used with caution in this population.
Thrombotic thrombocytopenic purpura (TTP); TTP has been reported rarely following use of Diloxol®, sometimes after a short exposure (<2weeks). TTP is a serious condition requiring prompt treatment. TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. TTP was not seen during clopidogrel's clinical trials, which included over 11,300 clopidogrel-treated patients.

In world-wide postmarketing experience, however, TTP has been reported at a rate of about four cases per million patients exposed, or about 11 cases per million
patient-years.
The background rate is thought to be about four cases per million person-years. Experience is limited in patients with severe renal impairment. Clopidogrel should be used with caution in this population.

Clopidogrel should be used with caution in patients with hypertension.

4.5 Interaction with other medicinal products and other forms of interaction

Acetylsalicylic acid: Acetylsalicylic acid did not modify the Diloxol® mediated inhibition of ADP induced platelet aggregation. However, Diloxol® potentiated the effect of acetylsalicylic acid on collagen-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by Diloxol®. It has not been determined whether or not the chronic coadministration of acetylsalicylic acid and Diloxol® is safe.

Heparin: In a study in healthy volunteers, Diloxol® did not change the total heparin consumption and did not change the effect of heparin on coagulation. Co- administration of

Diloxol® and heparin had no effect on inhibition of platelet aggregation induced by Diloxol®. Yet the safety of this combination has not been determined, therefore, co-administration should be done with caution.

Recombinant Human Tissue Plasminogen Activator (rt-PA): The safety of the combined use of Diloxol®, rt-PA and heparin has been evaluated on patients who have had recent myocardial infarction. Clinically significant bleeding incidence is the same with the bleeding incidence seen with the combined use of acetylsalicylic acid with rt-PA and heparin.

Warfarin: The safety of the concomitant use of warfarin with Diloxol® has not been determined. Therefore the concomitant administration of these two agents should be undertaken with caution.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In a study in healthy volunteers, concomitant administration of Diloxol® and naproxen has increased occult gastrointestinal blood loss. Therefore due to the potential of increasing gastrointestinal bleeding risk, NSAIDs and Diloxol® should be coadministered with caution (See Warnings/Precautions).

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when Diloxol® was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of Diloxol® was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen. The pharmacokinetics of digoxin or theophylline was not modified by the coadministration of Diloxol®. Antiacids have not affected the absorption degree of Diloxol®. Studies on human liver microsomes

have shown that Diloxol® inhibits the activity of one of the isoenzymes (CYP 2C9) of cytochrome P 450 (2C9) enzyme. This situation may result in the increase of plasma levels of drugs such as phenytoin and tolbutamide, which are metabolized by CYP 2C9.
There is no evidence of clinically significant adverse interactions due to concomitant use of diuretics, beta-blocking agents, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents, antiepileptic agents, hormone replacement therapy.

Concomitant use of clopidogrel with botanical drugs such as garlic, ginkgo biloba, ginseng, ginger, anacyclus pyrethum, aesculus hippocastanum, green tea, *uncaria tomentosa*, angelica archangelica, oenethera biennis, trifolium pratense having anti-platelet activity should be avoided.

4.6 Fertility, pregnancy and lactation

Use in pregnancy:

Pregnancy category: B

Reproduction studies performed in rats and rabbits revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, Diloxol® should be used during pregnancy only if clearly needed.

Use in lactation:

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

4.7 Effects on ability to drive and use machines

Following Diloxol® administration, no impairment on ability to drive or psychometric performance has been observed.

4.8 Undesirable effects

As with all drugs affecting heomostasis, bleeding may be seen due to administration of clopidogrel. Bleeding may occur in any part of the body. Risk depends on many factors including the combinative use with other drugs affecting heomostasis and sensitivity of the patient.

>10%:
Gastrointestinal: Overall, the incidence of gastrointestinal side effects (including abdominal pain, dyspepsia, gastritis and constipation) is documented as 27%.

%3-10%:
Cardiovascular system: Chest pain (8%), edema (%4), hypertension (4%)

Central nervous system: Headache (3-8%), dizziness (2-6%), depression (4), fatigue (3%), generalized pain (6%).

Skin reactions: Rash (4%), pruritus (3%).

Endocrin and metabolic system: Hypercholesterolemia (4%).

Gastrointestinal system: Abdominal pain (2-6%), dyspepsia (25%), diarrhea (2-5%), nausea (3%).

Genitourinary system: Urinary tract infections (3%).

Hematological system: Purpura (5), epistaxis (3%).

Hepatic system: Liver function test disorder (<3%); in 0,11% of the patients, clopidogrel administration is terminated).

