Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diacardyne SR 300mg prolonged-release capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains diltiazem hydrochloride 300 mg.
Excipients: Sucrose 60.87mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

Hard gelatin capsules with an opaque white body and opaque yellow cap, marked with '300 mg' in black ink on the body and containing off-white spherical micro granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of angina pectoris.

Treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Oral use only

Adults :

Hypertension: The usual initial dose is 90 mg twice daily (corresponding to 180 mg of diltiazem hydrochloride). Depending upon clinical response the patient's dosage may be increased gradually to 180 mg daily, 120 mg twice daily, 240 mg daily, 300 mg daily, or 180 mg twice daily if required.

Angina Pectoris: The usual initial dose is 90 mg twice daily (corresponding to 180 mg of diltiazem hydrochloride). Depending upon clinical response the patient's dosage may be increased to 180 mg daily, 120 mg twice daily, 240 mg daily, 300 mg daily, or 180 mg twice daily if required.

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Elderly patients and those with impaired renal or hepatic dysfunction :
Dosage should commence at the lower level of 60 mg twice daily and be increased slowly. Do not increase the dose if the heart rate falls below 50 beats per minute.

Children :

Diltiazem preparations are not recommended for children. Safety and efficacy in children has not been established.

4.3 Contraindications

- Use in women of child-bearing potential and lactation
- Concomitant administration of dantrolene infusion due to the risk of ventricular fibrillation
- Shock
- Acute cardiac infarct with complications (bradycardia, severe hypotension, left heart insufficiency)
- Bradycardia (pulse rate, at rest, of less than 50 bpm), hypotension (less than 90 mm Hg systole), second or third degree heart block or sick sinus syndrome, except in the presence of a functioning ventricular pacemaker
- Atrial fibrillation/flutter and simultaneous presence of a WPW (Wolff-Parkinson-White) syndrome (increased risk of triggering a ventricular tachycardia)
- Manifest myocardial insufficiency
- Left ventricular failure with stasis
- Hypersensitivity to diltiazem or any of the excipients

4.4 Special warnings and precautions for use

Capsules should not be sucked or chewed.

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

The product should be used with caution in patients with hepatic dysfunction. Abnormalities of liver function may occur during therapy. Very occasional reports of abnormal liver function have been received; these reactions have been reversible upon discontinuation of therapy.

First degree AV block or prolonged PR interval. Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second or third degree AV block (refer Section 4.5).

Mild bradycardia.

Patients with reduced left ventricular function.

Renally impaired patients.

Owing to the presence of sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

4.5 Interaction with other medicinal products and other forms of interaction

Diltiazem undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration with other agents which follow the same route of biotransformation may result in competitive inhibition of metabolism.

Diltiazem hydrochloride should only be administered with great care to patients receiving concurrent treatment with antihypertensives or other hypotensive agents including halogenated anaesthetics or drugs with moderate protein binding.

Diltiazem hydrochloride will not protect against effects of withdrawal of β-adrenoceptor blocking agents, nor the rebound effects seen with various antihypertensives. Combination with β-adrenoceptor blockers having a significant “first pass” loss, e.g. propranolol may require a decrease in their dose and may lead to bradycardia. There may be an additive effect when used with drugs which may induce bradycardia or with other antihypertensives.

Concomitant H_2 antagonist therapy may increase diltiazem blood levels.

Diltiazem may affect the blood levels of concomitant carbamazepine, theophylline, ciclosporin and digoxin. Careful attention should therefore be given to signs of overdosage. The levels should be determined and the dose of carbamazepine, theophylline, ciclosporin, or digoxin reduced if necessary. Patients receiving β-b1ockers, diuretics, ACE inhibitors or other antihypertensive agents should be regularly monitored. Use with alpha blockers should be strictly monitored.

The simultaneous administration of diltiazem with drugs such as β-blockers, antiarrhythmics or heart glycosides may cause a greater degree of AV blocking, reduce the heart rate or induce a hypotensive effect. Intravenous administration of β-blockers should be discontinued during therapy with diltiazem.

Anaesthetists should be warned that a patient is on a calcium antagonist. Calcium channel blockers may potentiate the depression of cardiac contractility, conductivity, and automaticity, as well as the vascular dilation associated with anaesthetics. When used concomitantly, anaesthetics and calcium channel blockers should be titrated carefully.

There have been reports in the literature of diltiazem interactions with warfarin, rifampicin, and lithium.

4.6 Fertility, pregnancy and lactation

Diltiazem hydrochloride is contra-indicated in pregnant women or women of child-bearing potential, and is not recommended in nursing mothers.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

In studies carried out to date, serious adverse reactions with diltiazem have been rare; however, it should be recognised that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

In 900 patients with hypertension, the most common adverse events were oedema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first degree AV block (3%). Only oedema and perhaps bradycardia were dose related. The most common adverse events (>1%) observed in clinical studies of over 2100 angina and hypertensive patients receiving diltiazem were: oedema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%) and rash (1.5%).

Less common adverse events have included the following:

Cardiovascular: angina, arrhythmia, AV block (second or third degree), congestive heart failure, hypotension, palpitations, syncope.

Nervous system: amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paraesthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: anorexia, constipation, diarrhoea, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT and LDH (see Special Warnings and Precautions), vomiting, weight increase, gingivitis.

