Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Adizem-XL 200 mg Prolonged Release Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 200 mg diltiazem hydrochloride.

Excipients: also contains soya lecithin, trace quantities per capsule.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsules, hard.

Size 1, hard gelatin capsules with brown body and brown cap marked ‘DCR 200’.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Management of angina pectoris.

2. Treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Oral.

The capsules should be swallowed whole and not chewed.

Adults:
The usual starting dose is one 240 mg capsule daily. However patients' responses may vary and dosage requirements can differ significantly between individual patients. There is no evidence of any decrease in efficacy at higher doses. If necessary the dose may be gradually increased to 300 mg or 360 mg per day. Doses of 480 mg/day have been used with benefit in some angina patients.

Elderly:
The usual starting dose is one 120 mg capsule daily. If necessary the dose may be gradually increased but careful monitoring of this group of patients is advised.

Children:
Not recommended for use in children.

Adizem XL should not be taken at the same time as an alcoholic beverage (refer to Section 4.5, Interactions with other Medicinal Products and Other Forms of Interaction).

4.3 Contraindications

Sick sinus syndrome not requiring pacemaker, second or third degree AV-block, bradycardia (less than 40 beats per minute). Congestive heart failure and in patients with left ventricular dysfunction following myocardial infarction. Pregnant women or those of child bearing potential. Concurrent use with dantrolene infusion is contraindicated because of the risk of ventricular fibrillation. Peanut or soya allergies.

4.4 Special warnings and precautions for use

Patients with mild bradycardia or a prolonged PR interval should be observed closely.
Diltiazem should be used with caution in patients with reduced left ventricular function.
Diltiazem should be used with caution in patients with hepatic dysfunction.
Diltiazem is considered unsafe in patients with acute porphyria.

Isolated cases of moderate and transient increased liver transaminases have been observed at the start of treatment. Isolated cases of clinical hepatitis have been reported, which resolved when diltiazem was withdrawn.

The use of diltiazem in diabetic patients may require adjustment of their control.

4.5 Interaction with other medicinal products and other forms of interaction

Diltiazem hydrochloride is extensively metabolised by CYP3A4, and as a result serum levels of diltiazem may be:

- Increased by concomitant usage of CYP3A4 inhibitors such as H_2 antagonists (e.g. cimetidine, ranitidine) and protease inhibitors (e.g. atazanavir, ritonavir)
- Decreased by concomitant usage of CYP3A4 inducers such as barbituates (phenobarbital, primidone), phenytoin and rifampicin

Diltiazem hydrochloride is also an inhibitor of CYP3A4, and may therefore increase serum levels of CYP3A4 substrates such as benzodiazepines (especially midazolam and triazolam), carbamazepine, ciclosporin, cilostazol, ivabradine, statins (simvastatin, atorvastatin, lovastatin), sirolimus, tacrolimus and theophylline. Care should be exercised in patients taking these drugs. Concomitant use of diltiazem hydrochloride with cilostazol and ivabradine should be avoided.

There may be an additive effect (increased depression of cardiac conduction with risk of bradycardia and AV block) when diltiazem hydrochloride is prescribed with drugs which may induce bradycardia or other anti-arrhythmic drugs (e.g. amiodarone and beta-blockers). Patients with pre-existing conduction defects should not receive the combination of diltiazem and beta-blockers.

Enhanced antihypertensive effect may occur with concomitant use of other hypertensive drugs (e.g. beta-blockers, diuretics, ACE-inhibitors) or drugs that cause hypotension such as aldesleukin and antipsychotics. Concomitant use with alph-blockers (e.g. prazosin) should be strictly monitored because of the possible synergistic hypotensive effect of this combination.

Diltiazem hydrochloride may cause small increases in plasma levels of digoxin, requiring careful monitoring of AV conduction.

Diltiazem hydrochloride may increase serum levels of phenytoin.

Diltiazem hydrochloride may increase bioavailability of tricyclic antidepressants.

Treatment with diltiazem hydrochloride has been continued without problem during anaesthesia, but the anaesthesist should be made aware of the treatment regimen.

