Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Co-Tenidone Tablets BP 100/25mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Atenolol 100mg and Chlorthalidone 25mg.

3 PHARMACEUTICAL FORM

Circular, white film coated tablets embossed 'Co-Ten 100' on one side, plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

The management of hypertension.

4.2 Posology and method of adminstration

Adults:
One tablet daily.
Older patients with hypertension who do not respond to low dose therapy with a single agent should have a satisfactory response to a single tablet daily of Co-Tenidone 50/12.5mg. Where hypertensive control is not achieved, addition of a small dose of a third agent e.g. a vasodilator may be appropriate.

Elderly:
Dosage requirements are often lower in this age group. Older patients with hypertension who do not respond to low dose therapy with a single agent should have a satisfactory response to a single tablet daily of Co-Tenidone 50/12.5mg. Where hypertensive control is not achieved, addition of a small dose of a third agent, e.g. a vasodilator may be appropriate.

Children:
There is no paediatric experience of this drug and it is therefore not recommended for use in children.

Renal Failure:
In patients with severe renal impairment a reduction in daily dosage or in frequency of administration may be necessary.

4.3 Contraindications

1. 2^{nd} or 3^{rd} degree atrioventricular block
2. Severe bradycardia
3. Uncontrolled or digitalis/diuretic refractory heart failure
4. Cardiogenic shock

4.4 Special warnings and precautions for use

Special precautions for use

Cardiac
Special care should be taken with patients whose cardiac reserve is poor. Beta-adrenoceptor blocking drugs should be avoided in overt heart failure. They should only be used with caution in patients with controlled congestive cardiac failure.

Pulse Rate
One of the pharmacological reactions of the beta-adrenoceptor blocking drugs is to reduce heart rate. In the rare instance where symptoms may be attributable to slow heart rate the dose may be reduced.

Hypoglycaemia
Co-Tenidone modifies the tachycardia of hypoglycaemia.

Obstructive airways disease
Although cardio selective beta blockers may have less effect on lung function than non selective blockers they should be avoided in patients with reversible obstructive airways disease unless there are compelling reasons for their use in which case they may be used with caution. Occasionally some increase in airways resistance may occur in asthmatic patients and this may usually be reversed by commonly used dosages of bronchodilators such as salbutamol or isoprenaline. Beta blockers should be used with caution in patients with a family history of asthma.

Sudden withdrawal in ischaemic heart disease
In patients suffering from ischaemic heart disease as with other beta blocking drugs treatment should not be stopped abruptly.

Metabolic effects
The metabolic effects of chlorthalidone are dose related and at the low dose in Co-Tenidone are unlikely to be troublesome.

Potassium status
As with other combinations of beta adrenoceptor blocking drugs and diuretics hypokalaemia may occur with Co-Tenidone. In most patients this appears to be of little clinical significance. Measurement of potassium levels is appropriate especially in the older patient, those receiving digitalis preparations for cardiac failure, taking abnormal (low in potassium) diets or suffering from gastrointestinal complaints.

Serum uric acid
Co-Tenidone is generally associated with only a minor increase in serum uric acid. In cases of prolonged elevation the concurrent use of a uricosuric agent will reverse the hyperuricaemia.

Diabetes
Co-Tenidone contains chlorthalidone which may decrease glucose tolerance during prolonged therapy. Regular tests for glycosuria should be carried out.

Sensitivity to Chlorthalidone
Care should be taken in patients with a history of sensitivity to chlorthalidone.

Anaesthesia
Care should be taken in the use of anaesthetic with chlorthalidone. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible.

Special Warnings

Renal impairment
In patients with severe renal impairment a reduction in daily dosage or in frequency of administration may be

necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised when transferring patients from clonidine to beta blocking drugs. If beta adrenoceptor blocking drugs and clonidine are given concurrently clonidine should not be discontinued until several days after withdrawal of the beta adrenoceptor blocking drug.

