DILZEM

Diltiazem hydrochloride

90 mg retard Tablets

Reference market: Germany

AfME Markets using same as LPD: Saudi Arabia

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dilzem 90 mg retard, prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: diltiazem hydrochloride

1 prolonged-release tablet contains 90 mg diltiazem hydrochloride.

Excipients with known effect:
Dilzem 90 mg prolonged-release tablet contains lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

– 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 Posology and method of administration

Posology

Unless otherwise prescribed, the following doses are recommended for adults.

Coronary heart disease
Twice daily 1 prolonged-release tablet Dilzem 90 mg retard (corresponding to 180 mg diltiazem hydrochloride per day).

If the effect is insufficient, the dose may be gradually increased up to a maximum of 360 mg diltiazem hydrochloride per day.

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 prolonged-release tablet Dilzem 90 mg retard (corresponding to 180 mg diltiazem hydrochloride per day).

If the blood pressure reduction is insufficient, the dose may be gradually increased to a maximum dose of 360 mg diltiazem hydrochloride per day.

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.

Method of administration

The medication is best swallowed whole with sufficient liquid after meals (e.g. 1 glass of water).

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.

Therapy with Dilzem 90 mg retard should not be withdrawn abruptly but tapered off, especially in angina pectoris patients.

4.3 Contraindications

Dilzem 90 mg retard must not be used in the presence of

- hypersensitivity (allergy) to the active substance diltiazem hydrochloride or any of the excipients of Dilzem 90 mg retard
- second or third-degree AV block, second or third-degree S-A block, sick sinus syndrome except in patients with a cardiac pacemaker
- shock
- acute myocardial infarction with complications (bradycardia, pronounced hypotension, left-ventricular failure)
- manifest heart failure
- atrial fibrillation/flutter and concurrent Wolff-Parkinson-White (WPW) syndrome (elevated risk of ventricular tachycardia)
- bradycardia (resting pulse less than 50 beats/minute)
- pregnancy and lactation (see section 4.6)
- concomitant intravenous administration of dantrolene (see section 4.5)
- concomitant oral administration of ivabradine (see section 4.5)
- concurrent use with lomitapide (see section 4.5)

Beta-receptor blockers should not be co-administered intravenously during treatment with Dilzem 90 mg retard.

4.4 Special warnings and precautions for use

Especially careful medical monitoring is required in the presence of:

- first-degree AV block or S-A block (risk of exacerbation and rarely of complete block)
- impaired intraventricular conduction (such as left or right bundle branch block)
- bradycardia (risk of exacerbation)
- hypotension (systolic less than 90 mmHg)
- patients with hepatic or renal insufficiency as well as elderly patients (prolonged elimination half-life) should be carefully observed with regard to blood pressure and heart rate; the dose should be adjusted, if required (see section 4.2)
- concurrent oral therapy with beta-receptor blockers (see section 4.5).

When Dilzem 90 mg retard is co-administered with carbamazepine, midazolam, triazolam, alfenatil, theophylline, cyclosporin A, digoxin or digitoxin, attention should be paid, as a precaution, to symptoms or signs of overdosage of these medicinal products (see section 4.5).

Prior to general anaesthesia, the anaesthetist must be informed of ongoing diltiazem treatment. Depression of cardiac contractility, conductivity and automaticity, as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.

Cases of acute renal failure secondary to decreased renal perfusion have been reported in patients with existing cardiac disease especially reduced left ventricular function, severe bradycardia or severe hypotension. Careful monitoring of renal function is advised.

Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression.

Like other calcium channel antagonists, diltiazem has an inhibitory effect on intestinal motility. Therefore it should be used with caution in patients at risk to develop an intestinal obstruction. Tablet residues from slow-release formulations of the product may pass into the patient’s stools; however, this finding has no clinical relevance.

Treatment of hypertension with this medicinal product requires regular medical controls.

Patients with the rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Dilzem 90 mg retard.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions between this medicinal product and other substances must be taken into account:

Dantrolene IV
In animal studies, lethal ventricular fibrillation has been observed when verapamil and intravenous dantrolene were administered concomitantly. Concomitant administration of diltiazem and intravenous dantrolene should therefore be avoided (see section 4.3).