Musculo-skeletal system: Arthralgia (6%), back pain (6%).
Respiratory system: Dyspnea (5%), rhinitis (4%), bronchitis (4%), coughing (3%), Upper respiratory tract infections (9%).

Other: Influenza-like syndrome (8%).

<1%: Agranulosytosis, allergic reactions, anaphilactic reaction, angioedema, aplastic anemia, bilirubinemia, bronchospasm, bullose eruption, liver fattening, fever, granulosytopenia, hematuria, hemoptysis, hemathorax, hepatitis, hypochromic anemia, interal head- bleeding (0,4%), ischemic necrosis, leukopenia, maculopapular rash, menoragia, neutropenia (0,05%),

occular bleeding, pulmoner bleeding, purpura, retroperitoneal bleeding, trombosytopenia, thrombotic thrombocytopenic purpura, urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Symptoms of acute toxicity include vomiting, difficult breathing, and gastrointestinal hemorrhage.

No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard tablets) of Diloxol® in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75 mg per day.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clopidogrel is an original and strong inhibitor of platelet aggregation Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation. However an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and return to normal platelet function occurs in consistent speed with the platelet cycle (approximately 7 days).

Statistically significant and dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel. Repeated doses of 75 mg (clopidogrel bisulfate) per day significantly inhibit ADP-induced platelet aggregation on the first day. This inhibition increases progressively and reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg per day is between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 7 days.

5.2 Pharmacokinetic properties

Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base). Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.

Clopidogrel is a pro-drug. Its main active metabolite, which is a thiol derivative, comes about with clopidogrel's oxidation to 2-oxo-clopidogrel and hydrolysis afterwards. The oxidation step is regulated primarily with cytochrome P450 isoenzymes 2B6 and 3A4 and also with 1A1, 1A2 and 2C19. The active thiol metabolite, which is isolated in vitro, binds with platelet receptors rapidly and irreversibly; and inhibits the platelet aggregation. This metabolite can not be determined in the plasma.
The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel.

Clopidogrel is extensively metabolized by the liver and the main circulating metabolite is the carboxylic acid derivative, and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug related compounds in plasma. This metabolite's peak plasma levels are reached approximately after one hour following administration of the drug.

Clopidogrel and the main circulating metabolite bind reversibly in vitro to human plasma proteins; 98% and 94%, respectively. It has been shown that this binding is nonsaturable in vitro up to a high concentration.

Approximately 50% of the drug is excreted in the urine and approximately 46% of it is excreted in the feces. The elimination half-life of the main circulating metabolite is 8 hours after single and repeated administration.

Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. After repeated doses of 75 mg/day (clopidogrel bisulfate), plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal-impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of clopidogrel per day.

5.3 Preclinical safety data

The most common effects during pre-clinical studies in rats and baboons are liver changes. These changes occurred at doses representing at least 25 times the clinical dose of 75 mg/day in humans, and are the result of an effect on metabolism enzymes in the liver. No effect on metabolizing enzymes in the liver was observed in humans receiving therapeutic doses of clopidogrel.

It has also been reported that clopidogrel is not tolerated in the stomach when given to rats and baboons at very high doses (gastritis, gastric erosion and/or vomiting).

When Clopidogrel was administered at doses of 77 mg/kg per day for 78 weeks in mice and 104 weeks in rats, no carcinogenic effects were observed (at doses representing at least 25 times the clinical dose of 75 mg/day in humans).

Clopidogrel has been tested for its genotoxic effects in a number of in vivo and in vitro studies and no genotoxic effects were seen.

Clopidogrel had no effect on the reproduction of male and female mice and had no teratogenic effects in rats or rabbits. Clopidogrel caused a slight delay in the development of the offspring when given to lactating rats. Special pharmacokinetic studies with radiolabelled clopidogrel have shown that the parent component or its metabolites pass into milk. Consequently, the possibility of a direct effect (slightly toxic effect) or an indirect effect (low palatability) cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl cellulose
Mannitol
Microcrystalline cellulose
Polyethylene glycol
Hydrogenated castor oil
Lactose monohydrate (bovine origin)
Hydroxypropyl methyl cellulose
Titanium dioxide
Triacetin
Red iron oxide

6.2 Incompatibilities

Not available.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C, at room temperature

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

28 film-coated tablets are presented in cartoon box, in PVC/PVDC-Al blister, along with package insert.

6.6 Special precautions for disposal <and other handling>

Unused products or waste materials should be disposed in accordance with the ' Regulation' on Medical Waste Control and 'Regulation on Packaging and Packaging Waste Control'.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Certificate No: 05040/07205/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: Mar 4, 2020

10. DATE OF REVISION OF THE TEXT

July, 2023

11. Reference