Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atecor CT 50 mg/12.5 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50mg of atenolol and 12.5mg of chlortalidone.

Excipients with known effect:
Each tablet contains 1.8mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, round, biconvex, film-coated tablet with a score-notch on one side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Atecor-CT tablets are indicated for the treatment of hypertension. The combination product may be suitable for use when satisfactory control of arterial blood pressure cannot be obtained with either a diuretic or a beta-blocking agent used 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.

Posology:

Adults
The usual maintenance dose of Atecor-CT 50 mg/12.5 mg is one tablet daily. There is little or no further fall in blood pressure with increased dosage, and where necessary, another antihypertensive drug, such as a vasodilator, can be added.
Patients can be transferred directly to Atecor-CT 50 mg/12.5 mg tablets from other antihypertensive treatments, with the exception of clonidine (see section 4.4).

Older people
Dosage requirements are often lower in this age group.

Paediatric population
Children and Adolescents (<18 years)
There is no paediatric experience with Atecor-CT tablets; therefore, this preparation is not recommended for children.

Renal Impairment
Due to the properties of the chlortalidone component, Atecor-CT tablets 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).

Hepatic Impairment
Dose adjustments are not required in patients with hepatic impairment.

Method of administration:
Oral

4.3 Contraindications

Atecor-CT tablets should not be used in patients with any of the following:
- Known hypersensitivity to atenolol and chlortalidone (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
- Uncontrolled heart failure
- Treatment with intravenous verapamil in the previous 48 hours
- Hypokalaemia
- Precoma associated with hepatic, renal or Addison's disease
- Severe renal failure
- Digitalis intoxication
- Pregnancy and lactation

4.4 Special warnings and precautions for use

Due to its beta-blocker component:

- Although contra-indicated in uncontrolled heart failure (see section 4.3) Atecor-CT 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 Atecor-CT may be considered although utmost caution must be exercised.

- Although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3), Atecor-CT 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 the warning signs of hypoglycaemia as tachycardia, palpitation and sweating.

- May mask the cardiovascular signs of thyrotoxicosis.

- May mask the symptoms of thyrotoxicosis and of hypoglycaemia by inhibition of sympathetic nervous system. The effects of hypoglycaemic agents may be increased, but to a lesser extent than the non-cardioselective beta-blockers.

- Will reduce heart rate, as a result of its pharmacological action. In the rare instances that symptoms may be attributable to the slow heart rate, the dose may be reduced.

- Should not be discontinued abruptly in patients suffering from ischaemic heart disease since sudden withdrawal of beta-adrenoceptor blocking agents may result in increased frequency or severity of anginal attacks.

- 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 (epinephrine) 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 Atecor-CT should be used and utmost caution must be exercised. If increased airways resistance does occur, Atecor-CT should be discontinued and bronchodilator therapy (eg salbutamol) administered if necessary. The beta blocker should only be used with caution in patients with a family history of asthma.

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

- In patients with phaeochromocytoma must be administered only after alfareceptor blockade. Blood pressure should be monitored closely.

- Caution must be exercised when using anaesthetic agents with Atecor-CT. 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. The metabolic effects of chlortalidone are dose-related and, at the low dose contained in Atecor-CT, are unlikely to be troublesome.

- Atecor-CT is associated with only minor changes in potassium status. Total body potassium is unaltered on chronic therapy, and changes in serum potassium are minor and probably clinically unimportant. Thus, in cases of uncomplicated hypertension, concurrent potassium supplements should be unnecessary.

- 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 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 or acute gout 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 initial treatment of severe malignant hypertension should be so designed as to avoid sudden reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:
Sulphonamide or sulphonamide 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 activity 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 for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

Atecor-CT contains lactose and sodium

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

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

4.5 Interaction with other medicinal products and other forms of interactions

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.

The concomitant administration of this preparation with the cardiac glycosides, (digitalis glycosides may increase atrioventricular conduction time) or non-depolarizing muscle relaxants may necessitate adjustment of the dosage of those drugs.

