Nefazan
Clopidogrel 75 mg

Coated tablets

MADE IN ARGENTINA
Sold under prescription

FORMULATION
Each Nefazan coated tablet contains: Clopidogrel bisulfate (equivalent to 75.0 mg of base Clopidogrel) 97.88 mg. Excipients: microcrystalline cellulose 45.339 mg; anhydrous lactose 88.291 mg; crospovidone 2.50 mg; colloidal silicon dioxide 1.20 mg; sodium stearyl fumarate 4.80 mg; Opadry II 32K150002 RED (hydroxypropylmethyl cellulose 4.68 mg, triacetin 0.96 mg, lactose monohydrate 3.36 mg, titanium dioxide 1.79 mg, FD & C Red 40 (CI 16035) 0.72 mg, FD & C Yellow 5 (CI 19140) 0.4416 mg, FD & C Blue 2 (CI 73015) 0.048 mg) 12.00 mg.

THERAPEUTIC ACTION
Antithrombotic, antiplatelet medicinal product. Code ATC: B01AC04.

INDICATIONS
Prevention of atherothrombotic events
Nefazan is indicated for:
• Adult patients suffering from myocardial infarction (from a few days after the event until less than 35 days), ischemic stroke (from 7 days after the event 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 thrombolytic 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, Nefazan is indicated in combination with ASA for the prevention of atherothrombotic and thromboembolic events, including stroke.

PHARMACOLOGICAL PROPERTIES
Pharmacological action
Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolized 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. 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. Repeated daily doses of 75 mg produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed at a daily dose of 75 mg was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

PHARMACOKINETICS
Absorption
After single and repeated daily oral doses of 75 mg, 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 metabolized by the liver. In vitro and in vivo, Clopidogrel is metabolized 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 metabolized to an intermediate metabolite: 2-oxo-Clopidogrel. Subsequent metabolism of the 2-oxo-Clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of Clopidogrel. In vitro, this metabolic pathway is mediated by CYP3A4, CYP2C19, CYP1A2 and CYP2B6. The active thiol metabolite which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

The C_{max} of the active metabolite is twice as high following a 300-mg Clopidogrel loading dose as it is after four days of 75-mg maintenance dose. C_{max} occurs approximately 30 to 60 minutes after administration.

Elimination
Following an oral dose of ^{14}C-labelled Clopidogrel in humans, approximately 50% was excreted in urine and approximately 46% in feces in the 120-hour interval after administration. 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.

Pharmacogenomics
CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-Clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by ex vivo platelet aggregation assays, differ according to CYP2C19 genotype. The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in Caucasian (85%) and Asian (99%) poor metabolizers. Other alleles associated with absent or reduced metabolism are less frequent and include CYP2C19*4, *5, *6, *7, and *8. A patient with poor metabolizer status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately 2% for Caucasians, 4% for Blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolizers. In poor metabolizers, active metabolite exposure was decreased by 63-71% compared to extensive metabolizers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolizers with mean IPA (5 µM ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolizers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolizers. When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in the poor metabolizers receiving the 300 mg/75 mg regimen, and were similar to the other CYP2C19 metabolizer groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical trials outcomes. Consistent with the above results, in a meta-analysis including 6 studies of 335 Clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolizers, and 72% for poor metabolizers while platelet aggregation inhibition (5 µM ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolizers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with Clopidogrel has not been evaluated in prospective, randomized, controlled trials. However, there have been a number of retrospective analyses to evaluate this effect in patients treated with Clopidogrel for whom there are genotyping results. None of these analyses were adequately sized to detect differences in outcome in poor metabolizers.

Special populations: characteristics
The pharmacokinetics of the active metabolite of Clopidogrel is not known in these special populations.

Elderly
When comparing plasma concentrations of the main circulating metabolite between young and elder healthy volunteers, such concentrations were significantly higher in the elderly, but with no clinic significance in platelet aggregation nor in bleeding time. Therefore, no dosage adjustment is required for this population.

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 16 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.

Race
The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race/ethnicity. From literature, limited data in Asian populations are avail able to assess the clinical implication of genotyping of this CYP on clinical outcome events.

DOSAGE AND METHOD OF ADMINISTRATION
Nefazan should be given as a single daily dose of 75 mg. It may be administered with or without food.
• Adult and elderly patients
- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction: treatment with Clopidogrel must be initiated with 300 mg loading dose followed by 75 mg/day (in combination with ASA 75-325 mg once daily). Since higher ASA doses have been associated with a greater risk of hemorrhage, it is recommended that ASA doses do not exceed 100 mg. Optimal therapy duration has not been formally established. Clinical trials data support a maximum use for 12 months, and the maximum benefit was observed at the third month of therapy.
- 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.

