SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ADIZEM -XL capsules 200 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diltiazem Hydrochloride 200 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release capsules.
ADIZEM-XL capsules 200 mg have a brown body and brown cap marked DCR 200.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Management of angina pectoris.
Treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Route of administration

Oral

Posology

Dosage requirements may differ between patients with angina and patients with hypertension. In addition, individual patients' responses may vary necessitating careful titration. This range of capsule strengths facilitates titration to the optimal dose.

The capsules should be swallowed whole and not chewed.

Adults:

For patients new to diltiazem therapy the usual starting dose is one 240 mg capsule daily.

Patients currently receiving a total daily dose of 180 mg diltiazem (as 90 mg b.d. or 60 mg t.i.d.) and transferring to ***ADIZEM-XL*** capsules should be given the 240 mg capsule (o.d.). A patient receiving 240 mg/day of diltiazem (as 120 mg b.d.) should commence treatment on the 240 mg capsule (o.d.), titrating to the 300 mg capsule (o.d.) if required.

Elderly and patients with impaired hepatic and renal function:

For patients new to diltiazem therapy, 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.

Elderly patients transferring to ***ADIZEM-XL*** capsules should receive the same total daily dose of diltiazem, titrating upwards as required

Children:

ADIZEM-XL capsules are not recommended for children. Safety and efficacy in children have not been established.

In order to avoid confusion, it is suggested that patients once titrated to an effective dose using ***ADIZEM-XL*** capsules, should remain on this treatment and should not be changed between different presentations.

ADIZEM-XL capsules 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

Pregnancy and in women of child bearing capacity. Patients with severe bradycardia (less than 40 bpm), second or third degree heart block, sick sinus syndrome, decompensated cardiac failure, patients with left ventricular failure with pulmonary congestion. Concurrent use with dantrolene infusion because of the risk of ventricular fibrillation (see section 4.5). Hypersensitivity to diltiazem or to any of the excipients.

4.4 Special warnings and precautions for use

The product should be used with caution in patients with reduced left ventricular function. Patients with bradycardia (risk of exacerbation), first degree AV block or prolonged PR interval should be observed closely.

Diltiazem is considered unsafe in patients with acute porphyria.

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. Diltiazem hydrochloride may

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

Beta-blockers: Possibility of rhythm disturbances (pronounced bradycardia, sinus arrest), sino-atrial and atrio-ventricular conduction disturbances and heart failure (synergistic effect). Patients with pre-existing conduction defects should not receive the combination of diltiazem and beta-blockers. Such a combination must only be used under close clinical and ECG monitoring, particularly at the beginning of treatment.

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.

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_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_2 agents. An adjustment in diltiazem daily dose may be necessary.

Protease inhibitors (atazanavir, ritonavir): Increase in plasma diltiazem concentrations.

Ciclosporin: Increase in circulating cyclosporin levels:
It is recommended that the cyclosporin dose be reduced, renal function be monitored, circulating cyclosporin 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 (e.g. cilostazol, ivabradine, sirolimus, tacrolimus). Care should be exercised in patients taking these drugs. Concomitant use of diltiazem with cilostazol and ivabradine should be avoided.

Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma 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.

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.

Diltiazem may increase bioavailability of tricyclic antidepressants.

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 (simvastatin, atorvastatin, lovastatin): 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.

ADIZEM-XL capsules should not be taken at the same time as alcohol, as it may increase the rate of release of diltiazem from the prolonged release preparation. In addition the combination of alcohol and diltiazem may have an additive vasodilatory effect.

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 contraindicated during pregnancy (see section 4.3), 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

Diltiazem has been reported to cause adverse reactions such as dizziness (common) and malaise (common), which may impair patients' ability to drive or operate machinery to a varying extent depending on the dosage and individual susceptibility. However, no studies have been performed. Therefore, patients should not drive or operate machinery if affected.