Lithium
Diltiazem hydrochloride may increase the susceptibility to lithium (neurotoxicity).

Diltiazem hydrochloride may potentiate the effect of other medicinal products to reduce blood pressure if taken at the same time.

Concurrent administration of Dilzem 90 mg retard and medicinal products which have an unfavourable effect 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 potentiation of effect, e.g. high-degree 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 medicinal products. Concurrent intravenous administration of beta-receptor blockers should be avoided during treatment with diltiazem hydrochloride (see section 4.3).

Other antihypertensive drugs: Enhanced antihypertensive effect may occur with concomitant use of other antihypertensive drugs (e.g. beta-blockers, diuretics, ACE-inhibitors) or drugs that cause hypotension such as aldesleukin and antipsychotics.

Diltiazem hydrochloride can inhibit the metabolism of medicinal agents that are broken down via certain P450 enzymes, particularly those from the cytochrome 3A family. These include CYP 3A4-metabolized HMG CoA-reductase inhibitors like, for example, simvastatin, lovastatin, or atorvastatin. For these medicinal products, this may result in an increased and/or prolonged effect including side effects (e.g. rhabdomyolysis, myositis, or hepatitis). When possible, a non CYP3A4-metabolized statin should be used together with diltiazem, otherwise close monitoring for signs and symptoms of a potential statin toxicity is required. Colchicine is a substrate for CYP3A4. In the presence of CYP3A4 or P-gp inhibitors, the concentrations of colchicine in the blood increase. Toxicity, including fatal cases, have been reported during concurrent use of CYP3A4 inhibitors such as diltiazem.

Mechanistic Target of Rapamycin (mTOR) Inhibitors
Sirolimus (CYP 3A4 substrate) Cmax and AUC were increased 1.4, and 1.6 fold, respectively following simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem. Diltiazem may increase everolimus blood concentrations by decreasing metabolism via CYP3A4 or the efflux of everolimus from intestinal cells via P-glycoprotein. A dose reduction of mTOR inhibitor such as sirolimus, temsirolimus, and everolimus, may be necessary if diltiazem is co-administered.

Plasma levels of carbamazepine, alfentanil, theophylline, cyclosporin 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).

Diltiazem significantly increases plasma concentrations of midazolam and triazolam and prolongs their half-life. Special care should be taken when prescribing short-acting benzodiazepines metabolized by the CYP3A4 pathway in patients using diltiazem (see section 4.4).

Rifampicin: Risk of decrease in diltiazem plasma levels after initiating therapy with rifampicin. The patient should be carefully monitored when initiating or discontinuing rifampicin treatment.

Nitrate derivatives: Increased hypotensive effects and faintness (additive vasodilatating effects): In all the patients treated with calcium antagonists, the prescription of nitrate derivatives should only be carried out at gradually increasing doses.

Concomitant treatment with alpha-antagonists may produce or aggravate hypotension. The combination of diltiazem with an alpha-antagonist should be considered only with the strict monitoring of the blood pressure.

Concurrent administration of diltiazem hydrochloride and midazolam or alfentanil may prolong the postoperative tracheal extubation time.

Concurrent administration of diltiazem hydrochloride and cimetidine or ranitidine may result in an increase in the diltiazem hydrochloride plasma level. Patients currently receiving diltiazem therapy should be carefully monitored when initiating or discontinuing therapy with H_2-antagonists. An adjustment in diltiazem daily dose may be necessary.

Concurrent use of Dilzem 90 mg retard and inhalation anaesthetics 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 treatment with diazepam may result in a significant decrease in the diltiazem hydrochloride plasma level, which is presumably based on a reduction of the absorption.

The concurrent use of ivabradine is contraindicated due to the heart rate-lowering effect of diltiazem hydrochloride on ivabradine (see section 4.3).

Lomitapide: Diltiazem (a moderate CYP3A4 inhibitor) may increase lomitapide plasma concentrations through CYP3A4 inhibition leading to increased risk of elevations in liver enzymes (see section 4.3).

Therefore, Dilzem 90 mg retard should not be used together with one of the above-mentioned substances unless the physician has expressly ordered it.

