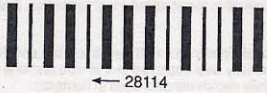


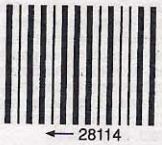
Troken™
Clopidogrel film-coated tablets 75 mg

Rx Prescription Only Medicine
Made in Argentina

Formula
CLOPIDOGREL (as clopidogrel bisulfate) 75 mg.
Excipients: Powdered cellulose, magnesium stearate, colloidal silicon dioxide, croscarmellose sodium, microcrystalline cellulose, Opadry II white YS-30-18056, ponceau red, Opadry clear YS-1-7006, saccharin sodium.

THERAPEUTIC ACTION
Antiplatelet– Antithrombotic.

INDICATIONS
Troken is indicated for reduction of atherosclerotic events (myocardial infarct, stroke, vascular death) in patients with documented atherosclerosis due to a recent stroke, recent MI or established peripheral arterial disease.



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 acts by irreversibly modifying the platelet ADP receptor, platelets exposed to the drug are affected for the remainder of their lifespan. It also inhibits platelet aggregation induced by other agonists by blocking amplification of platelet activation caused by released ADP. However, it does not inhibit phosphodiesterase activity.
The inhibitory effects (dose-dependent) are due to a not yet identified metabolite, and can be seen two hours after the administration of a 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) involving 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.

DOSAGE AND ADMINISTRATION
Dosage is adjusted to medical criteria and patient's clinical condition. The average recommended dose is: 1 film-coated tablet P.O., once daily with or without food. No dosage adjustment is necessary for elderly patients or patients with renal disease.

CONTRAINDICATIONS
Known hypersensitivity to any component of the product. Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage.

WARNINGS
This drug prolongs the bleeding time. 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 discontinued 7 days prior to 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 of increased bleeding from trauma, ulcers or other pathological conditions. It should be used with caution in patients with severe hepatic disease (due to the possibility of hemorrhagic diatheses) and in those receiving medication that can induce bleeding lesions (like aspirin and other NSAIDs).
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: Coadministration with naproxene was associated with occult GI blood loss in studies in healthy volunteers.
Warfarin: The safety of its coadministration 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 coadministered 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 blocking agents, diuretics, cholesterol lowering 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 by the coadministration.

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 in 4 in vitro and one in vivo test. CLOPIDOGREL was found to have no 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 revealed no evidence of impaired fertility or fetotoxicity, 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 of 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 have not been established, so its 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 similar to the one of aspirin, and regardless of 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% for aspirin. The 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 events 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, hypoaesthesia, paraesthesia.
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 ulcerations. Rarely: urticaria, bullous eruption, rash erythematous, rash maculopapular.
Metabolic and nutritional disorders: Occasionally: hypercholesterolemia, gout, urea increase, hyperuricemia.
Musculoskeletal system disorders: Occasionally: arthralgia, arthritis, arthrosis, back pain.
Respiratory system disorders: Occasionally: upper respiratory tract 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 case of overdose with 14 tablets, no associated adverse events occurred, and the patient recovered without sequels and no special therapy was instituted. Single oral doses of 1500 and 2000 mg/kg were 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 overdosed medication was necessary, a platelet transfusion would be adequate. If overdose occurs, refer to the nearest hospital or contact a Toxicology Center.

How supplied
Packages containing 28 film-coated tablets.

Storage
Store below 25ºC.

Shelf life
24 months

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

Medicinal product authorized to Química Montpellier by the Ministry of Health. Certificate Nº 50.126.

QUIMICA MONTPELLIER S.A.
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Bagó Group Company

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Código B