SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Co-Tenidone 50 mg/12.5 mg Tablets BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg Atenolol and 12.5 mg chlorthalidone.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablet.
Brown, film-coated, round, biconvex tablets, engraved: '3H2' on one side, 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 chlorthalidone alone.
Particularly suited to the older patient. The combination of low effective doses of a beta-blocking drug and diuretic may be suitable to older patients where full doses of both may be considered inappropriate.

4.2. Posology and Method of Administration

Posology
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 of Co-Tenidone 50 mg/12.5mg is one tablet daily. For patients who do not respond adequately to Co-Tenidone 50 mg/12.5mg, the dosage may be increased to 1 tablet of Co-Tenidone 100 mg/25 mg .

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

Special Populations:

Use in children and adolescents (< 18 years)

The safety and efficacy of Co-Tenidone in children and adolescents aged less than 18years has not yet been established. Therefore Co-Tenidone should not be administered to children and adolescents.

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 of Co-Tenidone. Where hypertensive control is not achieved, addition of a small dose of a third agent, e.g. a vasodilator, may be appropriate.

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.

Method of administration
For oral administration

4.3. Contra-indications

- Hypersensitivity to the active substances (or to sulphonamide derived medicinal products) or to any of the excipients listed in section 6.1
- Co-Tenidone tablets are contra-indicated in patients with a second or third degree heart block.
- They are not to be used in patients with cardiogenic shock
- Hypotension
- Bradycardia
- Severe peripheral arterial circulatory disturbance
- Severe renal failure
- Metabolic acidosis
- Uncontrolled heart failure
- Untreated phaeochromocytoma
- Sick sinus syndrome
- Co-Tenidone should not be given during pregnancy or lactation.

4.4 Special warnings and precautions for use

Due to its beta-blocker component:

- Although beta-adrenoceptor blockers are contraindicated in uncontrolled heart failure, (see section 4.3) they 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.

- Co-Tenidone has a negative effect on conduction time, so caution is required when treating patients with first degree heart block.

- May modify warning signs of hypoglycaemia as tachycardia, palpitation and sweating

- May mask the cardiovascular signs of thyrotoxicosis.

- Beta-adrenoceptor blocking drugs 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.

- In patients suffering from ischaemic heart disease, as with other beta-blocking agents, treatment should not be discontinued abruptly.

- Treatment with Co-Tenidone 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 increase in airways resistance. Atenolol is a beta-1-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 (e.g. salbutamol) administered if necessary.

- Systemic effects of oral beta-blockers may be potentiated when used concomitantly with ophthalmic beta-blockers.

- In patients with pheochromocytoma Co-Tenidone must be administered only after alpha-receptor blockade. Blood pressure should be monitored closely.

- Caution must be exercised when using anaesthetic agents with Co-Tenidone. The anaesthetist 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 and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Due to its chlorthalidone 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 chlorthalidone 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.

- The label will state - do not take this medicine if you have a history of wheezing or asthma.

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

Excipient(s)

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Due to atenolol:
Concurrent use of alcohol may increase the hypotensive effects of beta-adrenoceptor blocking agents.

As with all beta-adrenoceptor blocking agents, when used concurrently with insulin and oral antidiabetic drugs, Co-Tenidone may enhance the hypoglycaemic effect.

In most patients it is not necessary to withdraw beta-adrenoceptor blocking drugs prior to surgery. However, caution must be exercised when using anaesthetic agents with Co-Tenidone. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-adrenoceptor blocking drugs with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

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 (eg, disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Digitalis glycosides used concomitantly with beta-adrenoceptor blockers may increase atrio-ventricular 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 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 chlorthalidone:

The chlorthalidone 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.

4.6. Fertility, pregnancy and lactation

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

Breast-feeding: Co-Tenidone must not be given during lactation.

4.7 Effects on ability to drive and use machines

Co-Tenidone has no or negligible influence on the ability to drive and use machines. However, it should be taken into account that ccasionally 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.

List of adverse reactions

The frequencies of adverse events are ranked according to the following: 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).

Blood and lymphatic system disorders:

Rare: Purpura, thrombocytopenia, leucopenia (related to chlorthalidone).

Immune system disorders

Anaphylactic reactions have been reported.

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 disturbance

Not known: Choroidal effusion (due to chlortalidone)

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 chlorthalidone).

Rare: Dry mouth

Not known: Constipation

Hepatobiliary disorders:

Rare: Hepatic toxicity including intrahepatic cholestasis, pancreatitis (related to chlorthalidone).

Skin and subcutaneous tissue disorders:

Rare: Alopecia, psoriasiform skin reaction, exacerbation of psoriasis, skin rashes.

Musculoskeletal and connective tissue disorders:

Not known: Lupus-like syndrome.

Reproductive system and breast disorders:

Rare: Impotence.

General disorders and administration site conditions:

Common: Fatigue.

Investigations:

Common (related to chlorthalidone): 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.

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 website at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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: B Beta blocking agents, selective, and other diuretics , ATC Code: CO7C

Co-Tenidone combines the antihypertensive effects of the cardio-selective beta-blocker atenolol and the diuretic chlorthalidone.

Atenolol is $beta_1$-selective (i.e. it 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 it is therefore contra-indicated in uncontrolled heart failure).

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.

As with other beta-adrenoceptor blocking drugs, the mode of action in the treatment of hypertension is unclear.

Chlorthalidone, a monosulfonamyl diuretic, increases excretion of sodium and chloride. Natriuresis is accompanied by some loss of potassium. The mechanism by which chlorthalidone reduces blood pressure is not fully known but may be related to the excretion and redistribution of body sodium.

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

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

5.2. Pharmacokinetic Properties

Atenolol

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40-50%) with peak plasma concentrations occurring at 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 approximately 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 also low (approximately 3%).

Chlorthalidone

Absorption of chlorthalidone following oral dosing is consistent but incomplete (approximately 60%) with peak plasma concentrations occurring about 12 hours after dosing. The chlorthalidone 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 atenolol and chlorthalidone 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

Preclinical information has not been included because the safety profile of Co-Tenidone has been established after many years of clinical use. Please refer to section 4.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Tablet core:
Magnesium carbonate
Maize starch
Povidone (E1201)
Sodium starch glycollate (Type A)
Magnesium stearate (E572).

Coating:
Hypromellose (E464)
Purified talc (E553b)
Polyethylene glycol (E1520)
Yellow, red and black iron oxides (E172)
Titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

36 months.

6.4. Special Precautions for Storage

Store in a cool dry place at or below 25°C. Protect from light.

6.5. Nature and Contents of Container

HDPE or polypropylene containers with caps or child resistant closures in packs of 28, 30, 50, 56, 60, 100, 250, 500 and 1000 tablets.

Blister strips in packs of 10, 20, 28, 30, 56, 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6. Instruction for Use/Handling

Not applicable.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/0736

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

24.02.09

10. DATE OF (PARTIAL) REVISION OF THE TEXT

20/09/2022

POM