SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diltiazem Hydrochloride 60mg Modified Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains active ingredient Diltiazem Hydrochloride EP 60 mg.
Also contain lactose and castor oil. For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Modified release tablet

White to off- white biconvex round tablet embossed with 'DTZ60' on one side and 'PV' on the reverse. The tablet has nominal diameter of 8.0mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Prophylaxis and treatment of angina pectoris.

2. Treatment of mild to moderate arterial hypertension.

4.2 Posology and method of administration

Adults
The usual maintenance dose is one tablet (60 mg) three times daily.
As patient response may vary, the dose can be increased to a maximum of 360 mg daily in divided doses. Higher doses up to 480 mg/day have been used with benefit in some patients especially in unstable angina. There is no evidence of any decrease in efficacy at these high doses. Diltiazem has not been reported to precipitate angina.

Elderly and patients with impaired renal function: Initially 60 mg twice daily. Monitoring of the heart rate should be carried out. The dose should not

be increased if the rate falls below 50 beats per minutes.In patients suffering from liver problems, periodical checks of liver function are recommended during treatment with these tablets.

Children: Not recommended

Route of administration: Oral

4.3 Contraindications:

- Sick sinus syndrome except in the presence of a functioning ventricular pacemaker
- pregnancy; women of child-bearing potential, lactation
- congestive heart failure
- severe aortic stenosis
- cardiogenic shock
- severe hypotension (systolic Blood Pressure less than 90mmHg)
- Second- or third-degree AV block except in the presence of a functioning ventricular pacemaker
- Severe bradycardia (less than 50 beats per minute)
- Left ventricular failure with pulmonary congestion
- Hypersensitivity to diltiazem or to any of the excipients
- Concomitant use of dantrolene infusion (see section 4.5).
- Combination with ivabradine
- Concurrent use with lomitapide
- Concurrent use with asunaprevir

4.4 Special Warnings and Precautions for Use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Close observation is necessary in patients with reduced left ventricular function, bradycardia (risk of exacerbation) prolonged PR interval, or with a first degree AV block detected on the electrocardiogram (risk of exacerbation and rarely, of complete block).

Prior to general anaesthesia, the anaesthesist 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.

Increase of plasma concentrations of diltiazem may be observed in the elderly and in patients with renal or hepatic insufficiency. The contraindications and precautions should be carefully observed and close monitoring, particularly of heart rate, should be carried out at the beginning of treatment.

Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression. Early recognition of relevant symptoms is important, especially in predisposed patients. In such cases, drug discontinuation should be considered.

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.

Careful monitoring is necessary in patients with latent or manifest diabetes mellitus due to a possible increase in blood glucose.

Tablet residues from slow release formulations of the product may pass into the patient's stools; however, this finding has no clinical relevance.

The use of diltiazem may induce bronchospasm, including asthma aggravation, especially in patients with preexisting bronchial hyper-reactivity. Cases have also been reported after dose increase. Patients should be monitored for signs and symptoms of respiratory impairment during diltiazem therapy.

4.5 Interaction with other medicinal products and other forms of interaction

The plasma concentration of phenytoin is increased by diltiazem.

Phenobarbital and phenytoin reduce the effect of diltiazem. The effect of diltiazem is probably reduced by primidone.

There is an enhanced hypotensive effect when calcium-channel blockers are given with hydralazine, minoxidil or nitroprusside.

The effect of diltiazem is probably reduced by barbiturates.

There is an enhanced hypotensive effect when calcium-channel blockers are given with the doperminergenic levodopa.

Diltiazem increases the plasma concentration of the hormone antagonist dutasteride.

There is an enhanced hypotensive effect when calcium-channel blockers are given with muscle relaxants baclofen and tizanidine.

The hypotensive effect of calcium-channel blockers is antagonized by oestrogens.

Diltiazem increases the plasma concentration of immunosuppressants sirolimus and tacrolimus.

The hypotensive effect of calcium-channel blockers is antagonized by carbenoxolone.

Concomitant use contraindicated for safety reasons:
Dantrolene (infusion): Lethal ventricular fibrillation is regularly observed in animals when intravenous verapamil and dantrolene are administered concomitantly. The combination of a calcium antagonist and dantrolene is therefore potentially dangerous (see section 4.3).

Ivabradine: Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem to ivabradine (see section 4.3)

Concomitant use requiring caution:
• Lithium: Risk of increase in lithium-induced neurotoxicity

• 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.

• Theophylline: Increase in circulating theophylline levels.

• Alpha-antagonists: Increased antihypertensive effects: 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.

• Amiodarone, digoxin: Increased risk of bradycardia: caution is required when these are combined with diltiazem, particularly in elderly subjects and when high doses are used. In common with other calcium antagonists diltiazem may cause small increases in plasma levels of digoxin.

