

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Atenetic 100 mg/25 mg Film-coated Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

<u>Active constituents</u>	<u>mg/tablet</u>
Atenolol	100
Chlortalidone	25

For full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

White, biconvex, film-coated tablet embossed with 'AC 125' on one side and 'G' on the reverse.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Atenetic 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 maybe considered in patients whose blood pressure is not adequately controlled.

#### Posology

##### **Adults:-**

The recommended maintenance dose is one 50mg/12.5mg tablet daily. For patients whodo not respond adequatelyto Atenetic 50mg/12.5mg, the dosage maybe increased to one tablet of Atenetic 100mg/25mg

Where necessary, another antihypertensive drug, such as a vasodilator, can be added. Patients can be transferred directly to Atenetic 100 mg/25 mg Film-coated Tablets from other hypertensive treatments, with the exception of clonidine (see section 4.5).

##### **Special populations:**

###### *Use in older people:*

Dosage requirements are often lower in this age group.

###### *Paediatric population (children and adolescents < 18 years of age)*

The safety and efficacy of atenolol/chlortalidone in children and adolescents less than 18 years have not been established. Therefore, Atenetic is not recommended in children and adolescents.

###### *Use in patients with renal impairment:*

Due to the properties of the chlortalidone component, Atenetic 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 use

**4.3 Contraindications**

Atenetic should not be used in patients with any of the following:

- Known hypersensitivity to the active substances (or to sulphonamide derived medicinal products) or to any of the excipients listed in 6.1
- Second or third degree heart block
- bradycardia
- Hypotension
- Uncontrolled heart failure
- Cardiogenic shock
- Severe peripheral arterial circulatory disturbances
- Severe renal failure
- Metabolic acidosis
- Sick sinus syndrome
- Untreated phaeochromocytoma
- Hypokalaemia
- Precoma associated with hepatic, renal or Addison's disease
- Digitalis intoxication
- Treatment with intravenous verapamil in the previous 48 hours

Atenetic must not be given during 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) Atenetic may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- Atenetic 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 Atenetic may be considered although utmost caution must be exercised.
- although contraindicated in severe peripheral arterial circulatory disturbances (see section 4.3) Atenetic 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.
- may mask the cardiovascular signs of thyrotoxicosis.
- may mask the signs 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 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, since sudden withdrawal of beta-adrenoceptor blocking agents may result in increased frequency or severity of angina 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 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 beta<sub>1</sub>-selective beta-blocker, however this selectivity is not absolute. Therefore the lowest possible dose of Atenetic should be used and utmost caution must be exercised. If increased airways resistance does occur, Atenetic 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 Atenetic must be administered only after alpha-receptor blockade. Blood pressure should be monitored closely.
- caution must be exercised when using anaesthetic agents with Atenetic. 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.
  - 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 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 metabolic effects of chlortalidone are dose-related and, at the low dose contained in Atenetic, are unlikely to be troublesome. Atenetic are 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.

1. 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

Adjustment of the dosage of hypoglycaemic agents may be necessary if given to patients with uncontrolled or 'brittle' diabetes mellitus.

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.

Atenetic should only be used with caution in patients with controlled congestive cardiac failure or with a family history of

asthma. Evidence of recrudescence of either condition should be regarded as a signal to discontinue therapy.

Atenetic 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 interactions**

##### **Due to atenolol:**

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects eg, 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 a trial-conduction time and induce negative inotropic effect.

Digitalis glycosides, in association with beta-blockers, may increase a trioventricular 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), noradrenaline (norepinephrine) and isoprenaline may counteract the effect of beta-blockers.

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

Caution must be exercised when using anaesthetic agents (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.

Potassium depletion may be dangerous in patients receiving digitalis.

##### **Due to the combination product:**

Concomitant therapy with dihydropyridines eg, 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.

Administration in conjunction with other anti hypertensives may require adjustment of dosage particularly in the case of catecholamine depleting agents such as reserpine or guanethidine.

Neurone blocking agents such as guanethidine, reserpine, diuretics and other anti hypertensive agents, including the vasodilator group, will have an additive effect on the hypotensive action of the drug.