ADIZEM XL should not be taken at the same time as alcohol, as it may increase the release of diltiazem from the

prolonged release preparation. In addition the combination of alcohol and diltiazem may have an additive vasodilatory effect.

4.6 Fertility, pregnancy and lactation

Not recommended.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The adverse events listed below are classified by body system.

Blood and Lymphatic system disorders	Thrombocytopenia
Metabolism and nutrition disorders	Anorexia
Nervous system disorders	Dizziness
	Extrapyramidal disorder
	Headache
Cardiac disorders	Atrioventricular block
	Bradycardia
	Palpitations
	Sinoatrial block
Vascular disorders	Facial flushing
	Hypotension
	Vasculitis
Gastrointestinal disorders	Gastrointestinal disorder
	Gingival hyperplasia
	Nausea
Hepato-biliary disorders	Increased hepatic enzyme
	Hepatitis
Skin and subcutaneous disorders	Allergic dermatitis
	Erythema multiforme
	Exfoliative dermatitis
	Photosensitivity reaction
	Rash
	Angioneurotic oedema
Reproductive system and breast disorders	Gynaecomastia
General disorders	Fatigue
	Oedema legs

4.9 Overdose

The clinical symptoms of acute intoxication may include pronounced hypotension or even collapse and sinus bradycardia with or without atrioventricular conduction defects.

The patient should be closely monitored in hospital to exclude arrhythmias or atrioventricular conduction defects. Gastric lavage and osmotic diuresis should be undertaken when considered appropriate. Symptomatic bradycardia and high grade atrioventricular block may respond to atropine, isoprenaline or occasionally temporary cardiac pacing.

Hypotension may require correction with plasma volume expanders, intravenous calcium gluconate and positive inotropic agents. The formulation employs a prolonged release system which will continue to release diltiazem for some hours.

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Selective calcium channel blocker with direct cardiac effects.
ATC Code: C08D B01.

5.1 Pharmacodynamic properties

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 sarcoplasmic reticulum.
This results in a reduction in the amount of available intra-cellular calcium and consequently a (1) reduction of myocardial oxygen consumption, (2) dilation of small and large coronary arteries, (3) mild peripheral vasodilation, (4) negative dromotropic effects, (5) reflex positive chronotropic and inotropic effects due to reflex sympathetic activity are partially inhibited and result in a slight reduction or no change in heart rate.

The antihypertensive effect is due to the reduction in peripheral vascular resistance.

The antianginal effect is due to a reduction in the peripheral resistance, thereby decreasing the after-load, whilst a reduction in the vasomotor tone of the coronary circulation maintains the coronary blood flow. Cardiac contractility and ventricular ejection fraction are unchanged. Diltiazem increases exercise capacity and improves indices of myocardial ischaemia in the angina patient. Diltiazem relieves the spasm of vasospastic (Prinzmetal) angina.

5.2 Pharmacokinetic properties

An oral dose of diltiazem is almost completely absorbed. Despite this, diltiazem has a low bioavailability owing to hepatic first-pass metabolism. Diltiazem is metabolised extensively and only 1.0-3.0% of the dose is excreted in urine as unmetabolised diltiazem.

The release of the drug has been prolonged in the capsules by special pharmaceutical technology. The high peak concentrations of the absorption phase have been eliminated. This allows the capsules to be administered once daily.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Ethylcellulose N10
Colloidal anhydrous silica
Polysorbate 80
Dibutyl sebacate
Magnesium stearate

<u>Capsule shell</u>
Iron oxide Red (E172)
Iron oxide Yellow (E172)
Iron oxide Black (E172)
Titanium dioxide (E171)
Gelatin
Sodium laurilsulfate

<u>Printing Ink</u>

Shellac
Soya lecithin
2-ethoxyethanol
Dimeticone
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVdC coated PVC blister packs with aluminium foil backing (4, 28 and 30 capsules).

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited,
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Cambridge,
CB4 0GW,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER

PA 913/14/8

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19/04/02
Date of last renewal: 16/12/2009

10 DATE OF REVISION OF THE TEXT

November 2010