SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Co-tenidone 100/25mg Film- Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Atenolol 100mg
Chlortalidone 25.00mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Brownish pink, round, biconvex film-coated tablets marked CTE 100 on one side and CP on the other.

4.1 Therapeutic indications

The management of hypertension, particularly suited to older patients.

4.2 Posology and method of administration

Posology

Adults:

One tablet daily.

Elderly:

One tablet daily. The elderly 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. Where hypersensitive control is not achieved, addition of a small dose of a third agent e.g. as a vasodilator, may be appropriate.

Paediatric population:

The use of co-tenidone is not recommended in children. The safety and efficacy of co-tenidone in children has not yet been established.

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 administered to patients with severe renal impairment (see section 4.3).

Method of administration
Oral administration.

4.3 Contraindications

Co-tenidone should not be used in the following:

- hypersensitivity to the active substances (or to sulphonamide derived medicinal products) or to any of the excipients listed in section 6.1
- bradycardia
- cardiogenic shock
- hypotension
- metabolic acidosis
- severe peripheral arterial circulatory disturbances
- second- or third-degree heart block
- sick sinus syndrome
- untreated phaeochromocytoma
- severe renal failure
- uncontrolled heart failure

Co-tenidone tablets must not be given during pregnancy or lactation.

4.4 Special warnings and precautions for use

Due to its beta-blocker component Co-tenidone tablets:

- although contraindicated 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 modify warning signs of hypoglycaemia as tachycardia, palpitation and sweating. 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.

- may cause a hypersensitivity reaction including angioedema and urticaria

- 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.

  The label and patient information leaflet for this product state the following warning: “Do not take this medicine if you have a history of wheezing or asthma.”

- 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 alfa-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 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.

- impaired glucose tolerance may occur and 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 carries 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.

- Co-tenidone should be used with caution in patients with a predisposition to uricaemia or gout since chlorthalidone may cause a rise in serum uric acid levels. Prolonged elevation can be corrected by the use of a uricosuric agent.

- 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.

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

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 a potentiating effect on atrial-conduction time and induce negative inotropic effect.

Digitalis glycosides, in association with beta-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 (epinephrine), may counteract the effect of beta-blockers.

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

Caution must be exercised when using anaesthetic agents with Co-tenidone tablets (see section 4.4).

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).

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.

Concomitant use with insulin and oral antidiabetic drugs may lead to the intensification of the blood sugar lowering effects of these drugs.

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

Fertility:
No data on fertility available.

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Tabulated list of adverse reactions

Co-tenidone tablets were well tolerated in clinical studies, the undesired events reported are usually attributable to the pharmacological actions of its components.

The following undesired events, listed by body system, have been reported with the following frequencies: 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 available data):

System Organ Class	Frequency	Adverse Drug Reaction
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
	Not known	Depression
Eye disorders	Rare	Dry eyes, visual disturbances
	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
	Not known	Hypersensitivity reactions, including angioedema and urticaria
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 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

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

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: 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 and 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 may be countered by atropine 1-2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10mg intravenously. If required, 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 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 effect, 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-blocker 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective, and other diuretics, ATC code: C07C B03.

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-blockers, 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 dosing is consistent but incomplete (approximately 40-50%) with peak plasma concentrations occurring 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 about 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%).

Atenolol crosses the placenta and enters the breast milk.

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%).

Coadministration of chlortalidone and atenolol has little effect on the pharmacokinetics of either.

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

Most of the absorbed dose is bound to red cell carbonic anhydrase.

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.

6.1 List of excipients

Maize starch
Calcium hydrogen phosphate
Microcrystalline cellulose (PH101)
Povidone K30
Sodium starch glycollate
Magnesium stearate
Purified water

Film Coat

Opadry OY-6954

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25ºC.
Store in the original package in order to protect from light and moisture.

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

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8 MARKETING AUTHORISATION NUMBER(S)

PL 29831/0056

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