Note:
The following must be closely watched after transplantation:

The plasma level of cyclosporin A may increase under concurrent treatment with Dilzem 90 mg retard. In long-term therapy with cyclosporin A and diltiazem hydrochloride (oral) it is necessary to reduce the cyclosporin A dose in order to maintain the cyclosporin A level. The dose reduction should be made on an individual basis under control of the cyclosporin A level with a specific method (for example using monoclonal antibodies).

General information to be taken into account

Due to the potential for additive effects, caution and careful dose titration are necessary in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction.

Diltiazem is metabolized by CYP3A4. A moderate (less than 2-fold) increase of diltiazem plasma concentration in cases of co-administration with a stronger CYP3A4 inhibitor has been documented. Diltiazem is also a CYP3A4 isoform inhibitor. Co-administration with other CYP3A4 substrates may result in an increase in plasma concentration of either co-administered drug. Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.

- Protease inhibitors (atazanavir, ritonavir): Increase in plasma diltiazem concentrations.
- Barbiturates (phenobarbital, primidone): serum levels of diltiazem may be decreased by concomitant usage of CYP3A4 inducers.
- Phenytoin: serum levels of diltiazem may be decreased by concomitant usage of CYP3A4 inducers. Diltiazem may increase serum levels of phenytoin.

Glucocorticoids (methylprednisolone): Inhibition of methylprednisolone metabolism (CYP3A4) and inhibition of P-glycoprotein. The patient should be monitored when initiating methylprednisolone treatment. An adjustment in the dose of methylprednisolone may be necessary.

Diltiazem may increase bioavailability of tricyclic antidepressants.

4.6 Fertility, pregnancy and lactation

Diltiazem hydrochloride must not be taken during pregnancy or lactation.

Pregnancy
Only insufficient experience on the use of diltiazem hydrochloride in pregnant women is available. In two cases, cardiovascular defects in newborn infants after the use of diltiazem hydrochloride in the first trimester of pregnancy have been reported. Animal studies with diltiazem hydrochloride have shown reproduction toxicity including teratogenic effects (see section 5.3). Therefore, taking diltiazem hydrochloride during pregnancy is contraindicated (see section 4.3). In women of childbearing age, a possible pregnancy must be ruled out before treatment with diltiazem hydrochloride. During treatment with diltiazem hydrochloride, suitable contraceptive measures should be taken.

Breastfeeding
Since diltiazem hydrochloride is excreted in breast milk, the use of diltiazem hydrochloride is contraindicated during the lactation period. If it is absolutely necessary to administer diltiazem hydrochloride during the lactation period, the infant must be weaned (see section 4.3).

Fertility
Based on in vivo and in vitro studies (see section 5.3), reversible disturbances of male fertility cannot be ruled out during longer-term administration of diltiazem hydrochloride.

4.7 Effects on ability to drive and use machines

Even when used as directed, this medicinal product may alter the capacity to react to such an extent that the ability to actively take part in road traffic, operate machines, or work without a secure hand-/foothold is impaired. This applies to an increased extent at the start of treatment, after a dose increase or change in preparation, and in combination with alcohol. No studies have been performed.

4.8 Undesirable effects

The frequencies of undesirable effects are based on the following categories:
Very common: ≥ 1/10
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
Not known (cannot be estimated from the available data)

	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders					Severe allergic reactions such as eosinophilia and lymph-adenopathy	Thrombo-cytopenia
Psychiatric disorders			Nervousness, insomnia, hallucination; depressive mood, con-fusional state, sleep disturbance			Mood changes (including depression)
Nervous system disorders		Headache, dizziness, tiredness, feeling of weakness				Extrapyra-midal syndrome, myoclonus
Cardiac disorders		AV block** (1st, 2nd or 3rd degree; bundle branch block), palpitations, ankle or leg oedema	Brady-cardia**		S-A block**, hypotension, syncope, reduced cardiac output or heart failure	
Vascular disorders		Flushing	Orthostatic hypotension			Vasculitis (including leukocyte-

