Dilzem® 90 mg

Physican´s Information (Summary of Product Characteristics)

1. Name of the drug
Dilzem® 90 mg retard, retard tablets
2. Qualitative and Quantitative composition
Active ingredient: Diltiazem hydrochloride
1 retard tablet contains
90 mg diltiazem hydrochloride
For a full list of excipients, see section 6.1
3. Pharmaceutical Form
retard tablet
4. Clinical Particulars
4.1Therapeutic indications
– For treatment of symptomatic coronary heart disease
  – chronic stable angina pectoris (exertional angina)
  – unstable angina pectoris (crescendo angina, resting angina)
  – vasospastic angina pectoris (Prinzmetal angina, variant angina)
– Hypertension.
4.2 Dosage, mode and duration of administration
Unless otherwise prescribed, the following doses are recommended for adults.
Coronary heart disease
Twice daily 1 retard tablet Dilzem 90 mg retard (corresponds to 180 mg diltiazem hydrochloride/day). If response is inadequate, the dose may be gradually increased to a maximum daily dose of 360 mg Diltiazem hydrochloride.
In long-term therapy and continuous therapeutic effect, it is recommended that a check be made every 2-3 months whether the dose can be reduced.
Hypertension
Twice daily 1 retard tablet Dilzem 90 mg retard (corresponds to 180 mg diltiazem hydrochloride/day). If blood pressure reduction is inadequate, the dose may be gradually increased to a maximum daily dose of 360 mg Diltiazem hydrochloride.
Once a stable antihypertensive effect has been attained, the possibility of dose reduction should be checked.
Dilzem 90 mg retard must be carefully dosed for patients with impaired liver and/or kidney function and in elderly patients.
Mode of administration
The medication is best swallowed whole with enough liquid (e.g. 1 glass of water) after meals.
Duration of administration
Treatment with Dilzem 90 mg retard is usually long-term.
Interruption or change of dose may only be made at the advice of the physician. Withdrawal of therapy with Dilzem 90 mg retard should not be made abruptly but gradually tapered off, especially in angina pectoris patients.
4.3 Contraindications
Dilzem 90 mg retard should not be used in
– hypersensitivity (allergy) to the active ingredient diltiazem hydrochloride or one of the other excipients of Dilzem 90 mg retard
– AV block Grades II or III
– sinus node syndrome
– SA block Grades II or III
– shock
– acute myocardial infarction with complications (bradycardia, pronounced hypotension, left-heart failure)
– manifest heart failure
– atrial fibrillation/flutter and concurrent WPW syndrome (elevated risk of ventricular tachycardia)
– bradycardia (resting pulse less than 50 beats/minute)
– during pregnancy and lactation (see section 4.6).
Concurrent intravenous administration of beta-receptor blockers should not be made during treatment with Dilzem 90 mg retard.
4.4 Special warnings and precautions for use
Especially careful medical monitoring is required in:
– AV block or SA block Grade 1 and impaired intraventricular conduction (such as left or right bundle branch block)
– hypotension (systolic less than 90 mmHg)
– elderly patients (prolonged elimination half-life) (see section 4.2)
– patients with impaired hepatic function and/or impaired renal function (see section 4.2)
– concurrent oral therapy with beta-receptor blockers (see section 4.5).
As a precaution, in concurrent therapy with Dilzem 90 mg reard and carbamazepine, midazolam, triazolam, alfenatil, theophylline, ciclosporin A, digoxin or digitoxin, watch for symptoms of overdosing of these drugs (see section 4.5).
Treatment of hypertension with this medicinal product requires regular medical controls.
According to in vivo and in vitro studies (see section 5.3) reversible impairment of male fertility cannot be ruled out after prolonged administration of diltiazem hydrochloride.
Patients with the rare condition of hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not use Dilzem 90 mg retard.
4.5 Interactions with other medicinal products and other forms of interaction
The following interactions between these medicinal products must be taken into account:
Diltiazem hydrochloride may potentiate the effect of other drugs to reduce blood pressure if taken at the same time.
Concurrent administration of Dilzem 90 mg retard and drugs which have unfavorable effects on the heart's strength, which decrease the heart rate and/or inhibit conduction within the heart (AV conduction) (such as beta-receptor blockers, antiarrhythmics or cardiac glycosides) may result in a potentiation of effect, e.g. higher grade AV block, reduction of heart rate, greater decrease in blood pressure and possibly heart failure.
For this reason, careful monitoring of the patient is required in concurrent administration of diltiazem hydrochloride and these drugs. Concurrent intravenous administration of beta-receptor blockers should be avoided during treatment with diltiazem (see section 4.3).
