Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Entrydil 60 mg Modified-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release film-coated tablet contains 60 mg diltiazem hydrochloride.

Excipients:
Each modified release film-coated tablet contains 67.5 mg lactose as lactose monohydrate
Each modified release film-coated tablet contains 0.5 mg sucrose

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified-release film-coated tablet
White or almost white, capsule-shaped, film-coated tablet, with a score line on both sides and marked with code DL /60 on one side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Angina pectoris including Prinzmetal's angina
- Mild to moderate hypertension

4.2 Posology and method of administration

For oral administration.

Adults only:

The usual starting dose is 90mg twice daily or 60mg three times daily (corresponding to 180mg of diltiazem hydrochloride).

Depending upon clinical response the patient's dosage may be increased to 180 mg twice daily or 120 mg three times daily if required.

Elderly and those with renal and hepatic impairment:

Dosage should commence at the lower level of 60mg twice daily and be increased slowly. Do not increase the dose if the heart rate falls below 50 beats per minute.

Children (below 18 years of age):

There are no data available on use of diltiazem in children below the age of 18 years, and diltiazem is not recommended for use in children.

4.3 Contraindications

- Sick sinus syndrome or evidence of second or third degree AV block except in the presence of a functioning

pacemaker

- Hypotension (systolic blood pressure less than 90mmHg)
- Severe bradycardia (resting pulse rate of less than 40 beats per minute)
- Atrial fibrillation/flutter and simultaneous presence of WPW (Wolff-Parkinson-White) syndrome (increased risk of triggering a ventricular tachycardia)
- Decompensated cardiac insufficiency
- Acute complicated myocardial infarction (with bradycardia, severe hypotension, left heart insufficiency)
- Cardiogenic shock, left ventricular failure with stasis, pulmonary congestion
- Digitalis intoxication
- Pregnancy or lactation (Please see section 4.6)
- Use in women of child bearing potential (Please see section 4.6 Fertility, pregnancy and lactation)
- Known hypersensitivity to diltiazem hydrochloride or to any of the excipients (Please see section 6.1)
- Concomitant administration of dantrolene infusion due to the risk of ventricular fibrillation (see section 4.5).

4.4 Special warnings and precautions for use

1. The use of diltiazem hydrochloride in diabetic patients with impaired renal function or patients with renal or hepatic impairment may require adjustment of their control.

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

3. Prior to general anaesthesia, the anaesethist must be informed of ongoing diltiazem treatment. Depression of cardiac contractility, conductivity and automaticity, as well as the vascular dilatation associated with anaesthetics such as enflurane, halothane and isoflurane, may be potentiated by calcium channel blockers.

4. The risk of raised creatine kinease, myopathy and rhabdomyolisis due to statins (metabolised by CYP3A4) may be increased in case of a concomitant use of diltiazem. Closer monitoring for signs and symptoms is warranted in such case.

5. Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression.

6. 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.

7. Clearance of diltiazem can be decreased in patients with impaired hepatic or renal function and in elderly patients. Such patients should be treated cautiously.

8. Since diltiazem has shown porphyrogenic characteristics in *in vitro* and animal studies, caution should be exercised in the treatment of patients with acute porphyria.

9. Patients with impaired ventricular function, bradycardia, first degree AV block, prolonged PQ interval, aortic stenosis, and those treated with beta-blockers or other medicaments that impair cardiac conduction or contractility must be treated cautiously. 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. (Please see section 4.5)

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

11. This medicine contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

12. This medicine contains castor oil. This may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

- Diltiazem may increase the efficacy of other anti-hypertensive drugs and diuretics if used concomitantly. In all the patients treated with calcium antagonists, the prescription of nitrate derivatives should only be carried out at gradually increasing doses. It has decreased nifedipine clearance by over 50% and increased plasma levels of propranolol and metoprolol. The combination of diltiazem with an alpha-antagonist should be considered only with the strict monitoring of the blood pressure.

- Dantrolene (infusion) a lethal ventricular fibrillation is regularly observed in animals when intravenous verapamil and dantrolene are administered concomitantly. The combination of calcium antagonist and dantrolene is therefore potentially dangerous *(see section 4.3 Contraindications)*

- 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. Concomitant use with beta-blockers, amiodarone, digoxin, halothane and related anaesthetics, or other medicaments that impair cardiac conduction increases the risk of AV conduction disturbances (pronounced bradycardia, sinus arrest), sino-atrial and atrio-ventricular conduction disturbances and heart failure (synergistic effect). Concomitant administration should be used with caution and must only be used under close clinical and ECG monitoring, particularly at the beginning of treatment. Intravenous administration of beta-blockers should be discontinued during therapy with diltiazem.

- Diltiazem 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. 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.

