DILTIARETARD®

PRESENTATION
Sustained-release capsules of 90 mg (30 caps).

COMPOSITION
Diltiazem HCl 90 mg

PHARMACOLOGY
Calcic antagonist, antianginal. Diltiaretard® stops the transmembranous passage of calcium through the myocardial muscular fiber, and the soft muscular fiber of the vessels; thus it reduces the quantity of intracellular calcium attaining the contractible proteins.
In man
- Diltiaretard® increases the coronary blood flow by decreasing the coronary vascular resistances.
- By its moderate anticontractible action, and the moderate decrease of the systemic arterial resistances, Diltiaretard® reduces the heart rate.
- In normal subjects, it reduces moderately the contractible action of the myocarde, and lengthens the intranodal conduction.

PHARMACOKINETICS
In healthy volunteers, Diltiaretard® is well absorbed through the gastrointestinal tract (≥90%). The bioavailability of the sustained-release capsule is almost 40% due to hepatic metabolism.
Diltiaretard® is bound to plasmatic proteins in a proportion of 80-85%. The Diltiaretard® and its metabolite are a little bit dialysable. It is highly metabolized in the liver; the principle active metabolite is N-demethyl diltiazem. We cannot find more than 0.2 to 4% of unchanged diltiazem in the urine.
The plasmatic concentration pick is attained about 4 to 8 hours after the sustained-release capsule intake. The plasmatic half-life is between 7 and 8 hours.
After repeated administration of Diltiaretard®, the following parameters increased of 30%: C_{max}, AUC, C_{min}. In renal failure a reduction of the posology is necessary accordingly to the clinical response.

INTERACTIONS
- Contra-indicated association:

-Dantrolene (perfusion): in animal, cases of death by ventricular fibrillation are constantly observed when diltiazem is administered with dantrolene in I.V.

- Associations to be monitored:

-Alpha-1-Antagonists: increasing in the hypotensive effect.
-Beta-blockers: possibility of troubles in the automatism, troubles in the sino-auricular and auriculo-ventricular conduction, cardiac failure.
-Amiodarone, digoxine: excessive risk of bradycardia.
- Antiarrhythmics: Diltiaretard® has antiarrhythmic properties, its coprescription with other antiarrhythmics is unadvised because of the augmentation of cardiac undesirable effects.
- Nitrates: augmentation of the hypotensive effect and lopothymy. In subject under calcic blockers, the prescription of nitrates must be done in progressively growing doses.
- Cyclosporine: increasing of the circulant rate of cyclosporine. We must decrease the posology of cyclosporine, and control the renal function.
-Carbamazepine: increasing of the circulant rate of carbamazepine with overdosage signs by diminishing of the hepatic metabolism of the carbamazepine.
-Theophylline: increasing of the circulant rate of theophylline.
- Anti H_2 (cimetidine and ranitidine): increasing of diltiazem plasmatic concentration.

INDICATIONS
Preventive treatment of angina pectoris crises.

CONTRA-INDICATIONS
- Sinusal dysfunction, BAV II and III.
- Left ventricular insufficiency with pulmonary stase.
Pregnancy and lactation: due to its teratogenous effects in many animal species, this specialty is formally contra-indicated in pregnant women, or susceptible to be. Diltiaretard® is also able to pass into breast milk, breast feeding is prohibited.

PRECAUTIONS
- A surveillance must be exercised in patients with bradycardia or a BAV of first degree.
- In aged subjects, renal failure and hepatic failure, the plasmatic concentrations of Diltiaretard® may be increased.
- In case of general anesthesia, inform your anesthetist.
- Diltiaretard® may be used safely in patients with chronic respiratory diseases.

SIDE EFFECTS
Diltiaretard® is known with transitory, infrequent, benign side effects. We notice: headaches and/or vasomotrial rash and/or malaise, edema of the lower members, gastro-intestinal disturbances, cutaneous eruptions, asthenia, palpitations.
The vasodilation phenomena may be influenced by the age of the patient.
Exceptionally: symptomatic bradycardia, sino-auricular blocks, auriculoventricular blocks. The acquired experience has shown that the cutaneous eruptions are localized, and consisted of urticaria, simple erythema or, exceptionally, desquamative erythema, eventually febrile, when the treatment is stopped.

POSOLOGY
The treatment is initiated with 1 capsule morning and evening. In some exceptional cases, in aged patients, or in patients with bradycardia, in renal or hepatic failure the daily posology must not exceed 1 capsule of 90 mg day and night.

OVERDOSAGE
The clinical symptoms of the massive acute intoxication include a marked hypotension leading to a collapsus, a sinusale bradycardia with or without an isorythmic dissociation, and troubles in the auriculoventricular conduction.
The treatment is to be done in hospital and include: a gastric lavage, osmotic diuresis.
The conduction troubles may beneficiate from a temporary electrosystolic treatment.
The proposed antidotes are: atropine, adrenaline, glucagon, calcium gluconate.