Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diltiazem Hydrochloride Tablets 60 mg (Prolonged release).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Constituent	*mg/tablet*
Diltiazem Hydrochloride	60 mg
Excipients: Lactose monohydrate	260 mg

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet.

Prolonged release convex white tablet with “DT/60” on one side and “G” on the reverse, approximately 10 mm in diameter and approximately 5 mm in thickness.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the prophylaxis and treatment of angina pectoris and hypertension.

4.2 Posology and method of administration

Adults

The initial dose is 60 mg three times daily. Patient responses can vary and dosage may be increased to 360 mg daily in divided doses if required. Higher doses up to 480 mg per day have been used with benefit in some patients, especially in unstable angina. There is no evidence of any decrease in efficacy at these higher doses.

Elderly and patients with impaired hepatic or renal function

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

Children

The safety and efficacy of diltiazem in children has not been established.

4.3 Contraindications

- Use in pregnancy and women of child bearing capacity, (see Section 4.6).
- Diltiazem depresses atrioventricular node conduction and should not be used in patients with severe bradycardia (less than 50 b.p.m.); hypotension (less than 90 mmHg systole)left ventricular failure with stasis; second or third degree heart block except in the presence of a functioning pacemaker or sick sinus syndrome.
- Acute cardiac infarct with complications (bradycardia, severe hypotension, left heart insufficiency).
- Atrial fibrillation/flutter and simultaneous presence of a WPW (Wolff-Parkinson-White) syndrome (increased risk of triggering a ventricular tachycardia).
- Manifest myocardial insufficiency.
- As with any other calcium antagonist, diltiazem should not be administered concurrently with dantrolene infusion because of the risk of ventricular fibrillation.
- Hypersensitivity to diltiazem or any of the excipients.

4.4 Special warnings and precautions for use

Diltiazem should be used with caution in patients with reduced left ventricular function. Patients with mild bradycardia, first degree AV block or prolonged PR interval should be observed closely.

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

The product should be used with caution in patients with hepatic dysfunction. Abnormalities of liver function may appear during therapy.

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

4.5 Interaction with other medicinal products and other forms of interaction

Diltiazem hydrochloride has been safely used in combination with beta-blockers, diuretics, ACE inhibitors and other anti-hypertensive drugs. Patients on combined therapy should be regularly monitored. However, because of the possible synergistic hypotensive effect of diltiazem and alpha-blockers, patients receiving this combination should be strictly monitored.

Although anaesthesia has been performed without undue effect on patients receiving diltiazem, the anaesthetist should be informed that the patient is receiving a calcium antagonist.

As with other calcium antagonists, when diltiazem is used with drugs which may induce bradycardia or with other antiarrhythmic drugs, the possibility of an additive effect should be borne in mind.

Concurrent use with digitalis, carbamazepine, cyclosporin and theophylline may lead to increases in their plasma levels.

Concurrent use with cimetidine or any other H_2 antagonist may increase serum levels of diltiazem hydrochloride.

Use with diazepam may decrease serum levels of diltiazem hydrochloride.

Diltiazem is known to inhibit CYP3A4 and therefore may cause increased blood concentrations of substrates of this enzyme e.g. simvastatin, tacrolimus, sirolimus, erythromycin.

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

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.

The simultaneous administration of diltiazem with drugs such as β-blockers, antiarrythmics 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.

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

4.6 Pregnancy and lactation

Studies in animals have shown teratogenic and embryotoxic effects. The drug crosses the placenta and concentrates in foetal tissues. In the absence of adequate evidence of safety in human pregnancy, diltiazem should not be used during pregnancy or in women of child bearing potential.

Diltiazem is also excreted in breast milk and should not be used in women breast feeding infants.

4.7 Effects on ability to drive and use machines

None.

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 filure, hypotension, palpitations, syncope.
- Nervous system: Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paraesthesia, personality changes, 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, gingival enlargement.
- 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 eleveation, dyspnoea, epistaxis, eye irritation, hyperglycaemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

- Skin and subcutaneous tissue disorders: Acute generalised exanthemas pustules, hyper pigmentation.

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 ensure. 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 overdosage, gastric lavage should be performed and activated charcoal administered to reduce diltiazem absorption.

Hypotension should be corrected with plasma expanders, intravenous calcium cluconate and ionotropic agents (dopamine, dobutamine, 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

Diltiazem is a calcium channel blocking agent. It selectively reduces calcium entry into vascular smooth muscle cells and myocardial cells. This dilates the coronary arteries increasing the supply of oxygen to the heart. It reduces systemic vascular resistance, thereby reducing oxygen demand, and moderates the heart rate. These combined effects reduce cardiac work.

When given either alone or with a beta-blocker to patients with preserved ventricular function only minimal negative inotropic effects have been observed.

5.2 Pharmacokinetic properties

Diltiazem is well absorbed and undergoes first pass metabolism in the liver giving rise to two major circulating metabolites, desacetyl diltiazem and N-monodemethyl diltiazem. The mean plasma half-life is 5 hours. It is excreted mainly in faeces and to a lesser extent in urine. Only 0.2 to 4% of diltiazem is found unchanged in the urine.

5.3 Preclinical safety data

Administration to pregnant mice and rats has been associated with decreased foetal weight, vertebral and skeletal malformations. There is no data on teratological effects of diltiazem in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Methylhydroxypropylcellulose
Povidone
Ethylcellulose
Macrogol
Hydrogenated vegetable oil
Magnesium stearate
Talc

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

High density polypropylene tablet container with tamper-evident polyethylene cap – packs of 100 tablets.

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

Generics (UK) Limited
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8 MARKETING AUTHORISATION NUMBER

PA 0405/030/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th December 1990

Date of last renewal: 18th December 2005

10 DATE OF REVISION OF THE TEXT

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