Nefazan Clopidogrel

Coated tablets

Made in Argentina - Rx only

FORMULA

Each coated tablet contains: clopidogrel bisulfate 97.87 mg (equivalent to clopidogrel 75 mg).
Excipients: anhydrous lactose, pregelatinized starch, microcrystalline cellulose, hydrogenated castor oil, hydroxypropyl methylcellulose, polyethylene glycol 6000, titanium dioxide, red iron oxide, magnesium stearate, triethyl citrate, talc, q.s.

THERAPEUTIC ACTION

Antithrombotic and antiplatelet agent.

INDICATIONS

Nefazan is indicated for the reduction of atherosclerotic events as follows:
Recent myocardial infarction (MI), recent ischemic stroke or established peripheral arterial disease
For patients with a history of recent MI, recent stroke or established peripheral arterial disease, clopidogrel has demonstrated to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not) and other deaths due to vascular cause.
Acute coronary syndrome
For patients with acute coronary syndrome (unstable angina or non-Q-wave MI), including those patients who must be treated medically and those who are to be managed with angioplasty (with or without stent) or CABG, clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

PHARMACOLOGICAL ACTION

Clopidogrel is an 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. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan and a normal platelet function will only be possible during platelet renewal.
Repeated doses of 75 mg clopidogrel per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg clopidogrel per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

PHARMACOKINETICS

After repeated 75-mg oral doses per day, clopidogrel is rapidly absorbed.
Plasma concentrations of the parent compound are very low and are generally below the quantification limit (0.00025 mg/L) beyond 2 hours after dosing.
Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.
Clopidogrel is extensively metabolized by the liver. 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. Maximum plasma concentration of this metabolite is observed 1 hour after administration.
The pharmacokinetics of the main circulating metabolite is linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel.
Clopidogrel and its main circulating metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively). The binding is non-saturable in vitro at a wide range of concentrations.
Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration.
After repeated doses of 75 mg clopidogrel per day, 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. No dosage adjustment is needed in patients with renal impairment.

DOSAGE AND ADMINISTRATION

Recent MI, recent stroke or established peripheral arterial disease
The recommended daily dose of Nefazan is 75 mg once daily.
Acute coronary syndrome
For patients with acute coronary syndrome (unstable angina/non-Q-wave MI), Nefazan should be initiated with a single 300 mg loading dose and then continued at 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination with Nefazan.
Nefazan can be administered with or without food.
No dosage adjustment is necessary for elderly patients or patients with renal disease.

CONTRAINDICATIONS

Hypersensitivity to the drug substance or any component of the product.
Severe hepatic impairment.
Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.
Lactation.

WARNINGS

Thrombotic thrombocytopenic purpura (TTP)
TTP has been reported rarely following use of clopidogrel, sometimes after a short exposure (< 2 weeks). TTP was not observed during clinical trials with clopidogrel, which included more than 17,500 patients treated with clopidogrel. But in further worldwide marketing experience, TTP has been reported in four cases per million of patients.

PRECAUTIONS

General: 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. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel should be discontinued 5 days prior to surgery.
GI bleeding: Clopidogrel extends the time of bleeding. In patients of an international study who received clopidogrel or aspirin, clopidogrel was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. In patients of an international study who received clopidogrel + aspirin vs. placebo + aspirin, the incidence of major gastrointestinal bleeding was 1.3% vs. 0.7% (clopidogrel + aspirin vs. placebo + aspirin, respectively). Clopidogrel should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions should be used with caution in patients taking clopidogrel.
Hepatic impairment: Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. Clopidogrel should be used with caution in this population.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

There was no evidence of carcinogenic effect when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at doses up to 77 mg/kg per day, representing at least 25 times the plasma exposure observed in humans at the recommended daily dose of 75 mg.
Clopidogrel was not teratogenic in in vitro tests.
Clopidogrel was found to have no effect on fertility of male and female rats at oral doses 52 times the recommended human dose.

PREGNANCY

Pregnancy Category B. Reproduction studies performed in animals revealed no evidence of impaired fertility or foetotoxicity 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, clopidogrel should be used during pregnancy only if clearly needed.

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. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, 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.

PEDIATRIC USE

Safety and effectiveness in the pediatric population have not been established.