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), noradrenaline (norepinephrine) and isoprenaline may counteract the effect of betablockers.

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

Caution must be exercised when using anaesthetic agents with Atecor-CT (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.

Adjustment of the dosage of hypoglycaemic agents may be necessary if given with uncontrolled or ‘brittle’ diabetes mellitus.

Due to 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.

Adrenergic-neurone blocking agents such as guanethidine, reserpine, diuretics and other antihypertensive agents, including the vasodilator group, will have an additive effect on the antihypertensive action of the drug.

4.6 Fertility, pregnancy and lactation

Pregnancy
Atecor-CT must not be given in pregnancy.

Breast-feeding
Atecor-CT must not be given during lactation.

4.7 Effects on ability to drive and use machines

The use of Atecor-CT 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

Atecor-CT is well tolerated. In clinical studies, the undesired events reported 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 (≥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: Thrombocytopenia, purpura 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.

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.

Discontinuance of Atecor-CT should be considered if, according to clinical judgment, 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 HPRA Pharmacovigilance; website: www.hpra.ie.

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 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

ATC Code: Beta blocking agents.
C07CB03 Beta blocking agents, selective and other diuretics

Atecor-CT combines the antihypertensive activity of two agents, a beta-adrenergic receptor blocking agent (atenolol) and a diuretic (chlortalidone).

Atenolol:
Atenolol is beta1-selective (i.e. acts preferentially on beta1-adrenergic receptors in the heart). Selectivity decreases with increasing dose.

It has no intrinsic sympathomimetic activity and no membrane stabilising activity. Because of their inotropic effects, beta-blockers should be avoided in uncontrolled heart failure.
Atenolol reduces raised blood pressure by an unknown mechanism and also inhibits exercise-induced tachycardia and decreases plasma renin concentrations and free fatty acids.

Atenolol is the most cardioselective of the available beta-blockers in that it produces significantly less antagonism of the beta2-effects. In addition, and in contrast to the non-selective agents, atenolol preserves the beta2-bronchodilatory actions of inhaled isoprenaline. Furthermore prolongation of insulin-induced hypoglycaemia is less unlikely to happen with cardioselective atenolol and at a daily dose of 50mg no changes in plasma lipids are observed.

Atenolol is hydrophilic and relatively low concentrations are found in brain tissue leading to a very low incidence of CNS-related side-effects in contrast with lipophilic beta-blockers.

Atenolol is effective and well-tolerated in most ethnic populations although the responses may be less in black patients.

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.

Chlortalidone:
Chlortalidone is a benzothiadiazine derivative with long-acting efficacy.

Thiazides directly act at the kidneys by increasing sodium chloride and thus related fluid excretion. Their clinically relevant main target site is the distal tubule. There they inhibit the electroneutral NaCl-co-transport in the luminal cell membrane. Potassium and magnesium are excreted to an increased extent, calcium to a lower extent.

Chlortalidone is a monosulfonamyl diuretic, which differs chemically from thiazide diuretics in that a double ring system is incorporated in its structure. It is an oral diuretic with prolonged action and low toxicity.

The diuretic effect of the drug occurs within 2 hours of an oral dose and continues for up to 72 hours. It produces copious diuresis and greatly increased excretion of sodium chloride.

At maximal therapeutic dosage, chlortalidone is approximately equal in its diuretic effect to comparable maximal therapeutic doses of benzothiadiazine diuretics.

The site of action appears to be the cortical dilating segment of the ascending lines of Henle's loop of the nephron.

Due to high chlortalidone doses, bicarbonate can increasingly be excreted as a consequence of inhibition of the carbonic anhydratase, so that urine is alkalised.

The saluretic or diuretic effect of chlortalidone is not essentially influenced by acidosis or alkalosis.

During long-term therapy with chlortalidone, calcium excretion via the kidney is reduced, so that hypercalcaemia may result from.

