SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-tenidone 50/12.5mg Tablets BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Atenolol 50mg and Chlortalidone 12.5mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Brownish pink, round, biconvex film-coated tablets marked CT/50 on one side and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-tenidone is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on atenolol or chlortalidone alone.

4.2 Posology and method of administration

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

Adults:

The usual maintenance dose is one tablet daily containing 50mg atenolol and 12.5mg chlortalidone. For patients who do not respond to this dose, the dosage can be increased to the 100mg atenolol and 50mg chlortalidone dose Co-tenidone.

Where necessary, another antihypertensive drug, such as a vasodilator, can be added.

Special Populations:

Elderly:

Dosage requirements are often lower in this age group.

Use in children and adolescents (< 18 years)

There is no experience of using Co-tenidone in children and adolescents. Therefore Co-tenidone should not be administered to children and adolescents.

Use in patients with renal impairment

Due to the properties of the chlortalidone component, Co-tenidone has reduced efficacy in the presence of renal insufficiency. This fixed dose combination should thus not be administrated to patients with severe renal impairment (see section 4.3).

Use in patients with hepatic impairment

Dose adjustments are not required in patients with hepatic impairment.

4.3 Contraindications

Co-tenidone should not be used in patients with any of the following:

- known hypersensitivity to atenolol and chlortalidone (or to sulphonamide derived medicinal products) or any other component of the product
- second or third degree heart block
- sick-sinus syndrome
- bradycardia
- uncontrolled heart failure
- cardiogenic shock
- hypotension
- severe peripheral arterial circulatory disturbances
- severe renal failure
- metabolic acidosis
- untreated phaeochromocytoma
- pregnancy and lactation

4.4 Special warnings and precautions for use

Due to its Atenolol component:

- although contra-indicated in uncontrolled heart failure (see section 4.3) may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha receptor mediated coronary artery vasoconstriction. Atenolol is a beta-1 selective beta-blocker; consequently the use of Co-tenidone may be considered although utmost caution must be exercised.
- although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3) Co-tenidone may also aggravate less severe peripheral arterial circulatory disturbances.
- due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.
- may mask the symptoms of hypoglycaemia, in particular, tachycardia. Beta-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels. (see Section 4.5).
- may mask the cardiovascular signs of thyrotoxicosis.
- will reduce heart rate, as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate, the dose may be reduced.
- should not be discontinued abruptly in patients suffering from ischaemic heart disease.
- may cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.
- patients with bronchospastic disease should, in general, not receive beta blockers due to increasing in airways resistance. Atenolol is a beta1-selective beta-blocker; however this selectivity is not absolute. Therefore the lowest possible dose of Co-tenidone should be used and utmost caution must be exercised. If increased airways resistance does occur, Co-tenidone should be discontinued and bronchodilator therapy (eg salbutamol) administered if necessary.
- systemic effects of oral beta-blockers may be potentiated when used concomitantly with ophthalmic beta-blockers.
- in patients with phaeochromocytoma Co-tenidone must be administered only after alfa-receptor blockade. Blood pressure should be monitored closely.
- Caution must be exercised when using anaesthetic agents with Co-tenidone. The anesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia (slower heart rate) and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Due to its chlortalidone component:

- plasma electrolyte should be periodically determined in appropriate intervals to detect possible electrolyte imbalance especially hypokalaemia and hyponatraemia
- hypokalaemia and hyponatraemia may occur. Measurement of electrolytes is recommended, especially in the older patient, those receiving digitalis preparations for cardiac failure, those taking an abnormal (low in

potassium) diet or those suffering from gastrointestinal complaints. Hypokalaemia may predispose to arrhythmias in patients receiving digitalis.

- because chlortalidone may impair glucose tolerance diabetic patients should be aware of the potential for increased glucose levels. Close monitoring of glycaemia is recommended in the initial phase of therapy and in prolonged therapy test for glucosuria should be carried out at regular intervals.
- in patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma.
- hyperuricaemia may occur. Only a minor increase in serum uric acid usually occurs but in cases of prolonged elevation, the concurrent use of a uricosuric agent will reverse the hyperuricaemia.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy

The product label will state 'Do not take this medicine if you have a history of wheezing or asthma'.

Patients with anamnestically known psoriasis should take atenolol only after careful consideration.

4.5 Interaction with other medicinal products and other forms of interaction

Due to atenolol:

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects e.g., verapamil, diltiazem can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Class I anti-arrhythmic drugs (e.g., disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be

delayed for several days after clonidine administration has stopped.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs. The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (see section 4.4).

Concomitant use of sympathomimetic agents, e.g. adrenaline, may counteract the effect of beta-blockers.

Concomitant use of prostaglandin synthetase inhibiting drugs (e.g., ibuprofen, indomethacin) may decrease the hypotensive effects of beta-blockers.

Due to chlortalidone:

The chlortalidone component may reduce the renal clearance of lithium leading to increased serum concentrations. Dose adjustments of lithium may therefore be necessary.

Due to the combination product:

Concomitant therapy with dihydropyridines e.g., nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Concomitant use of baclofen may increase the antihypertensive effect making dose adjustments necessary.

In general, beta-adrenoceptor-blocking agents should not be given concomitantly with adrenaline, amphetamines, sympathomimetic amines, ergotamine, local anaesthetic-type anti-arrhythmic agents, clonidine and calcium channel blocking agents such as nifedipine and verapamil. Reduced absorption may occur if calcium or aluminium hydroxide is administered concurrently. Calcium antagonists eg verapamil in combination with atenolol have a negative influence on contractility and atrio-ventricular conduction. Beta-blockers may enhance the effects of anti-diabetic agents and mask the warning signs of hypoglycaemia such as tremor and tachycardia (abnormal rapid heart rate)

Like other thiazide diuretics, Chlortalidone may potentiate bone marrow suppression caused by cancer chemotherapy and may impair the control of diabetes mellitus by diet and oral hypoglycaemic agents. Aminoglycoside nephrotoxicity may be potentiated.Care should be taken when using anaesthetic agents with co-tenidone; hypokalaemia can prolong the effects of tubocurarine. Also the choice of anaesthetic should be an agent with as little negative inotropic activity as possible.