Diltiazem hydrochloride may inhibit the metabolization of medical substances decomposed by certain P-450 enzymes, especially those of the cytochrome-3A family such as CYP3A4- metabolized HMG-CoA reductase inhibitors, e.g. simvastatin, lovastatin or atorvastatin. This may result in an increased and/or prolonged effect of these drugs and adverse reactions (e.g. rhabdomyolysis, myositis or hepatitis)
Plasma levels of carbamazepine, midazolam, triazolam, alfentanil, theophylline, cyclosporine A as well as digoxin and digitoxin may increase under concurrent treatment with diltiazem hydrochloride. For this reason, attention should be paid to symptoms of overdosing, plasma levels determined and the dose of the active substance involved reduced as appropriate (see section 4.4).
Concurrent administration of diltiazem hydrochloride and midazolam or alfentanil may prolong the postoperative tracheal extubation time.
Concurrent administration of diltiazem hydrochloride and cimtidine or ranitidine may result in an increase in the diltiazem hydrochloride plasma level.
Concurrent use of Dilzem 90 mg retard and inhalation anesthetics may result in hypotension or bradycardia in rare cases.
Diltiazem hydrochloride reduces nifedipine clearance. In concurrent treatment, the patient must be carefully monitored and the nifedipine dose reduced if necessary.
Concurrent use with diazepam may significantly decrease the diltiazem hydrochloride plasma level, which is probably due to reduced absorption.
For this reason, Dilzem 90 mg retard should not be used together with any of the above substances without the physician's explicit instruction.
Note
The following must be closely watched after transplantation:
The plasma level of cyclosporine A may increase under concurrent treatment with Dilzem 90 mg retard. In long-term therapy with cyclosporine A and diltiazem hydrochloride (oral) it is necessary to reduce the cyclosporine A dose in order to maintain the cyclosporine A level. The dose reduction should be made on an individual basis under control of the cyclosporine A level with a specific method (for example using monoclonal antibodies).
4.6 Pregnancy and lactation
Diltiazem hydrochloride may not be taken during pregnancy or lactation.
Pregnancy
Insufficient experience is available concerning the safety of use of diltiazem hydrochloride by pregnant women. In two cases in which diltiazem hydrochloride had been used in the first trimester cardiovascular defects were observed in the newborn. Animal studies with diltiazem hydrochloride showed reproduction toxicity including teratogenic effects (see section 5.3).
For this reason, the use of diltiazem hydrochloride is contraindicated during pregnancy (see section 4.3). Possible pregnancy has to be ruled out in women of childbearing potential prior to starting treatment with diltiazem hydrochloride.
Adequate contraception should be used during treatment.
Lactation
As diltiazem hydrochloride passes into breast milk, its use is contraindicated during lactation.
If its use cannot be avoided during lactation, the infant must be weaned prior to starting treatment with this medication.
4.7 Effects on ability to drive and use machines
Even if used as directed, this medicinal product may change reactions so much that the capability of participating in vehicular traffic, operating machinery or working in exposed places may be impaired. This applies particularly at the start of treatment, if the dose is increased, or a change is made to another preparation, or in conjunction with alcohol.
4.8 Adverse events
Assessment of adverse events is based on the following frequencies:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1000 to <1/100
Rare: ≥ 1/10.000 to <1.000
Very rare: < 10.000
Unknown (frequency not assessable on the basis of the available data)
Nervous system diseases
Common: headache, fatigue, dizziness and a feeling of weakness.
Uncommon: insomnia, hallucinations and depressive mood
Skin mucosal and subcutaneous tissue diseases
Common: allergic skin reactions such as reddening, itching and exanthema.
Very rare: severe allergic skin reactions such as erythema exsudativum multiforme, Stevens-Johnson syndrome, epidermal necrolysis (Lyell syndrome), Lupus erythematodes-like syndrome
Very rarely gingival hyperplasia may occur in long-term treatment (watch oral hygiene).This abates completely after withdrawal of Dilzem 90 mg retard.
Gastrointestinal diseases
Uncommon: gastrointestinal complaints (nausea, vomiting, heartburn, diarrhea, constipation)
Liver and gallbladder diseases
Uncommon: reversible increase in hepatic enzymes (SGOT, SGPT, gamma-GT, LDH) and in alkaline phosphatase as an expression of acute liver damage.
It is therefore recommended that hepatic parameters be monitored at regular intervals.
Cardiac and vascular diseases
Common: edema of the ankle and leg.
Very Rare: especially under high doses and/or in the presence of corresponding prior damage to the heart: bradycardia, impaired impulse conduction in the heart (SA and AV blocks), hypotension, palpitations, syncopes, reduction in cardiac output and heart failure.
Blood and lymphatic system diseases
Very rare: severe allergic reactions such as eosinophilia and lymphadenopathy.
Kidney and urinary tract diseases
Very rare: temporary impotence
Metabolic and nutritional disorders
Very rare: hyperglycemia
This should be especially considered in patients with diabetes mellitus.
4.9 Overdosing
Symptoms of overdosing
Overdosing with diltiazem hydrochloride may lead to serious hypotension, bradycardia, heart failure, AV block up to cardiovascular arrest.