• Beta-blockers: Possibility of rhythm disturbances (pronounced bradycardia, sinus arrest), sino-atrial and atrio-ventricular conduction disturbances and heart failure (synergistic effect). Such a combination must only be used under close clinical and ECG monitoring, particularly at the beginning of treatment.

• The blood levels of beta blockers with a low bioavailability (*eg* propranolol) may be increased and small increases in the plasma levels of digitalis glycosides have been observed.

• Other antiarrhythmic agents: since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents is not recommended

(additive risk of increased cardiac adverse effects). This combination should only be used under close clinical and ECG monitoring.

• Carbamazepine: Increase in circulating carbamazepine levels: It is recommended that the plasma carbamazepine concentrations be assayed and that the dose should be adjusted if necessary.

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

• H_2 antagonists (cimetidine, ranitidine): Increase in plasma diltiazem concentrations. 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.

• Ciclosporin: Increase in circulating ciclosporin levels: It is recommended that the ciclosporin dose be reduced, renal function be monitored, circulating ciclosporin levels be assayed and that the dose should be adjusted during combined therapy and after its discontinuation.

Combinations to be taken into account

• 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.

• Benzodiazepines (midazolam, triazolam): 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.

• Corticosteroids (methylprednisolone): Diltiazem can increase methylprednisolone levels (through inhibition of CYP3A4 and possible inhibition of P-glycoprotein). The patient should be monitored when initiating methylprednisolone treatment. An adjustment in the dose of methylprednisolone may be necessary.

• Statins: Diltiazem is an inhibitor of CYP3A4 and has been shown to significantly increase the AUC of some statins. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with statins metabolised by CYP3A4 (e.g. atorvastatin, fluvastatin and simvastatin)..An adjustment dose of statin may be necessary (see also product information of relative statin). When possible, a non CYP3A4-metabolised statin (e.g.pravastatin) should be used together with diltiazem.

• Diltiazem increases plasma concentration of imipramine and possibly other tricyclic antidepressants.

• Drugs that increase hepatic microsomal activity (*eg* phenobarbital, phenytoin) lead to decreased plasma diltiazem levels.

• Diltiazem has been used safely in combination with diuretics. It is recommended that patients receiving these combinations should be regularly monitored.

• Diltiazem hydrochloride treatment has been continued without problem during anaesthesia, but the anaesthetist should be informed that the patient is receiving a calcium antagonist. (see section 4.4)

• There is a possibility that calcium channel blockers may occasionally impair glucose tolerance.

General information to be taken into account:
• Due to the potential for additive effects, caution and careful titration are necessary in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction.

4.6 Fertility, pregnancy and lactation

Pregnancy: There is very limited data from use of diltiazem in pregnant patients.Diltiazem has shown to have reproductive toxicity (see section 5.3) in certain animal species (rat,mice,rabbit). Diltiazem is therefore not recommended during pregnancy as well as in women of child bearing potential not using effective contraception.

Diltiazem Hydrochloride is excreted in breast milk at low concentrations. Breast-feeding while taking this drug should be avoided. If use of diltiazem is considered medically essential, an alternative method of infant feeding should be instituted.

4.7 Effects on ability to drive and use machines

On the basis of reported adverse drug reactions, i.e. dizziness (common), malaise (common), the ability to drive and use machines could be altered. However, no studies have been performed.

4.8 Undesirable Effects:

The following CIOMS frequency rating is used, when applicable: 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).
Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

	Very common	**common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders					Thrombocytopenia
Psychiatric disorders			Nervousness, insomnia		Mood changes (including depression)
Nervous system disorders		Headache, dizziness			Extrapyramidal syndrome
Cardiac disorders		Atrioventricular block (may be of first, second or third degree, bundle branch block may occur), palpitations	Bradycardia		Sinoartrial block, congestive heart failure, sinus arrest, cardiac arrest (asystole)
Vascular disorders		Flushing	Orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis)
Gastrointestinal disorders		Constipation, dyspepsia, gastric pain, nausea	Vomiting, diarrhoea	Dry mouth	Gingival hyperplasia
Metabolism and nutrition disorders					Hyperglycemia
Hepatobiliary disorders			Hepatic enzymes increase (AST, ALT, LDH, ALP increase)		Hepatitis

Skin and subcutaneous tissue disorders		Erythema		Urticaria	Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, rash, erythema multiforme (including StevenJohnson's syndrome and toxic epidermal necrolysis), sweating, exfoliative dermatitis, acute generalized exanthematous pustulosis, occasionally desquamative erythema with or without fever
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Peripheral oedema	Malaise			
Respiratory, thoracic and mediastinal disorders					Bronchospasm (including asthma aggravation)

The current literature suggests that the effects of vasodilation particularly ankle oedema are dose dependent and are more frequent in the elderly.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Features:

Diltiazem can cause severe hypotension (profound cardiac depression and/or vasodilation). Effects on the AV node cause bradyarrhytymias (including complete heart block and asystole).