The anti-hypertensive effects of Atecor-CT tablets have been shown to be greater than those of atenolol or chlortalidone given alone. In patients with more severe hypertension, Atecor-CT may be administered with other anti-hypertensives such as vasodilators.

5.2 Pharmacokinetic properties

The effect of ATECOR-CT tablets following a single oral dose is sustained for at least twenty-four hours.

Atenolol:
In man absorption of atenolol following an oral dose of Atecor-CT tablets is rapid and consistent but incomplete. Approximately 35% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the faeces. Peak atenolol blood levels of approximately 300ng/ml are reached between 2 and 4 hours after ingestion and these vary only three-fold between subjects. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

Atenolol is not significantly bound to plasma proteins and, in spite of this, and because of its high degree of hydrophilicity it has a low volume of distribution of about 0.7 l/kg. There is a very low concentration of atenolol in the brain. Atenolol has been shown to cross the placental barrier and it accumulates in breast milk without detriment to the neonate.

Atenolol is eliminated by renal excretion with a half-life of 5-7 hours which is not altered after chronic administration but does alter in renal insufficiency closely correlated with glomerular filtration rate. Accumulation of atenolol may occur in patients with a glomerular filtration rate less than 15 ml/min.

Atenolol is removed by haemodialysis.

The degree of beta-blockade is linearly related to the logarithm of the atenolol blood concentration but there is little correlation with anti-hypertensive effects.

Co-administration with chlortalidone in Atecor-CT tablets does not affect the systemic availability of atenolol.

Chlortalidone:
In man absorption of chlortalidone following an oral dose of Atecor-CT is relatively slow but consistent. Peak chlortalidone blood levels of approximately 950ng/ml are reached between 8 and 16 hours after ingestion and these vary only four-fold between subjects. There is no significant hepatic metabolism of chlortalidone.

Approximately 75% of a chlortalidone dose is bound to plasma proteins and 58% of the drug is bound to albumin. This is caused by an increased affinity of chlortalidone for erythrocyte carbonic anhydrase.

An average volume of distribution of 7.6 l/kg has been reported.

Chlortalidone has been shown to cross the placental barrier and to accumulate in breast milk without detriment to the neonate.

Chlortalidone is eliminated unchanged by renal excretion with a half-life of the order of 60 hours which is not altered after chronic administration but does alter in renal insufficiency.

Co-administration with atenolol in Atecor-CT tablets does not affect the systemic availability of chlortalidone.

5.3 Preclinical safety data

Atenolol and chlortalidone are drugs on which extensive clinical experience has been obtained.

Reproductive toxicology:
Both substances pass the placenta. Atenolol reaches similar concentrations in foetal and maternal blood.
For chlortalidone insufficient experience is available regarding administration in humans. A study involving 22 women exposed in early pregnancy showed evidence of an increased risk for malformations.
For atenolol, insufficient experience is available regarding exposure during early pregnancy. Neonates of women treated with atenolol during pregnancy showed a markedly lower birth weight in several studies than neonates of untreated mothers or than neonates whose mothers were treated with other beta-blockers, respectively with the severity of the maternal disease also being possibly a causal factor. Lowered heart rate in exposed foetuses or neonates, respectively, was also observed. One case of beta-blockage in a neonate has been described.
Both substances pass into mother's milk, atenolol accumulates in milk. Due to the high concentrations of both active agents, a pharmaceutical effect is to be expected in the breastfed infant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Maize Starch
Magnesium Carbonate, heavy
Sodium Laurilsulfate
Hyprolose
Sodium Starch Glycolate (Type A)
Magnesium Stearate

Film-Coating
Lactose Monohydrate
Hypromellose
Titanium Dioxide (E171)
Macrogol 4000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 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

Aluminium/Polypropylene blister pack. Tablets are available in packs of 30 and sample packs of 10.

Not all pack sizes may be marketed.

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

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/020/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 November 1999

Date of last renewal: 26 November 2009

10 DATE OF REVISION OF THE TEXT

August 2020