4.8 Undesirable effects

The following frequencies are the basis for assessing undesirable effects:
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	Not known
Blood and lymphatic system disorders					Thrombocytopenia
Immune system disorders			Hypersensitivity		
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		Sinoatrial block, congestive heart failure
Vascular disorders		Flushing	Orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis), hypotensio

	Very common	Common	Uncommon	Rare	Not known
Gastrointestinal disorders		Constipation, dyspepsia, gastric pain, nausea	Vomiting, diarrhoea	Dry mouth	Gingival hyperplasia,
Hepatobiliary disorders			Hepatic enzymes increase (AST, ALT, LDH, ALP increase)		Hepatitis
Skin and subcutaneous tissue disorders		Erythema Pruritus		Urticaria	Photosensitivity (including lichenoid keratosis at sun expose skin areas), angioneurotic oedema, rash, erythema multiforme (including Steven-Johnson's syndrome and toxic epidermal necrolysis), hyperhidrosis, exfoliative dermatitis, acute generalized exanthematous pustulosis, occasionall desquamative erythem with or without fever, allergic dermatitis
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Peripheral oedema	Malaise, fatigue			

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.

4.9 Overdose

The clinical effects of acute overdose can involve pronounced hypotension possibly leading to collapse, sinus bradycardia with or without isorthythmic 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.

Symptomatic bradycardia and high grade atrioventricular block may respond to atropine and isoprenaline.

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

<u>Absorption</u>

An oral dose of diltiazem is almost completely absorbed. Despite this, diltiazem has a low bioavailability of approximately 40% owing to extensive first pass metabolism. This process is saturable at higher doses of the drug resulting in a non-linear accumulation and higher blood concentrations at steady state than would be anticipated from those following a single dose.

ADIZEM-XL capsules reduce the degree of saturation by presenting diltiazem in a retarded fashion therefore eliminating the high peak concentrations of the absorption phase. This allows the capsule to be administered once daily.

In pharmacokinetic studies in healthy volunteers, diltiazem was well absorbed. The controlled release capsules provided prolonged absorption of the drug, producing peak steady state plasma concentrations between 4 and 14 hours post-dose. The availability of diltiazem from ADIZEM-XL capsules 120 mg (o.d.) relative to a prolonged release 60 mg diltiazem preparation (b.d.) was approximately 79% at steady state. Similarly, the availability of diltiazem from the 240 mg capsule (o.d.) relative to ADIZEM-SR tablets 120 mg (b.d.) was approximately 78%. The extent of absorption of diltiazem was not affected when ADIZEM-XL capsules were co-administered with a high-fat meal.

Biotransformation
Diltiazem is extensively metabolised by the liver. The desacetyl metabolite is considered to be approximately 25% to 50% as potent a coronary vasodilator as diltiazem and is present in plasma at concentrations of 10% to 20% of parent.

Elimination
The mean elimination half life of diltiazem is around 4 hours, but this is extended from prolonged-release formulations. Mean plasma concentrations in elderly subjects and patients with renal and hepatic insufficiency are higher than in young subjects.

Linearity/non-linearity
This process of first-pass metabolism process is saturable at higher doses of the drug. This results in a non-linear accumulation and higher blood concentrations at steady state than would be anticipated from those following a single dose. From modified-release preparations, the prolonged delivery of diltiazem can significantly reduce the degree of non-linearity associated with conventional formulations.

5.3 Preclinical safety data

Genotoxicity and carcinogenicity
Diltiazem was not genotoxic when tested in vitro in two bacterial mutation tests with and without metabolic activation, and in two clastogenicity assays.

Diltiazem was not carcinogenic in two long term carcinogenicity studies, in rats and mice.

Reproductive and developmental toxicity
Diltiazem was toxic to the developing embryo in studies in mice, rats and rabbits when dosed to the mother at critical stages during organ development. Skeletal malformations occurred in the limbs, tail and ribs of all three species.

Diltiazem had an adverse effect upon male fertility in rats, with decreases in sperm count, sperm motility and epididymal weight, although these effects were reversible on cessation of dosing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Microcrystalline Cellulose

Ethylcellulose N10

Colloidal Anhydrous Silica

Polysorbate 80

Dibutyl Sebacate

Magnesium Stearate

Capsule shells

Iron oxide (E172)

Titanium dioxide (E171)

Sodium laurilsulfate

Gelatin

Printing ink

Shellac

Simeticone

Propylene glycol

Titanium dioxide (E171)

6.2. Incompatibilities

None known

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

PVC/PVdC blister packs with aluminium foil (containing 4, 28 or 30 capsules).

6.6. Instructions for Use/Handling

None.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Ltd
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW

8. MARKETING AUTHORISATION NUMBER

PL 16950/0121

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10th September 2001 / 23rd September 2003

10 DATE OF REVISION OF THE TEXT

07/04/2017