Care should be taken when prescribing a beta adrenoceptor blocking drug with class I antidysrhythmic agents such as disopyramide. Beta adrenoceptor blocking drugs should be used with caution in combination with verapamil in patients with impaired ventricular function. This combination should not be given to patients with conduction abnormalities. Preparations containing lithium generally should not be given with diuretics because it may reduce its renal clearance.

4.6 Pregnancy and lactation

Co-Tenidone should not be given during pregnancy and lactation unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

Co-Tenidone is unlikely to result in any impairment of the ability of the patient to drive or to operate machinery.

4.8 Undesirable effects

Co-Tenidone is generally well tolerated. Side effects associated with it are generally mild and infrequent. Minor side effects include cold extremities, muscular fatigue and in isolated cases bradycardia. Sleep disturbances of the type noted with other beta adrenoceptor blocking drugs have rarely been reported. There have been reports of skin rashes and/or dry eyes associated with the use of beta adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared on withdrawal of the drug. Discontinuation of the drug should be considered if such reactions are otherwise inexplicable. Cessation of therapy with beta adrenoceptor blocking drugs should be gradual. Nausea and dizziness have been reported occasionally with chlorthalidone and idiosyncratic drug reactions such as thrombocytopenia and leucopenia have occurred rarely.

4.9 Overdose

Excessive bradycardia may be countered with atropine 1-2mg i.v. followed if necessary by a bolus dose of 10mg glucagon intravenously. If necessary this may be repeated or followed by an intravenous infusion of glucagon 1-10mg/hour depending on response. If no response to glucagon occurs or if it is unavailable a beta adrenoceptor stimulant such as prenalterol 5mg intravenously, followed if necessary by an intravenous infusion of 5mg/hour or, dobutamine 2.5-10µg/kg/minute by intravenous infusion may be given. Any risk of hypotension occurring following the use of a beta adrenoceptor agonist will be reduced by the use of more selective agents, e.g. prenalterol or dobutamine. Excessive diuresis should be countered by maintaining normal fluid and electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Co-Tenidone combines the anti-hypertensive activity of two agents, a beta adrenergic receptor blocking agent (atenolol) and a diuretic (chlorthalidone). Atenolol predominantly blocks beta receptors and does not possess membrane stabilising or intrinsic sympathomimetic (partial agonist activities).

The mechanism of the antihypertensive activity of atenolol has not been established. Chlorthalidone a monosulphamoyl diuretic increases the excretion of sodium and chloride. Natriuresis is accompanied by some loss of potassium. The mechanism by which chlorthalidone works usually does not decrease normal blood pressure. The combination of atenolol with thiazide like diuretics has been shown to be compatible and generally more effective than

either drug used alone as an anti-hypertensive agent.

5.2 Pharmacokinetic properties

Co-administration of atenolol and chlorthalidone has little effect on the pharmacokinetics of either drug. Approximately 50% of an oral dose of atenolol and 60% of an oral dose of chlorthalidone is absorbed from the gastrointestinal tract. Atenolol is only poorly bound to plasma proteins. Chlorthalidone is 75% plasma protein bound. The T_{max} for atenolol is three hours and the T_{max} for chlorthalidone is twelve hours. Metabolism of atenolol, occurs to only a minor extent and both atenolol and pharmacologically active metabolite of atenolol is present in man but represents only 2% of the dose. This metabolite is not detected in plasma. The elimination half life of atenolol is 6-9 hours and that for chlorthalidone is approximately 50 hours.

5.3 Preclinical safety data

N/A

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Heavy magnesium carbonate
Maize starch
Gelatin
Sodium lauryl sulphate
Magnesium stearate
Hypromellose
Macrogol
Talc
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

Polypropylene tubes with low density polyethylene caps containing 30, 100, 500 or 1000 tablets.
PVdC/Al blister packs containing 28, 30 and 100 tablets.

6.6 Instructions for use and handling

None.

7 MARKETING AUTHORISATION HOLDER

Norton Waterford
IDA Industrial Estate
Cork Road
Waterford

8 MARKETING AUTHORISATION NUMBER

PA 436/30/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 October 1996
Date of last renewal: 10 October 2001

10 DATE OF REVISION OF THE TEXT

January 2002