4.6 Pregnancy and lactation

Pregnancy: Co-tenidone must not be given during pregnancy.

Lactation: Co-tenidone must not be given during lactation.

4.7 Effects on ability to drive and to use machinery

Use is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

In clinical studies, the possible adverse reactions are usually attributable to the pharmacological actions of its components.

The following undesirable effects, listed by body system, have been reported with the following frequencies: Very common (≥10%), common (1-9.9%), uncommon (0.1-0.9%), rare (0.01-0-09%), very rare (<0.01%), not known (cannot be estimated from available data):

Blood and lymphatic system disorders:
Rare: Purpura, thrombocytopenia, leucopenia (related to chlortalidone).

Psychiatric disorders:
Uncommon: Sleep disturbances of the type noted with other beta-blockers. Rare: Mood changes, nightmares, confusion, psychoses and hallucinations.

Nervous system disorders:
Rare: Dizziness, headache, paraesthesia.

Eye disorders:
Rare: Dry eyes, visual disturbances.
Frequency not known: choroidal effusion

Cardiac disorders:
Common: Bradycardia
Rare: Heart failure deterioration, precipitation of heart block.

Vascular disorders:
Common: Cold extremities.
Rare: Postural hypotension which may be associated with syncope, intermittent claudication may be increased if already present, in susceptible patients Raynaud's phenomenon.

Respiratory, thoracic and mediastinal disorders:
Rare: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

Gastrointestinal disorders:
Common: Gastrointestinal disturbances (including nausea related to chlortalidone).
Rare: Dry mouth.
Not known: Constipation

Hepatobiliary disorders:
Rare: Hepatic toxicity including intrahepatic cholestasis, pancreatitis (related to chlortalidone).

Skin and subcutaneous tissue disorders:
Rare: Alopecia, psoriasiform skin reaction, exacerbation of psoriasis, skin rashes.

Reproductive system and breast disorders:
Rare: Impotence.

General disorders and administration site conditions:
Common: Fatigue.

Investigations:
Common (related to chlortalidone): Hyperuricaemia, hyponatraemia, hypokalaemia, impaired glucose tolerance.
Uncommon: Elevations of transaminase levels.
Very rare: An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear.

Musculoskeletal and connective tissue disorders:
Not known: Lupus-like syndrome

Discontinuation of Co-tenidone should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock. The possible use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be countered with atropine 1-2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effects could be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

Excessive diuresis should be countered by maintaining normal fluid and electrolyte

balance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Beta-blocking agents, selective, and thiazides-
ATC code: C07BB03

Co-tenidone tablets combines the antihypertensive activity of two agents, a beta-blocker (atenolol) and a diuretic (chlortalidone).

Atenolol

Atenolol is $beta_1$-selective (i.e. acts preferentially on $beta_1$-adrenergic receptors in the heart). Selectivity decreases with increasing dose.

Atenolol is without intrinsic sympathomimetic and membrane-stabilising activities and, as with other beta ⁻ adrenoceptor blocking drugs, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

As with other beta-blockers, the mode of action in the treatment of hypertension is unclear.
It is unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Atenolol is effective and well-tolerated in most ethnic populations. Black patients respond better to the combination of atenolol and chlortalidone, than to atenolol alone.

The combination of atenolol with thiazide-like diuretics has been shown to be compatible and generally more effective than either drug used alone.

Chlortalidone

Chlortalidone, a monosulfonamyl diuretic, increases excretion of sodium and chloride. Natriuresis is accompanied by some loss of potassium. The mechanism by

which chlortalidone reduces blood pressure is not fully known but may be related to the excretion and redistribution of body sodium.

5.2 Pharmacokinetic properties

***Atenolol*:** Absorption of atenolol following oral doing is consistent but incomplete (approximately 40-50%) with peak plasma concentrations occuring 2-4 hours after dosing. The Atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered. The Plasma half-life is 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination. Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

Chlortalidone:

Absorption of chlortalidone following oral dosing is consistent but incomplete (approximately 60%) with peak plasma concentrations occurring about 12 hours after dosing. The chlortalidone blood levels are consistent and subject to little variability. The plasma half-life is about 50 hours and the kidney is the major route of elimination. Plasma protein binding is high (approximately 75%).

Co-administration of chlortalidone and atenolol has little effect on the pharmacokinetics of either.

Co-tenidone is effective for at least 24 hours after a single oral daily dose. This simplicity of dosing facilitates compliance by its acceptability to patients.

5.3 Preclinical safety data

Atenolol and chlortalidone are drugs on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose (PH101)
Povidone K30
Sodium starch glycollate (Type A)
Magnesium stearate

Film Coat
Hydroxypropylmethylcellulose (HPMC) 2910 5cp (E464)
Titanium dioxide (E171)
Iron oxide red (E172)
Macrogol
Iron oxide yellow (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister packs of white opaque PVC film (250 micron) and hard tempered aluminium foil (20 micron). Pack sizes: 28, 30, 56, 60.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None stated.

7 MARKETING AUTHORISATION HOLDER

Medreich PLC,
Warwick House,
Plane Tree Crescent,
Feltham TW13 7HF, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 21880/0102

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 April 2002

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03/02/2026