Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

DTZ 180mg Prolonged-Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Diltiazem (as Hydrochloride) 180mg in a prolonged release formulation.

3 PHARMACEUTICAL FORM

A prolonged release capsule (size 1), hard with natural transparent cap, and opaque pink body with the marking ‘DTZ 180’ imprinted, containing white-grey to light yellow almost spherical pellets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mild to moderate hypertension.

4.2 Posology and method of adminstration

Adults
Hypertension: 240 mg once daily. Dosage titration in 60mg to 120mg steps at 2-weekly intervals may be required to obtain satisfactory clinical response (240mg to 360mg daily will usually suffice).

Dosage should be reduced in the presence of adverse reactions or if the pulse rate falls below 50 per minute.

Elderly and patients with impaired hepatic or renal function
Hypertension: Starting dose 120 mg once daily.

Children
Not recommended.

4.3 Contraindications

1. DTZ should not be used in patients with a known hypersensitivity to any of the ingredients.

2. Use in pregnancy and in women of childbearing potential.

3. ‘DTZ’ depresses atrioventricular node conduction and is therefore contraindicated in patients with marked bradycardia, sick sinus syndrome, uncontrolled heart failure or second or third degree AV block.

4.4 Special warnings and special precautions for use

‘DTZ’ should be used with caution in patients with reduced left ventricular function. Patients with mild bradycardia, and/or having a prolonged PR interval, should be observed closely.

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

4.5 Interaction with other medicinal products and other forms of interaction

In common with other calcium antagonists, when 'DTZ' is used with drugs which may induce bradycardia (e.g. amiodarone and beta-blockers) or with other antihypertensive drugs, the possibility of an additive effect should be borne in mind.

Diltiazem has been used safely in combination with beta-blockers, diuretics, ACE inhibitors and other antihypertensive agents. It is recommended that patients receiving these combinations should be regularly monitored. Concomitant use with alpha-blockers such as prazosin should be strictly monitored because of the possible marked synergistic hypotensive effect of this combination.

Case reports have suggested that blood levels of carbamazepine, cyclosporin and theophylline may be increased when given concurrently with diltiazem hydrochloride. Care should be exercised in patients taking these drugs. In common with other calcium antagonists, diltiazem may cause small increases in plasma levels of digoxin.

In patients taking H_2 receptor antagonists concurrently with 'DTZ', increased levels of Diltiazem may be produced.

Diltiazem hydrochloride treatment has been continued without problem during anaesthesia, but the anaesthetist should be informed that the patient is receiving a calcium antagonist.

4.6 Pregnancy and lactation

Diltiazem hydrochloride is teratogenic in some animal species. In the absence of adequate evidence of safety in human pregnancy 'DTZ' should not be used in pregnancy or in women of child bearing potential.

Nursing mothers: Diltiazem hydrochloride is excreted in breast milk. One report suggests that concentrations in breast milk reach similar levels to those in serum. If use of 'DTZ' is considered essential, an alternative method of infant feeding should be instituted.

4.7 Effects on ability to drive and use machines

The product is assumed to be safe and unlikely to produce an effect on ability to drive and use machines.

4.8 Undesirable effects

The following undesirable effects have been reported: ankle oedema, malaise, headache, hot flushes, gastro-intestinal disturbances and very rarely, symptomatic bradycardia, sino-atrial block and atrio-ventricular block. Rash has been reported in association with diltiazem.

These reactions are generally mild and resolve on cessation of therapy, however, severe vascular skin reactions have been reported occasionally.

Isolated cases of moderate and transient elevation of liver transaminases have been observed at the start of treatment. Isolated cases of clinical hepatitis have been reported which resolved on cessation of therapy.

The current literature suggests that the effects of vasodilation, particularly ankle oedema, are dose dependent and are more frequent in the elderly.

4.9 Overdose

Signs and symptoms: Acute intoxication can lead to severe hypotension, bradycardia, first to third degree atrioventricular block and, on occasion, to cardiac arrest. Hyperglycaemia may require treatment. Onset of symptoms may be delayed for several hours after ingestion and have been described after as little as 900mg diltiazem.

Treatment: Observation in a coronary or intensive care unit is advisable if a substantial overdose has been ingested. Soon after ingestion, gastric lavage followed by 50 to 100 mg activated charcoal may reduce absorption. Profound hypotension requires plasma expanders, IV calcium gluconate and inotropic agents (e.g. dopamine, dobutamine or isoprenaline).

Symptomatic bradycardia and heart block may respond to atropine, isoprenaline or, if necessary, cardiac pacing.

'DTZ' are extended release capsules and effects may be slow in onset and prolonged.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Diltiazem hydrochloride is a calcium antagonist.

Mechanism of Action

Diltiazem selectively reduces calcium entry through voltage-dependant calcium channels into vascular smooth muscle cells and myocardial cells. This lowers the concentration of intracellular calcium which is available to activate contractile proteins. In vascular tissue, diltiazem relaxes arterial smooth muscle, reducing systemic peripheral resistance and dilating the coronary arteries. In cardiac muscle, diltiazem reduces contractility and slows the heart rate through its negative chronotropic and inotropic actions. Cardiac work and oxygen demand can therefore be reduced without reflex tachycardia.

5.2 Pharmacokinetic properties

(a) General Characteristics of the Active Substance(s)

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%.

DTZ is about 80-85% plasma protein bound. Plasma levels above 40-50 ng/mL are associated with pharmacological activity.

Diltiazem is extensively metabolised by the liver, the plasma half life being on average 3-4.5 hours.

The two major active circulating metabolites, desacetyl diltiazem and N-monodemethyl diltiazem, possess coronary artery vasodilatory activity equivalent to about 50% of that of diltiazem. Only 0.2 to 4% of diltiazem is found unchanged in the urine.

The sustained release pellets in this presentation usually achieve maximum plasma diltiazem levels six to eight hours after dosing and have a plasma elimination half life of approximately 7 hours, allowing once daily dosing.

The bioavailability of diltiazem from the 'DTZ' formulation given once a day is equivalent to that obtained from a conventional release tablet given three times a day, when the same total daily dose is administered.

(b) Characteristics in patients

Data from studies in patients and healthy volunteers have also demonstrated that trough plasma levels (i.e. 24 hours post dosing) can be maintained within the minimum therapeutic range by appropriate dose titration.

Plasma concentrations in elderly patients and in hepatic failure are in general higher than in young subjects, due to an increase in apparent bioavailability. In renal failure, a reduction in dosage is only necessary as a function of the clinical response.

5.3 Preclinical safety data

No findings have been reported from pre-clinical safety studies which add to the prescribing information given in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Maize starch
Povidone
Shellac
Ethylcellulose
Talc
Erythrosin E127
Indigotin E132
Titanium dioxide E171
Gelatin
Black iron oxide (E172)

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

Blister packages comprising heat-sealable PVC/PVdC and aluminium foil. Blister sizes are 4, 28 and 56 capsules in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Helsinn Birex Therapeutics Limited,
Damastown,
Mulhuddart,
Dublin 15.
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 915/5/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th September 1999

Date of last renewal: 7th September 2004

10 DATE OF REVISION OF THE TEXT

November 2004