Core Safety Profile

Active substance: Diltiazem
Pharmaceutical form(s)/strength:
- Tablets 60 mg;
- Prolonged release capsule
  90, 120, 200, 300 mg;
- Modified release capsule
  90, 120, 180, 300 mg;
- Intravenous Injection 25 mg, 100 mg

P-RMS: DK/H/PSUR/0017/001
Date of FAR: 17.05.2010
4.3 Contraindications

- Sick sinus syndrome except in the presence of a functioning ventricular pacemaker
- Second- or third-degree AV block except in the presence of a functioning ventricular pacemaker
- Severe bradycardia (below 40 bpm)
- Left ventricular failure with pulmonary congestion
- Hypersensitivity to diltiazem or to any of the excipients
- Concomitant use of dantrolene infusion (see section 4.5).

Additionally, for the intravenous forms, patients known to have an accessory bypass (Wolf-Parkinson-White syndrome or short PR syndrome), and who develop atrial fibrillation or flutter, should not be administered intravenous diltiazem.

4.4 Special warnings and precautions for use

Close observation is necessary in patients with reduced left ventricular function, bradycardia (risk of exacerbation) 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated:
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).

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.

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.

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.

Anti-H\textsubscript{2} agents (cimetidine, ranitidine): Increase in plasma diltiazem concentrations. Patients currently receiving diltiazem therapy should be carefully monitored when initiating or discontinuing therapy with anti-H\textsubscript{2} agents. An adjustment in diltiazem daily dose may be necessary.

Ciclosporin: Increase in circulating cyclosporin 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.

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.

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): 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.
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 due to statins metabolised by CYP3A4 may be increased with concomitant use of diltiazem. When possible, a non CYP3A4-metabolised statin should be used together with diltiazem, otherwise close monitoring for signs and symptoms of a potential statin toxicity is required.

4.6 Pregnancy and lactation

There is very limited data from the use of diltiazem in pregnant patients. Diltiazem has been shown to have reproductive toxicity 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 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.

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
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<td></td>
<td>Thrombocytopenia</td>
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<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>Nervousness, insomnia</td>
<td>Mood changes (including depression)</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness</td>
<td>Extrapyramidal syndrome</td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations</td>
<td>Bradycardia</td>
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<td></td>
<td></td>
<td>Sinoatrial block, congestive heart failure</td>
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<tr>
<td><strong>Very common</strong></td>
<td><strong>Common</strong></td>
<td><strong>Uncommon</strong></td>
<td><strong>Rare</strong></td>
<td><strong>Not known</strong></td>
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<td><strong>Vascular disorders</strong></td>
<td>Flushing</td>
<td>Orthostatic hypotension</td>
<td></td>
<td>Vasculitis (including leukocytoclastic vasculitis)</td>
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<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td>Constipation, dyspepsia, gastric pain, nausea</td>
<td>Vomiting, diarrhea</td>
<td>Dry mouth</td>
<td>Gingival hyperplasia</td>
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<td><strong>Hepatobiliary disorders</strong></td>
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<td>Hepatic enzymes increase (AST, ALT, LDH, ALP increase)</td>
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<td>Hepatitis</td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Erythema</td>
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<td>Urticaria</td>
<td>Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, rash, erythema multiforme (including Steven-Johnson's syndrome and toxic epidermal necrolysis), sweating, exfoliative dermatitis, acute generalized exanthematous pustulosis, occasionally desquamative erythema with or without fever</td>
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<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
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<td>Gynecomastia</td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Peripheral oedema</td>
<td>Malaise</td>
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### 4.9 Overdose

The clinical effects of acute overdose can involve pronounced hypotension possibly leading to collapse, sinus bradycardia with or without isorhythmic dissociation, and atrioventricular conduction disturbances.

Treatment, in a hospital setting, will include gastric lavage and/or osmotic diuresis. Conduction disturbances may be managed by temporary cardiac pacing. Proposed corrective treatments: atropine, vasopressors, inotropic agents, glucagon and calcium gluconate infusion.