DRUG INTERACTIONS

Study of specific drug interactions yielded the following results:
Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-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 clopidogrel. Clopidogrel potentiated the effect of aspirin on collagen-induced platelet aggregation. Clopidogrel and aspirin have been administered together for up to one year.
Heparin: In a study in healthy volunteers, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by clopidogrel.
Nonsteroidal antiinflammatory drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of clopidogrel was associated with increased occult gastrointestinal blood loss. NSAIDs and clopidogrel should be coadministered with caution.
Warfarin: As the safety of the concomitant administration of warfarin with clopidogrel has not been established, the concomitant administration of these two agents should be undertaken with caution.
Other concomitant therapy: No clinically significant pharmacodynamic interactions were observed when clopidogrel was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of clopidogrel 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 clopidogrel. At high concentrations in vitro, clopidogrel inhibits P450 (2C9). Accordingly, clopidogrel may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with clopidogrel.
In addition to the above specific interaction studies, patients enrolled in clinical trials with clopidogrel received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents, hormone replacement therapy, heparins (unfractionated and LMWH) and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions. There are no data on the concomitant use of clopidogrel with oral contraceptives and chronic treatment with NSAIDs.

ADVERSE REACTIONS

Clopidogrel has been evaluated for safety in more than 17,500 patients, including over 9,000 patients treated for 1

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year or more. The overall tolerability of clopidogrel in an International Study was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observed in two international studies are discussed below.

Hemorrhagic disorders: In patients of an international study receiving clopidogrel (75 mg) or aspirin (325 mg), gastrointestinal hemorrhage occurred at a rate of 2.0% in those receiving clopidogrel, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for clopidogrel compared to 0.5% for aspirin. In another international study, with patients receiving clopidogrel (75 mg) + aspirin (300 mg) or placebo + aspirin (300 mg), there was an excess in major bleeding in patients receiving clopidogrel + aspirin compared with placebo + aspirin, primarily gastrointestinal and at puncture sites. The incidence of intracranial hemorrhage (0.1%), and fatal bleeding (0.2%), were the same in both groups. There was no excess in major bleeding within seven days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (event rate 4.4% clopidogrel + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel + aspirin, and 6.3% for placebo + aspirin.

Neutropenia / agranulocytosis: Ticlopidine, a drug chemically similar to clopidogrel, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/ml). In the study with patients receiving clopidogrel or aspirin, severe neutropenia was observed in six patients, four on clopidogrel and two on aspirin. Two of the 9,599 patients who received clopidogrel and none of the 9,586 patients who received aspirin had neutrophils count of zero. One of the four clopidogrel patients in this study was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with clopidogrel. In the study with patients receiving clopidogrel + aspirin or placebo + aspirin, the numbers of patients with thrombocytopenia (19 clopidogrel + aspirin vs. 24 placebo + aspirin) or neutropenia (3 vs. 3) were similar. Although the risk of myelotoxicity with clopidogrel appears to be quite low, this possibility should be considered when a patient receiving clopidogrel demonstrates fever or other sign of infection.

Gastrointestinal: Overall, the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving clopidogrel was 27.1%, compared to 29.8% in those receiving aspirin in the study with patients receiving clopidogrel or aspirin. In the study with patients receiving clopidogrel + aspirin or placebo + aspirin, the incidence of these gastrointestinal events for patients receiving clopidogrel + aspirin was 11.7% compared to 12.5% for those receiving placebo + aspirin. In the study with patients receiving clopidogrel or aspirin, the incidence of peptic, gastric or duodenal ulcers was 0.7% for clopidogrel and 1.2% for aspirin. In the study with patients receiving clopidogrel + aspirin or placebo + aspirin, the incidence of peptic, gastric or duodenal ulcers was 0.4% for clopidogrel + aspirin and 0.3% for placebo + aspirin. Cases of diarrhea were reported in the study with patients receiving clopidogrel or aspirin in 4.5% of patients in the clopidogrel group compared to 3.4% in the aspirin group. However, these were rarely severe (clopidogrel =0.2% and aspirin=0.1%). In the study with patients receiving clopidogrel + aspirin or placebo + aspirin, the incidence of diarrhea for patients receiving clopidogrel + aspirin was 2.1% compared to 2.2% for those receiving placebo + aspirin. In the study with patients receiving clopidogrel or aspirin, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for clopidogrel and 4.0% for aspirin. In the study with patients receiving clopidogrel + aspirin or placebo + aspirin, the incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 0.9% for clopidogrel + aspirin compared with 0.8% for placebo + aspirin.

Rash and other skin disorders: In the study with patients receiving clopidogrel or aspirin, the incidence of skin and appendage disorders in patients receiving clopidogrel was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious). In the study with patients receiving clopidogrel + aspirin or placebo + aspirin, the incidence of rash or other skin disorders in patients receiving clopidogrel + aspirin was 4.0% compared to 3.5% for those receiving placebo + aspirin. In the study with patients receiving clopidogrel or aspirin, the overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for clopidogrel and 0.8% for aspirin. In the study with patients receiving clopidogrel + aspirin or placebo + aspirin, the incidence of patients withdrawing because of skin and appendage disorders adverse reactions was 0.7% for clopidogrel + aspirin compared with 0.3% for placebo + aspirin. The median duration of therapy was 20 months, with a maximum of 3 years.