• Pediatric population
Clopidogrel safety and efficacy have not been established in children and adolescents below 18 years of age.

• 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 or to any of its excipients.
• Severe hepatic impairment.
• Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS AND PRECAUTIONS
Bleeding and hematological disorders
Due to the risk of bleeding and hematological 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). 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 (particularly gastrointestinal and intraocular lesion).

Patients should be told 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 characterized by thrombocytopenia and microangiopathic hemolytic anemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

Acquired hemophilia
Acquired hemophilia 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 hemophilia should be managed and treated by specialists, and Clopidogrel should be discontinued.

Recent ischemic stroke
In view of the lack of data, Clopidogrel cannot be recommended during the first 7 days after acute ischemic stroke.

Cytochrome P450 2C19 (CYP2C19)
Pharmacogenetics: In patients who are poor CYP2C19 metabolizers, Clopidogrel at recommended doses forms less of the active metabolite of Clopidogrel and has a smaller effect on platelet function. Tests are available to determine a patient's CYP2C19 genotype.
Since Clopidogrel is metabolized 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
Cautionis 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 hematological cross-reactions such as thrombocytopenia and neutropenia. Patients who had developed a previous allergic reaction and/or hematological 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
Therapeutic experience is limited in patients with moderate hepatic disease who may have bleeding diatheses. Therefore, Clopidogrel should be used with caution in those patients.

Excipients
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. This product contains hydrogenated Castor oil, which may cause stomach discomfort or diarrhea.

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 Normalized 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. 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, leading to increased risk of bleeding. Therefore, concomitant use should be undertaken with caution. However, Clopidogrel and ASA have been administered together for up to one year.

Heparin: in a clinical study conducted in healthy subjects, Clopidogrel did not required 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: in a clinical study conducted in healthy volunteers, 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.

Selective serotonin reuptake inhibitors (SSRIs): SSRIs affect platelet activation and increase the risk of bleeding, concomitant administration of SSRIs with Clopidogrel should be undertaken with caution.

Other concomitant therapies: Since Clopidogrel is metabolized 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 (PPIs): 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.

Inconsistent data on the clinical implications of this pharmacokinetic (PK)/pharmacodynamic (PD) interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of omeprazole or esomeprazole should be discouraged.

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. These results indicate that Clopidogrel can be administered with pantoprazole.

There is no evidence that other medicinal products that reduce stomach acid such as H2 blockers or antacids interfere with antiplatelet activity of Clopidogrel.

Other medicinal products: A number of other clinical studies have been conducted with Clopidogrel and other concomitant medicinal products to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when Clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of Clopidogrel was not significantly influenced by coadministration of phenobarbital or estrogen.

Pharmacokinetics of digoxin or theophylline were not modified by the co-administration of Clopidogrel. Antacids did not modify the extent of Clopidogrel absorption.

Data from the CAPRIE study indicate that phenytoin and tolbutamide which are metabolized by CYP2C9 can be safely coadministered with Clopidogrel.

CYP2C8 substrates medicinal products: Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. In vitro studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of Clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of Clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.

Apart from the specific medicinal product interaction information described above, interaction studies with Clopidogrel and some medicinal products commonly administered in patients with atherothrombotic disease have not been performed. However, patients entered into clinical trials with Clopidogrel received a variety of concomitant medicinal products including diuretics, beta blockers, ACEI, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents (including insulin), antiepileptic agents and GPIIb/IIIa antagonists without evidence of clinically significant adverse interactions.

Carcinogenesis, mutagenesis and impairment of fertility

During non clinical studies in rat and baboon, the most frequently observed effects were liver changes. These occurred at doses representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day and were a consequence of an effect on hepatic metabolizing enzymes. No effect on hepatic metabolizing enzymes was observed in humans receiving Clopidogrel at the therapeutic dose.

At very high doses, a poor gastric tolerability (gastritis, gastric erosions and/or vomiting) of Clopidogrel was also reported in rat and baboon.

Clopidogrel was not shown to alter fertility in animal studies.

There was no evidence of carcinogenic effect when Clopidogrel was administered for 78 weeks to mice and for 104 weeks to rats when given at doses up to 77 mg/kg per day (representing at least 25 times the exposure seen in humans receiving the clinical dose of 75 mg/day).

Clopidogrel has been tested in a range of in vitro and in vivo genotoxicity studies, and showed no genotoxic activity.

Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits. When given to lactating rats, Clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled Clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

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/fetal development, parturition or postnatal development.

Lactation

It is unknown whether Clopidogrel is excreted in human breast milk. Animal studies have shown excretion of Clopidogrel in breast milk. As a precautionary measure, breast-feeding should not be continued during treatment with Clopidogrel.