Pharmacokinetic interactions

Effect of other drugs on diltiazem

- Diltiazem is mainly metabolised by CYP3A4. Agents that inhibit CYP3A4 (such as macrolide antibiotics, azole antifungals, fluoxetine, tamoxifen, nifedipine, cimetidine, HIV protease inhibitors) may increase the concentration of diltiazem, which can cause toxic effects.

- Agents that induce CYP3A4 (such as carbamazepine, phenobarbital, moricizine, rifampicin, phenytoin) may decrease the concentration of diltiazem, which can decrease the clinical effect. The patient should be carefully monitored when initiating or discontinuing rifampicin treatment.

- Diazepam has decreased diltiazem plasma levels by 20%

- Concomitant H_2 antagonist (cimetidine, ranitidine) therapy may increase diltiazem blood levels. 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.

Effect of diltiazem on other drugs

- Diltiazem and its metabolites inhibit the activity of CYP3A4, which may increase the concentration of drugs metabolised by that enzyme.

- Clearance of simvastatin, atorvastatin and lovastatin is inhibited by diltiazem, which may cause significantly increased plasma levels of those drugs. If taken concomitantly, a small dose of statin must be used and symptoms of rhabdomyolysis and hepatic damage must be closely monitored. 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.

- The serum concentration and/or signs of toxicity of carbamazepine, phenytoin, ciclosporin, sirolimus, tacrolimus, digoxin, methylprednisolone, and theophylline should be monitored if they are used concomitantly with diltiazem and after its discontinuation. If necessary the levels should be determined and the dose of carbamazepine, theophylline, ciclosporin A, or digoxin be reduced if necessary. Diltiazem has increased the plasma levels and kidney toxicity of ciclosporin, the combination should be used with caution. In one study diltiazem has decreased theophylline clearance by 25%, but only in male smokers. Diltiazem has increased plasma levels and kidney toxicity of tacrolimus in kidney and liver transplant recipients.

- Clearance of other drugs metabolised by CYP3A4 (such as nifedipine, quinidine, moricizine, imipramine, nortriptyline, sildenafil, buspirone, midazolam, triazolam, alprazolam, alfentanil, and cisapride) may be inhibited by diltiazem, and their plasma levels may be increased. The possible interaction should be taken into account. Special care should be taken when prescribing short-acting benzodiazepines metabolized by the CYP3A4 pathway in patients using diltiazem.

- Lithium neurotoxicity may occur when used concomitantly with diltiazem. Therefore serum concentrations of lithium should be monitored.

- There have been reports in the literature of diltiazem interactions with warfarin.

4.6 Fertility, pregnancy and lactation

There is very limited data from the use of diltiazem in pregnant patients. High diltiazem doses have been observed to induce increased fetal mortality and malformations. Diltiazem is therefore not recommended during pregnancy, as well as in women of child-bearing potential not using effective contraception. No effects on female fertility have been observed.

Diltiazem is excreted in breast milk. Women should not breastfeed while on diltiazem treatment. 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

At the beginning of treatment with diltiazem the decrease in blood pressure may induce dizziness especially when standing up. If this occurs, the patient should refrain from driving and using machines. The patient's reaction to diltiazem should be known before she/he is allowed to drive or use machinery. Well balanced treatment with diltiazem is not known to affect the patient's ability to drive or operate machines. 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		Sinotrial block, congestive heart failure, syncope
Vascular disorders		flushing	orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis)
Gastrointestinal disorders		constipation, dyspepsia, gastric pain, nausea	vomiting, diarrhoea	dry mouth	Gingival hyperplasia
Hepatobiliary disorders			hepatic enzymes increase (AST, ALT, LDH, ALP increase)		Hepatitis
Musculoskeletal and connective tissue disorders					Arthralgia
Skin and subcutaneous tissue disorders		erythema		urticaria	Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, 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
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	lower limb oedema (peripheral oedema)	malaise			Asthenia/fatigue

As with some other calcium channel blockers, exceptional cases of extrapyramidal symptoms and gynaecomastia have been reported, reversible after discontinuation of calcium antagonists. Raised creatine kinase, myopathy and rhabdomyolisis due to statins metabolised by the CYP3A4 system when taken concomitantly with diltiazem, see section 4.5, Interactions with Other Medicinal Products and Other Forms of Interaction.

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. The symptoms of overdose include tiredness, irritability, somnolence, sinus bradycardia, first to third degree AV blocks, cardiac arrest, hypotension, collapse, hypothermia, hyperglycaemia and nausea.

There is no specific antidote for diltiazem. The elimination half-life of diltiazem after overdosage is estimated to be about 5.5 – 10.2 hours. Absorption should be prevented by use of gastric lavage and administration of activated charcoal if the patient presents early after overdose.