Adverse events occurring in > 2.5% of patients on clopidogrel in the study with patients receiving clopidogrel or aspirin, regardless of relationship to clopidogrel

Body as a whole: Chest Pain, accidental inflicted injury, influenza-like symptoms, pain, fatigue.
Cardiovascular disorders: edema, hypertension.
Central and peripheral nervous system disorders: headache, dizziness.
Gastrointestinal system disorders: abdominal pain, dyspepsia, diarrhea, nausea.
Metabolic and nutritional disorders: hypercholesterolemia.
Musculo-skeletal system disorders: arthralgia, back pain.
Platelet, bleeding, and clotting disorders: purpura/bruise, epistaxis.
Psychiatric disorders: depression.
Respiratory system disorders: upper respiratory tract infection, dyspnea, rhinitis, bronchitis, coughing.
Skin and appendage disorders: rash, pruritus.
Urinary system disorders: urinary tract infection.

Adverse events occurring in >2.0% of patients on clopidogrel in the study with patients receiving clopidogrel + aspirin or placebo + aspirin, regardless of relationship to clopidogrel

Body as a whole: Chest pain.
Central and peripheral nervous system disorders: headache, dizziness.
Gastrointestinal system disorders: abdominal pain, dyspepsia, diarrhea.

Adverse events ocurring in 1% to 2.5% of the patients receiving clopidogrel in the study with patients receiving clopidogrel or aspirin regardless of relationship to clopidogrel

Autonomic nervous system disorders: syncope, palpitation.
Body as a whole-general disorders: asthenia, fever, hernia.
Cardiovascular disorders: cardiac failure.
Central and peripheral nervous system disorders: cramps legs, hypoaesthesia, neuralgia, paraesthesia, vertigo.
Gastrointestinal system disorders: constipation, vomiting.
Heart rate and rhythm disorders: fibrillation atrial.
Liver and biliary system disorders: hepatic enzymes increased.
Metabolic and nutritional disorders: gout, hyperuricemia, non-protein nitrogen (npn) increased.
Musculo-skeletal system disorders: arthritis, arthrosis.
Platelet, bleeding & clotting disorders: GI hemorrhage, hematoma, platelets decreased.
Psychiatric disorders: anxiety, insomnia.
Red blood cell disorders: anemia.
Respiratory system disorders: pneumonia, sinusitis.
Skin and appendage disorders: eczema, skin ulceration.
Urinary system disorders: cystitis.
Vision disorders: cataract, conjunctivitis.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in the studies of patients who received clopidogrel or clopidogrel + aspirin, regardless of relationship to clopidogrel. In general, the incidence of these events was similar to that in patients receiving aspirin or placebo + aspirin

Body as a whole: allergic reaction, ischemic necrosis.
Cardiovascular system disorders: generalized edema.
Gastrointestinal system disorders: perforated gastric ulcer, hemorrhagic gastritis, upper GI hemorrhagic ulcer.
Liver and biliary system disorders: bilirubinemia, infectious hepatitis, fatty liver.
Platelet, bleeding and clotting disorders: hemarthrosis, hematuria, hemoptysis, intracranial hemorrhage, retroperitoneal hemorrhage, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, allergic purpura, thrombocytopenia.
Red blood cell disorders: aplastic anemia, hypochromic anemia.
Reproductive disorders, female: menorrhagia.
Respiratory system disorders: hemothorax.
Skin and appendage disorders: bullous eruption, erythematous rash, maculopapular rash, urticaria.
Urinary system disorders: abnormal renal function, acute renal failure.
White cell and reticuloendothelial system disorders: agranulocytosis, granulocytopenia, leukemia, leukopenia, neutrophils decreased

PATIENT INFORMATION

Patients should be told that it may take them longer than usual to stop bleeding, when they take clopidogrel, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.

OVERDOSE

A voluntary overdose case was reported: a woman took a 1,050 mg dose of clopidogrel not presenting adverse events. It did not require special treatment and the patient recovered without sequels.
No adverse events were reported after an oral administration of 600 mg, in a single dose, or in healthy volunteers. Bleeding time increased by 1.7, similar to the value observed with therapeutic doses (75 mg/day).
Treatment: there are no known antidotes for clopidogrel. A platelet transfusion may be appropriate to reverse the pharmacological effects of clopidogrel.
In case of a possible overdose, seek medical attention in the nearest hospital or toxicology center.

HOW SUPPLIED

Packages of 30 coated tablets.

STORE BELOW 30°C.

KEEP OUT OF THE REACH OF CHILDREN.

PHOENIX
Compromiso por la Salud

Manufactured by Laboratorios Phoenix S.A.I.C. y F.
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Recyclable Material

"The sale package of this product has its trade name printed in Braille, in order to allow its identification by blind patients."

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