TROKEN TABLET 75 MG
(Clopidogrel film-coated tablets 75 mg)

Rx Prescription Only Medicine
Made in Argentina

DESCRIPTION:
Round, biconvex, pink, film-coated tablets

COMPOSITION:
Each TROKEN TABLET 75 MG contains Clopidogrel Bisulfate 97.875mg (Equivalent to 75 mg of clopidogrel).
Excipients: Microcrystalline cellulose Sodium stearyl fumarate Colloidal silicon dioxide Crospovidone Anhydrous lactose Opadry II white YS-30-18056 Ponceau red 4R Opadry clear YS-1-7006 Saccharin sodium Purified Water.

THERAPEUTIC ACTION
Antiplatelet- Antithrombotic

INDICATIONS
CLOPIDOGREL is indicated for the prevention of atherothrombotic events in:
a) 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.
b) Patients suffering from acute coronary syndrome:
- Non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), in combination with acetylsalicylic acid (ASA).
- ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

PHARMACOLOGIC CHARACTERISTICS:
PHARMACOLOGICAL ACTION:
CLOPIDOGREL is a selective inhibitor of the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent activation of glycoprotein IIb/IIIa complex, inhibiting platelet aggregation. Because CLOPIDOGREL irreversibly acts on said receptor, platelets exposed to the drug are affected for their life span. It also inhibits platelet aggregation induced by other agonists by blocking platelet activation amplification caused by released ADP. However, it does not inhibit phosphodiesterase activity.
The inhibitory effects (dose-dependent) are due to a yet unidentified metabolite, and can be seen two hours after the administration of one single oral dose; they reach a steady state after 3 to 7 days. Under these conditions, the average inhibition is 40 to 60%. After drug discontinuation, platelet aggregation and bleeding time return to baseline in about 5 days.

PHARMACOKINETICS
After repeated oral doses, plasma levels of CLOPIDOGREL (which has no platelet inhibiting effect) are very low. It is extensively metabolized by liver, mainly producing a carboxilated metabolite with no effect on platelet aggregation. Peak plasma levels of this metabolite are reached approximately one hour after dosage, having a half-life of about 8 hours. The drug and its main metabolite reversibly bind to human plasma proteins (98% and 94% respectively). Food does not significantly modify bioavailability of the product.
Following a single oral dose, about 50% of the drug is excreted in urine and 46% in feces within 5 days after the administration. Both in plasma and in urine, the glucuronid derivative of the main metabolite is observed.
Clinical studies:
An international comparative study with CLOPIDOGREL (75 mg daily dose) and Aspirin (325 mg daily dose) was performed in 19,185 patients with recent MI, recent ischemic stroke, or already established cardiovascular disease, who have been under treatment for up to 3 years. It was shown that those patients treated with CLOPIDOGREL had a lesser chance of relapse of a cardiovascular problem. As Aspirin itself is effective in reducing cardiovascular manifestations compared with placebo, it could be inferred (although it hasn't been experimentally demonstrated) that differences between CLOPIDOGREL and placebo are significant. Analysis of results showed

higher benefits in patients with a history of peripheral arterial disease, less important benefits in patients with a history of ischemic stroke, and comparable to Aspirin in those who had a recent MI. The oxidative step is regulated primarily by Cytochrome P450 isoenzymes 2B6, 3A4, 1A1, 1A2 and 2C19.

DOSAGE AND ADMINISTRATION
Dosage is adapted to medical criteria and patient's clinical condition. The average recommended dose is:
1film-coated tablet orally,once daily with or without food.
No dose adjustment is necessary in elderly or renally impaired patients.
Safety and efficacy in children and adolescents below the age of 18 have not been established.

CONTRAINDICATIONS
Known hypersensitivity to any of the components of the formula.
Active pathologic bleeding such as peptic ulcer or intracranial hemorrhage.
Severe liver impairment

WARNINGS
This drug prolongs the time needed to stop a hemorrhage. This should be taken into account in patients who undergo medical or dental surgery. If an antiplatelet effect is not desired during these Interventions, drug should be stopped 7 days before surgery.
Any unusual bleeding should be immediately reported to the physician.

PRECAUTIONS
As with any other antiplatelet drug, CLOPIDOGREL should be used with caution in patients at risk for increased bleeding from trauma, ulcers or other pathologic conditions. It should be given cautiously in patients with severe hepatic disease (due to the possibility of hemorrhagic diathesis) and in those receiving medication that can induce bleeding lesions (like aspirin and other NSAIDs).
Pharmacogenetics:
Based on literature data, patients with genetically reduced CYP2C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.

Drug Interactions
Aspirin: Aspirin does not significantly modify platelet aggregation inhibition caused by CLOPIDOGREL, but this latter potentiates aspirin's effect on collagen-induced platelet aggregation.
NSAIDs: Co-administration with naproxene was related to occult GI blood loss in studies on healthy volunteers.
Warfarin: The safety of its co-administration with CLOPIDOGREL has not been established.
Heparin: No interaction between both drugs was observed on healthy volunteers. Nevertheless, the safety of the association has not been established.
Other interactions: No significant interactions were observed when CLOPIDOGREL was administered together with cimetidine, phenobarbital, estrogens, atenolol, nifedipine and combinations of atenolol and nifedipine. No effects on the pharmacokinetics of theophylline or digoxin were observed. In clinical studies, CLOPIDOGREL was used with the following medications without significant drug interaction: calcium antagonists, beta blockers, diuretics, cholesterol reducing agents, coronary vasodilators, antidiabetics, ACE inhibitors, antiepileptics, and hormone replacement therapies.
In vitro studies showed that CLOPIDOGREL inhibits P450, so interferences in the metabolism of tamoxifen, tolbutamide, warfarin, phenytoin, fluvastatin and many NSAIDs should be expected if administered simultaneously.
Interaction with other medicinal products and other forms of interaction
Since clopidogrel is metabolized to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy.