Such patients should be taken care of at intensive care units with cardiac (ECG) monitoring. The effect of diltiazem can be antagonised by i.v. calcium gluconate or calcium chloride to restore stable sinus activity. Hypotension should be corrected with plasma expanders, and intravenous inotropic agents (dopamine, dobutamine, isoprenaline). Symptomatic bradycardia and high grade AV block may respond to atropine, isoprenaline or occasionally cardiac pacing. Otherwise treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code C08D B01 – Benzothiazepine derivatives.

Diltiazem is a benzothiazepine derivative that effectively blocks the slow calcium channels (L channels) of vascular smooth muscle and cardiac muscle cells. Slow calcium channels play an important role especially in the regulation of sinoatrial and atrioventricular node function in the cardiac muscle cells.

Diltiazem possesses both peripheral and coronary vasodilator properties. However, diltiazem-induced fall in blood pressure is not commonly followed by reflectory tachycardia which is probably due to the depressive effect of the drug on the stimulation of sinoatrial node function. Diltiazem slows atrioventricular conduction. It also has a weak negative inotropic effect on the heart. Diltiazem improves relaxation of the cardiac muscle and diastolic function which together with decreased afterload improves the left ventricular function. In spite of coronary dilatation the total flow in healthy

coronary arteries does not usually change, but some improvement in the circulation of contracted arteries has been observed. Diltiazem relaxes smooth muscle also elsewhere in the body, eg. the lower oesophageal sphincter muscle. Diltiazem has not been shown to have an effect on electrolyte-, lipid- or glucose balance in healthy or diabetic persons.

5.2 Pharmacokinetic properties

Diltiazem is completely absorbed after oral administration, but owing to its first-pass metabolism in the liver, the absolute bioavailability of diltiazem hydrochloride is only about 40% (with interindividual variability ranging from 24 to 74%). The bioavailability is independent of formulation or therapeutic dose. A diet rich in fat and protein slightly increases the bioavailability of a sustained-release capsule formulation, but this has no clinical significance. The release of the drug has been prolonged in the controlled-release formulation by special pharmaceutical technology. The peak plasma concentrations are reached 2-3 hours after dosing. The high peak concentrations of the absorption phase have been eliminated. This allows the Entrydil S.R. 90mg tablets to be administered twice each day.

About 80% of diltiazem is bound to proteins, about 40% of this to plasma albumin. Protein binding does not appear to be influenced by phenylbutazone, warfarin, propranolol, salicylic acid or digoxin. Diltiazem is widely distributed to various tissues. The apparent volume of distribution is 5 l/kg and the volume of central compartment is 0.9 l/kg. In the blood, diltiazem is evenly distributed to the plasma and blood cells. Steady state is reached within 3 days with the dosage of one 60mg tablet 3 times daily.

Diltiazem is extensively metabolised in the liver, and less than 4% is excreted unchanged in the urine. The total clearance of diltiazem is between 0.7 and 1.3 l/kg/h. Five unconjugated metabolites have been found in the urine, two of them also in conjugated forms. Diltiazem is metabolised through deacetylation, N-demethylation, and O-demethylation. Deacetyldiltiazem is an active metabolite (40-50% of the activity of diltiazem) with concentrations of about 15 to 35% of those of diltiazem. The pharmacodynamic significance of this metabolite is minor. Diltiazem is metabolised mainly by CYP3A4 and to a lesser extent by CYP2D6. Diltiazem and its N-demethylated metabolites also act as inhibitors of CYP3A4 enzyme. In liver function disorders delayed metabolism in the liver is likely. These metabolites are converted to conjugates, generally the glucuronide or the sulphate.

According to 3-compartment model, the half-life of diltiazem ranges from about 0.1 hours in the first phase to 2.1 hours in the middle and 9.8 hours in the terminal phase. The elimination half-life varies between 4 and 7 hours.

The pharmacokinetics of diltiazem has not been observed to change after repeated administrations. The drug is not accumulated and it does not induce its own metabolism. Studies with renal insufficiency and angina pectoris patients did not show difference in the pharmacokinetic profile of diltiazem as compared with studies on healthy volunteers.

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

The acute toxicity of diltiazem was low (oral LD50>500 mg/kg) in toxicity studies on rodents. The toxicity of diltiazem was mainly directed to the heart (transient ECG changes). In teratogenicity studies, diltiazem induced foetal mortality and malformations.

Chronic toxicity studies in rats revealed no remarkable changes at oral doses up to 125mg/kg/day although there was 60% mortality at this dose. In dogs chronically treated with oral doses of 20mg/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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Castor oil, hydrogenated
Dried aluminium hydroxide gel
Polyacrylate dispersion 30 per cent
Talc
Magnesium stearate

Film coating:
Hypromellose
Sucrose
Glycerol (85 per cent)
Titanium dioxide (E171)
Magnesium stearate
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Pack sizes: 30 & 100 tablets
Container: 40ml white high density polyethylene (HDPE) jar with a 32mm white high density polyethylene (HDPE) screw cap.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FIN-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER

PA 1327/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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