Dermatologic: petechiae, pruritus, photosensitivity, urticaria. Allergic skin reactions including erythema multiforme, vasculitis, lymphadenopathy and eosinophilia have been observed in isolated cases. Dermatological events may be transient and may disappear despite continued use of diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Other: amblyopia, CK elevation, dyspnoea, epistaxis, eye irritation, hyperglycaemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

4.9 Overdose

Experience of overdosage in man is limited but cases of spontaneous recovery have been reported. However, it is recommended that patients with suspected overdose should be placed under observation in a coronary care unit with facilities available for treatment of any possible hypotension and conduction disturbances that may occur. Most patients suffering from overdosage of diltiazem become hypotensive within 8 hours of ingestion. With bradycardia and first to third degree atrioventricular block also developing cardiac arrest may ensue. Hyperglycaemia is also a recognised complication. The elimination half-life of diltiazem after overdosage is estimated to be about 5.5 - 10.2 hours. If a patient presents early after overdose, gastric lavage should be performed and activated charcoal administered to reduce diltiazem absorption.

Hypotension should be corrected with plasma expanders, intravenous calcium gluconate and inotropic agents (dopamine, dobutamine or isoprenaline). Symptomatic bradycardia and high grade AV block may respond to atropine, isoprenaline or occasionally cardiac pacing which may be useful if cardiac standstill occurs.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Diltiazem has pharmacologic actions similar to those of other calcium channel blocking agents such as nifedipine or verapamil. The principal physiologic action of diltiazem is to inhibit the transmembrane influx of extracellular calcium ions across the membranes of myocardial cells and vascular smooth muscle cells.

Calcium plays important roles in the excitation-contraction coupling processes of the heart and vascular smooth muscle cells and in the electrical discharge of the specialised conduction cells of the heart. The membranes of these cells contain numerous channels that carry a slow inward current and that are selective for calcium.

By inhibiting calcium influx, diltiazem inhibits the contractile processes of cardiac and vascular smooth muscle, thereby dilating the main coronary and systemic arteries. Dilation of systemic arteries by diltiazem results in a decrease in total peripheral resistance, a decrease in systemic blood pressure and a decrease in the afterload of the heart. The reduction in afterload, seen at rest and with exercise, and its resultant decrease in myocardial oxygen consumption are thought to be responsible for the beneficial effects of diltiazem in patients with chronic stable angina pectoris. In patients with prinzmetal variant angina, inhibition of spontaneous and ergonovine-induced coronary artery spasm by diltiazem results in increased myocardial oxygen delivery.

5.2 Pharmacokinetic properties

General Characteristics

Absorption: Capsules seem to have a similar bioavailability to tablets (30-40%), with peak concentrations for the prolonged release product after 5.5 hours compared with 1-2 hours after the conventional release product. The relatively low bioavailability is due to first pass metabolism in the liver to an active metabolite.

Distribution: Diltiazem hydrochloride is lipophilic and has a high volume of distribution. Typical study results are in the range of 3-8 litres/kg. Protein binding is about 80% and is not concentration-dependent at levels likely to be found clinically. Protein binding does not appear to be influenced by phenylbutazone, warfarin, propranolol, salicylic acid or digoxin.

Metabolism: Diltiazem hydrochloride is extensively metabolised in the liver. N-monodesmethyl diltiazem is the predominant metabolite followed quantitatively by the desacetyl metabolite, which has some pharmacological activity. The efficacy of the metabolites, desacetyl diltiazem and N-monodesmethyl diltiazem is 25-50% and about 20% respectively of that of diltiazem. In liver function disorders delayed metabolism in the liver is likely. These metabolites are converted to conjugates, generally the glucuronide or the sulphate.

Elimination: Diltiazem is excreted in the form of its metabolites (about 35%) and in the non-metabolised form (about 2-4%) via the kidneys while about 60% is excreted via the faeces. The average elimination half life period for diltiazem is 6-8 hours but may vary between 2 and 11 hours. Although the elimination half life is not changed after repeated oral administration, diltiazem and also the desacetyl metabolite show a slight accumulation in the plasma.

Characteristics in Patients

Decreased first-pass metabolism in the elderly tends to result in increased plasma concentrations of calcium antagonists but no major changes have been found with diltiazem. Renal impairment did not cause significant changes in diltiazem pharmacokinetics. Plasma concentrations of diltiazem also tend to be higher in hepatic cirrhosis due to impaired oxidative metabolism.

5.3 Preclinical safety data

Chronic toxicity studies in rats revealed no remarkable changes at oral doses up to 125 mg/kg/day although there was 60% mortality at this dose. In dogs chronically treated with oral doses of 20 mg/kg/day, transient rises in SGPT were observed. Embryotoxicity has been reported in mice, rats and rabbits following i.p. administration of diltiazem. Main types of malformations included limb and tail defects with a small number of vertebral and rib deformities also noted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sugar spheres consisting of
Sucrose and maize starch
Povidone K30
Sucrose
Ethylcellulose 4mPa.s
Talc
Dispersion of ethylcellulose (Aquacoat ECD 30) containing:
- Ethylcellulose
- Sodium laurilsulfate
- Cetyl alcohol

Dibutyl sebacate

<u>Composition of capsule shell:</u>

Titanium dioxide (E 171)
Gelatin
Black iron oxide (E 172)
Yellow iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

Aluminium/PVC blisters packed in cardboard cartons containing 28, 30, 56 or 60 capsules.
Sample blister pack of 14 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

Ethypharm S.A.
17-21 Rue Saint Matthieu
78550 Houdan
FRANCE

8 MARKETING AUTHORISATION NUMBER

PA 549/1/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th January 1991
Date of last renewal: 18th January 2006

10 DATE OF REVISION OF THE TEXT

April 2007