Carcinogenesis, Mutagenesis, Impairment of fertility:
There was no evidence of carcinogenicity when CLOPIDOGREL was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg (more than 25 times the plasma concentration in humans at the recommended daily dose). No genotoxicity was observed on 4 in vitro and one in vivo test, nor did it have any effect on fertility of male and female rats at, oral doses of up to 400 mg/kg/day (52 times the daily recommended dose in humans).

Pregnancy and breastfeeding:
Even though studies performed in mice and rabbits did not produce a reduction of fertility or toxicity on fetus, adequate studies in pregnant women have not been conducted, so the use of the medication is not recommended, unless benefits for the mother widely outweigh possible risks for the fetus.
Due to the possibility that the drug and its metabolites are excreted in human milk (as its excretion has been proved in rats), and the potential danger for serious adverse reactions in nursing infants, a decision should be made whether to discontinue breastfeeding or to discontinue the drug in nursing women.
Pediatric use:
Safety and efficacy in children haven't been established, so it use is not recommended in this population.

ADVERSE REACTIONS
At therapeutic doses the medication is generally well tolerated, Clinical studies have shown the overall tolerability is similar to that of aspirin, and not dependant on age, gender or race. The proportion of patients that had to stop treatment due to adverse reactions was practically the same for both drugs (approximately 13%). Main adverse reactions were as follows:
Gastrointestinal disorders: Overall, the incidence of gastrointestinal events was 27.1 % compared to 29.8% in those receiving aspirin. Those most common include diarrhea, abdominal pain, gastritis,constipation, dyspepsia, vomiting and nausea. Peptic, gastric, and duodenal ulcers rarely appeared.
Blood disorders: Even though severe neutropenia incidence was very low during clinical trials, the risk of myelotoxicity should be considered if fever or other signs of infection occur during treatment. Other occasional adverse effects observed include purpura, gastrointestinal hemorrhage, hematoma, decrease in platelets, epistaxis, anemia. Rarely observed: intracranial hemorrhage, hemartrosis, hemoptysis, hematuria, retroperitoneal, ocular or pulmonary hemorrhage, thrombocytopenia, agranulocytosis, granulocytopenia,leukemia, and leucopenia.
Nervous system disorders: Occasionally: headaches, dizziness, palpitations, syncope, neuralgia, vertigo, leg cramps,hipoesthesia,paresthesia.
Cardiovascular disorders: Occasionally: edema, cardiac failure,hypertension. Rarely: generalized edema.
Skin and appendage disorders: The total incidence of these disorders was 15.8%. Most common disorders include rash, pruritus, eczema, skin ulceration. Rarely: urticaria, bullous eruption, erythematous rash, maculopapular rash.
Metabolic and nutritional disorders: Occasionally: hypercholesterolemia, gout, urea increase, hyperuricemia.
Muscular-skeletal system disorders: Occasionally: arthralgia, arthritis, arthrosis, back pain
Respiratory system disorders: Occasionally: upper airways infection, dyspnea, rhinitis, bronchitis, pneumonia, sinusitis,cough. Rarely: hemothorax.
Psychiatric disorders: Occasionally: depression, insomnia, anxiety.
Vision disorders: Cataract, conjunctivitis.
Urinary tract disorders: Occasionally: urinary infection, cystitis.
Liver and biliary system disorders: Occasionally: increase in hepatic enzymes. Rarely: hyperbilirubinemia, fatty liver, infectious hepatitis.
General disorders: Occasionally: chest pain, accidental trauma, fatigue, pain, influenza-like symptoms, hernia,asthenia. Rarely: allergic reactions, ischemic necrosis.

OVERDOSAGE
In a case of overdose with 14 tablets, no associated adverse effects occurred, and the patient recovered without squeals and no special therapy was instituted. A single oral dose of 1500 and 2000 mg/kg was lethal to mice and rats, respectively, in monkeys, the lethal dose was 3000 mg/kg. The main symptoms of acute toxicity were vomiting (in monkeys), difficulty in breathing, prostration, and gastrointestinal hemorrhage. If a rapid reversion of effects caused by medication were necessary,
a platelet transfusion would be adequate.
If overdose occurs, refer to the nearest hospital or contact a Toxicology Center.

How supplied
Packages containing 14 and 28 film-coated tablets.

Storage
Store below 30° C

Shelf life
36 months from the date of manufacturing

CLOPIDOGREL AS ALL MEDICINES, SHOULD BE KEPT OUT OF THE REACH OF CHILDREN

Medicinal product authorized to Ouímica Montpellier by the Ministry of Health. Certificate N° 50.126.

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