Features common to cardiac/ cardiotoxic agents involved in mixed overdoses may be more severe and/or prolonged.

Management:

Diltiazem is potentially very toxic.
Serious cases should be discussed with the local poisons information service (UK NPIS: Ireland NPIS)

- Maintain clear airway and ventilate unconscious patients
- Good neurological outcomes after cardiac arrest may occur following prolonged resuscitation (continue for at least 1hour: discuss with poisons information service)
- Monitor blood pressure and cardiac rhythm. Check U&Es, calcium and glucose. Check arterial blood gases in symptomatic patients.
- The benefits of gastric decontamination is uncertain so advice from poisons information services is required. The following may be considered appropriate
    - activated charcoal if the patient presents within 1hour of ingesting a toxic amount (later for overdose with sustained/modified forms).
    - gastric lavage in adults within 1hour of ingesting potentially life threatening amounts (provided airway can be protected)
    - whole bowel irrigation in large overdose of sustained/modifies release forms
- Monitor 12 lead ECG – measure QRS duration and QT interval
- Correct hypotension (raise foot of bed : appropriate IV fluids)
- Asyymptomatic patients should be observed for at least 12 hours post-overdose (cardiac/cardiotoxic agents) monitored for atleast the longest period of any of the individual agents.
- Seek expert advice if the patient fails to respond satisfactorily and for specific treatment if the following occur

- bradycardia
- dysrrhythmias
- poor myocardial contractability/ heart failure
- poor systemic perfusion

hypotension (non-responsive to measures above)

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium-channel blocker ATC code C08D801.

Diltiazem is a calcium antagonist. It restricts the slow channel entry of calcium ions into the cell and so reduces the liberation of calcium from stores in the sacroplasmic reticulum. This results in a reduction in the amount of available intracellular calcium reducing myocardial oxygen consumption. It increases exercise capacity and improves all indicies of myocardial ischaemia in the angina patient. Diltiazem relaxes large and small coronary arteries and relieves the spasm of vasopastic (prinzmetals) angina and the response to catecholamines but has little effect on the peripheral vasculature. There is therefore no possibility of reflex tachycardia. A small reduction in heart rate occurs which is accompanied by an increase in cardiac input, improved myocardial perfusion and reduction of ventricular work. In animal studies, Diltiazem protects the myocardium against the effects of ischaemia and reduces the damage produced by excessive entry of calcium into the myocardial cell during reperfusion.

5.2 Pharmacokinetic properties

Diltiazem hydrochloride is effective in angina, protecting the heart against ischaemia, vasodilating coronary arteries and reducing myocardial oxygen requirements.
It is well tolerated and does not generally give rise to side effects associated with peripheral vasodilators, nor cause significant myocardial depression.
Diltiazem is rapidly and almost completely absorbed from gastro intestinal tract following oral administration, but undergoes extensive first pass hepatic metabolism. The Bioavailability has been reported to about 40 %, although there is considerable inter-individual variation in plasma concentration. Diltiazem is about 80% bound to plasma proteins. It is extensively metabolized in the liver; one of the metabolites, desacetyldiltiazem has been reported to have 25 to 50 % of the activity of the parent compound. The half life is reported to be 3 to 5 hours. Approximately 2 to 4 % of a dose is excreted in urine as unchanged diltiazem with remainder excreted as metabolites in bile and urine.

There is a linear relationship between dose and plasma concentration. During long-term administration to any one patient, plasma concentrations of diltiazem remain constant.
Mean plasma concentrations in elderly subjects and patients with renal and hepatic insufficiency are higher than young subjects.
Diltiazem and its metabolites are poorly dialysed.

5.3 Preclinical safety data

Pregnancy: Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60-kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights, pup survival, as well as prolonged delivery times and an increased incidence of stillbirths.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose monohydrate	Ph Eur
Hydrogenated Castor oil	USNF
Polyethylene Glycol	USNF
Magnesium stearate	Ph Eur

6.2. Incompatibilities

None known.

6.3. Shelf-Life

5 years.

6.4. Special Precautions for Storage

Store below 25°C, in a dry place.
Keep out of the reach of children.

6.5 Nature and contents of container

The tablet are blister packed (10's) in 250µ PVC film faced with 48 µ PVDC and sealed with hard tempered aluminum lidding foil. The blistered strips are subsequently packed in printed boxboard cartons in sizes 23, 30,56,60,84,100 and 500 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmavit Ltd
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Perivale,
Greenford,
Middlesex.
UB6 7HQ

8. MARKETING AUTHORIZATION NUMBER

PL 04556/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 November 2004
Date of latest renewal: 18 March 2009

10 DATE OF REVISION OF THE TEXT

01/10/2024