Therapy of overdosing
There is no known specific antidote, countermeasures depend on the clinical symptoms.
All possibilities of primary toxin elimination should be applied (gastric lavage, vomiting, lavage of the small intestine, etc.)
The vital parameters must be monitored under intensive medical monitoring and corrected where necessary in:
– decreased blood pressure: position the patient supine, volume substitution, IV administration of sympathomimetics (e.g. dopamine, dobutamine, noradrenalin) if appropriate
– bradycardia, AV block Grade II or III: IV administration of parasympatholytics (such as atropin) or sympathomimetics (such as orciprenalin). Temporary pacemaker therapy if appropriate
– signs of heart failure: recompensation by IV administration of cardiac glycosides, diuretics, catecholamines (such as dopamine, dobutamine) as appropriate
– cardiovascular arrest: external cardiac massage, artificial ventilation, ECG monitoring, pacemaker therapy or defibrillation as appropriate.
Secondary toxin elimination
– Continuous membrane plasma separation via plasmapheresis with human albumin
5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmadynamic properties
Pharmacotherapeutic group: calcium antagonist
ATC Code: C08DB01
Diltiazem hydrochloride belongs to the group of calcium antagonists. These substances inhibit calcium influx through the cell membranes.
As a calcium antagonist, diltiazem hydrochloride acts on the smooth musculature, especially in the vascular area. Diltiazem causes a decrease in total peripheral resistance as a result of vasodilatation, whereby the cardiac afterload is reduced. This results in decreased blood pressure. Diltiazem hydrochloride, as a calcium antagonist, also has a marked effect on the myocardium. In therapeutic doses, diltiazem hydrochloride has a direct negative chronotropic cardiac effect, so that reflectory rate increase is inhibited. Diltiazem also delays atrioventricular stimulation conduction. A negative inotropic effect may occur in the working myocardium.
5.2 Pharmacokinetic properties
Diltiazem hydrochloride is absorbed to 80-90% from the gastrointestinal tract following oral administration.
Diltiazem hydrochloride undergoes a pronounced first-pass metabolism, so that the systemic availability is only about 40%. Maximum plasma concentrations of diltiazem hydrochloride are attained 3-4 hours after oral administration. The distribution volume of diltiazem hydrochloride is about 5 L/kg body weight. Plasma protein binding is 70-85%, whereby 35-40% bind to albumin.
The following biotransformation pathways have been demonstrated for diltiazem hydrochloride, which is almost completely metabolized in the liver:
– Desacetylation to the primary metabolite I
– Oxidative O and N-demethylations
– Conjugation of the phenyolic metabolites
Compared to the unchanged substance, the primary metabolites N-desmethyldiltiazem and desacetyldiltiazem show a weaker pharmacological effect, about 20% or about 25-50%, respectively, of the efficacy of diltiazem hydrochloride. The other metabolites are pharmacologically inactive. Delayed metabolization must be expected in the presence of impaired hepatic function.
Diltiazem hydrochloride is eliminated to about 70% in the form of its conjugated metabolites and unmetabolized to less than 4% via the kidneys and the rest with feces.
The mean elimination half-life of diltiazem hydrochloride is 6 hours, but may vary in a range from 2-11 hours. The elimination half-life of diltiazem hydrochloride may be prolonged, especially in elderly patients and patients with impaired hepatic function.
Diltiazem hydrochloride and the metabolite desacetyldiltiazem may accumulate slightly in plasma after repeated application.
5.3 Preclinical safety data
Results of extensive mutagenicity tests on in-vivo and in-vitro systems and cancerogenicity tests in-vivo have been negative.
Diltiazem hydrochloride had embryolethal and teratogenic effects in mice, rats and rabbits (malformations of the spine and extremities) and affected rat fertility. Moreover, a minor incidence of cardiovascular defects was observed in rats after high dose i.p. administration.
Administration at the end of pregnancy in rats resulted in dystocia and an increased rate of perinatal mortality in the offspring.
6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Carmellose sodium, simethicone, hypromellose, lactose monohydrate, Macrogol 6000, magnesium stearate (Ph.Eur.), hydrogenated castor oil, stearic acid (Ph.Eur.), talc, titanium dioxide (E 171).
6.2 Incompatibilities
Not applicable
6.3 Shelf-life
Please refer to the instructions on the outer carton
6.4 Special storage instructions
Store in a cool dry place not exceeding 25°C.
6.5 Nature and contents of container
30 retard tablets
100 retard tablets
6.6 Special instructions for disposal
No special requirements
7. Name of authorization holder
GÖDECKE GmbH
Pfizerstr. 1
76139 Karlsruhe
Germany
8. Marketing authorization number
22571.00.01
9. Name of the Manufacturer
Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg, Germany
10. Status of information
January 2009
11. Prescription status
Ethical

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children

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