	Very common	Common	Uncommon	Rare	Very rare	Not known
						oclastic vasculitis)
Gastrointestinal disorders		Constipation, dyspepsia, gastric pain, nausea	Gastro-intestinal complaints (vomiting, heartburn, diarrhoea)	Dry mouth	Gingival hyperplasia	
Hepatobiliary disorders			Increase in hepatic enzymes (increase in AST, ALT, LDH, ALP, gamma GT) and alkaline phosphatase as a sign of acute liver damage*			Hepatitis
Skin and subcutaneous tissue disorders		Erythema, allergic skin reactions like reddening of the skin, itching and exanthema		Urticaria	Severe allergic skin reactions like erythema exsudativum multiforme, Stevens-Johnson syndrome, epidermal necrolysis (Lyell's syndrome), lupus erythe-matodes-like skin changes	Photo-sensitivity (including lichenoid keratosis at sun exposed skin areas), angioneuro-tic oedema, rash, sweat-ing, exfolia-tive derma-titis, acute exanthemato us pustulosis, occasionally desquamativ e erythema with or with-out fever, Lupus-like syndrome
Reproductive system and breast disorders						Gynaeco-mastia
General disorders and administration site conditions	Peripheral oedema	Malaise				
Renal and urinary disorders					Potency disturbance	
Metabolism and nutrition disorders					Hyper-glycemia***	

Very rarely, gingival hyperplasia may occur during long-term treatment (watch oral hygiene) that subsides completely after discontinuation of Dilzem 90 mg retard.

* It is therefore recommended that hepatic parameters be checked at regular intervals.

** In particular in the higher dosage range and/or in the presence of a corresponding previous cardiac damage
*** This should be taken into account above all in patients with diabetes mellitus.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to National Pharmacovigilance Centre (NPC).

To report any side effect(s):

- **Saudi Arabia**

National Pharmacovigilance Center (NPC)
- Call center: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa

- **Other GCC States**

- *Please contact the relevant competent authority.*

4.9 Overdose

Symptoms of overdose
Overdosing with diltiazem hydrochloride may lead to serious hypotension and acute kidney injury, bradycardia with or without isorhythmic dissociation, heart failure, AV block up to cardiovascular arrest and renal impairment.

Therapy of overdose
There is no known specific antidote to diltiazem; 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, second or third-degree AV block:
  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 Pharmacodynamic properties

Pharmacotherapeutic group: calcium channel blocker
ATC code: C08DB01

Diltiazem hydrochloride is a calcium channel blocker. These substances inhibit calcium influx through the cell membranes. As a calcium channel blocker, diltiazem hydrochloride acts on the smooth musculature, especially in the vascular area. Diltiazem hydrochloride 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 channel blocker, 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 hydrochloride 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 metabolisation must be expected in the presence of impaired hepatic function.

Diltiazem hydrochloride is excreted to about 70% in the form of its conjugated metabolites and unmetabolised to less than 4% via the kidneys. The remainder is eliminated with the faeces.

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 following repeated administration.

5.3 Preclinical safety data

Results of extensive mutagenicity studies on in vivo and in vitro systems as well as in vivo carcinogenicity studies have been negative.

Diltiazem had embryolethal and teratogenic effects in mice, rats and rabbits (malformations of the spine and extremities) and impaired fertility in rats. In addition, a low incidence of cardiovascular defects was

detected in rats after IP administration of high doses. Administration at the end of pregnancy in rats resulted in dystocia and an increased incidence rate of perinatal mortality in the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose sodium, simeticone, Hydroxypropyl methylcellulose, lactose monohydrate, Polyethylene Glycol 6000, magnesium stearate (Ph. Eur.), hydrated castor oil, stearic acid (Ph. Eur.), talc, titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Do not use Dilzem 90 mg Retard after the expiry date which is stated on the carton after EXP:. The expiry date refers to the last day of that month.

Shelf life: 24 months.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

30 prolonged-release tablets.

6.6 Special precautions for disposal

Keep out of the sight and reach of children.

No special requirements

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. FURTHER INFORMATION

MARKETING AUTHORISATION HOLDER
Pfizer Pharma GmbH
Germany

MANUFACUTRED BY
Pfizer Manufacturing Deutschland GmbH
Germany

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12-Mar-1992

9. DATE OF REVISION OF THE TEXT

November 2023