Fertility

Clopidogrel was not shown to alter fertility in animal studies.

Effects on ability to drive and use machines

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

Undesirable effects

Clopidogrel has been evaluated for safety in more than 44,000 patients who have participated in clinical studies, including over 12,000 patients treated for 1 year or more. Overall, Clopidogrel 75 mg/day was comparable to ASA 325 mg/day in CAPRIE regardless of age, gender and race. The clinically relevant adverse reactions observed in the studies discussed below. In addition to clinical studies experience, adverse reactions have been spontaneously reported.

Bleeding is the most common reaction reported both in clinical studies as well as in post-marketing experience where it was mostly reported during the first month of treatment.

In a study, in patients treated with either Clopidogrel or ASA, the overall incidence of any bleeding was 9.3%.

The incidence of severe cases was similar for Clopidogrel and ASA. In other study, there was no excess in major bleeds with Clopidogrel plus ASA within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery. In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for Clopidogrel plus ASA, and 6.3% for placebo plus ASA.

In other study, there was an overall increase in bleeding in the Clopidogrel plus ASA group vs. the placebo plus ASA group. The incidence of major bleeding was similar between groups. This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytic or heparin therapy.

In another study, the overall rate of noncerebral major bleeding or cerebral bleeding was low and similar in both groups.

In other study, the rate of major bleeding was greater in the Clopidogrel + ASA group than in the placebo + ASA group (6.7% versus 4.3%). Major bleeding was mostly of extracranial origin in both groups (5.3% in the Clopidogrel + ASA group; 3.5% in the placebo +ASA group), mainly from the gastrointestinal tract (3.5% vs. 1.8%). There was an excess of intracranial bleeding in the Clopidogrel + ASA treatment group compared to the placebo + ASA group (1.4% versus 0.8%, respectively). There was no statistically significant difference in the rates of fatal bleeding (1.1% in the Clopidogrel + ASA group and 0.7% in the placebo +ASA group) and hemorrhagic stroke (0.8% and 0.6%, respectively) between groups.

Adverse reactions that occurred either during clinical studies or that were spontaneously reported are presented in the table below Frequency is defined using the following conventions: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare
Blood and lymphatic system disorders		Thrombocytopenia, leucopenia, eosinophilia	Neutropenia, including severe neutropenia	Thrombotic thrombocytopenic purpura (TTP), aplastic anemia, pancytopenia, agranulocytosis, severe thrombocytopenia, acquired haemophilia A, granulocytopenia, anaemia
Cardiac disorders				Kounis syndrome (vasospastic allergic angina /allergic myocardial infarction) in the context of a hypersensitivity reaction due to Clopidogrel*
Immune system disorders				Serum sickness, anaphylactoid reactions, cross reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel)
Psychiatric disorders				Hallucinations, confusions
Nervous system disorders		Intracranial bleeding (some cases were reported with fatal outcome), headache, paraesthesia, dizziness		Taste disturbances
Eye disorders		Eye bleeding (conjunctival, ocular, retinal)		
Ear and labyrinth disorders			Vertigo	
Vascular disorders	Hematoma			Serious haemorrhage, hemorrhage of operative wound, vasculitis, hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis			Respiratory tract bleeding (haemoptysis, pulmonary haemorrhage), bronchospasm, interstitial pneumonitis, eosinophilic pneumonia
Gastrointestinal disorders	Gastrointestinal hemorrhage, diarrhea, abdominal pain, dyspepsia	Gastric ulcer and duodenal ulcer, gastritis, vomiting, nausea, constipation, flatulence	Retroperitoneal hemorrhage	Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, pancreatitis, colitis (including ulcerative or lymphocytic colitis), stomatitis
Hepato-biliary disorder				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, acute generalized exanthematous pustulosis [AGEP]), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), rash erythematous or exfoliative, urticaria, eczema, lichen planus
Reproductive systems and breast disorders			Gyanecomastia	
Musculoskeletal, connective tissue and bone disorders				Musculoskeletal bleeding hemarthrosis), arthritis, arthralgia, myalgia
Renal and urinary disorders		Hematuria		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		

* Information related to Clopidogrel with frequency "not known".

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.
Upon any overdose event, go to the nearest hospital.

STORE AND RESERVATION

Store at temperatures below 30ºC.

HOW SUPPLIED

Packages containing 30 coated tablets.

Keep this and all medications out of the reach of children.

Medicinal product authorized by the Ministry of Health.
Certificate Nº 49.624. Technical Director: Alfredo Boccardo - Pharmacist.
Manufactured by Laboratorio Elea Phoenix S.A.,
Gral. Lemos Nº 2809, Los Polvorines,
Buenos Aires, Argentina.

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