The concomitant administration of this preparation with the cardiac glycosides, or non-depolarising muscle relaxants may necessitate adjustment of the dosage of those drugs.

#### **4.6 Fertility, pregnancy and lactation**

Pregnancy

Atenetic must not be given during pregnancy.

Breast-feeding

Atenetic must not be given during breast-feeding.

Fertility

No data on fertility available.

**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 operate machinery. However, it should be taken into account that occasionally dizziness and fatigue may occur.

**4.8 Undesirable effects**

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

The following undesirable effects, listed by system organ class, have been reported with the following frequencies: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $1/10$ ), uncommon ( $\geq 1/1,000$  to  $1/100$ ), rare ( $\geq 1/10,000$  to  $1/1,000$ ), very rare ( $< 1/10,000$ ), 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.

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, psoriasisiform 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 Atenetic 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 HPRC Pharmacovigilance, website: [www.hpra.ie](http://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 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 may be countered by maintaining normal fluid and electrolyte balance.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Beta-blocking agents, selective and other diuretics; ATC Code: C07CB03

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

### Mechanism of action

#### **Atenolol**

Atenolol is beta<sub>1</sub>-selective (i.e. acts preferentially on beta<sub>1</sub>-adrenergic receptors in the heart). Selectivity decreases with increasing dosage.

Atenolol is without intrinsic sympathomimetic activity and membrane stabilising properties. 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 beta<sub>2</sub>-effects. In addition, and in contrast to the non-selective agents, atenolol preserves the beta<sub>2</sub>-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 50 mg 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.

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 monosulfonyl 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 lasts for 72 hours. It produces copious diuresis and greatly increased excretion of sodium chloride.

At maximal therapeutical 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 limb of Henle's loop of the nephron.

### Clinical efficacy and safety

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 antihypertensive effects of combination of atenolol and chlortalidone has been shown to be compatible and generally more effective than either drug used alone. In patients with more severe hypertension, Atenetic may be administered with other hypertensives such as vasodilators.

## **5.2 Pharmacokinetic properties**

### **Atenolol**

#### Absorption

Oral dose of atenolol appears to be incompletely but rapidly and consistently absorbed from the gastrointestinal tract (approximately 35). Peak atenolol blood levels of approximately 300 ng/ml are reached between 2 and 4 hours after ingestion and these vary only three-fold between subjects.

#### Distribution

Atenolol penetrates tissues poorly due to its high degree of hydrophilicity it has a low volume of distribution of about 0.7 l/kg. Atenolol concentration in brain tissue is low. Atenolol has been shown to cross the placental barrier and it accumulates in breast milk without detriment to the neonate.

### Biotransformation

There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered. The degree of beta-blockade is linearly related to the logarithm of the atenolol blood concentration but there is little correlation with antihypertensive effects.

### Elimination

The remainder of unabsorbed atenolol is being excreted unchanged in the faeces.

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.

## **Chlortalidone**

### Absorption

Oral dose of chlortalidone is consistently absorbed but relatively slow. Peak chlortalidone blood levels of approximately 950 ng/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..

### Distribution

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.

### Biotransformation

There is no significant hepatic metabolism of chlortalidone.

### Elimination

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.

## **Atenolol/chlortalidone**

Co-administration of atenolol and chlortalidone does not affect the systemic availability of either.

## **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**

Magnesium carbonate (heavy)  
Sodium laurilsulfate  
Povidone K29/32  
Pregelatinised starch  
Maize starch  
Stearic acid  
Magnesium stearate  
Sodium starch glycolate (Type A)  
Hypromellose  
Macrogol 400  
Titanium dioxide (E171)

Talc

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

5 years.

## **6.4 Special precautions for storage**

Do not store above 25°C.

## **6.5 Nature and contents of container**

PVC/aluminium foil blister packs of 28 and 98.  
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**

McDermott Laboratories Ltd., T/A Gerard Laboratories  
35/36 Baldoyle Industrial Estate  
Grange Road  
Dublin 13  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0577/194/002

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 21<sup>st</sup> May 1991  
Date of last renewal: 21<sup>st</sup> May 2006

## **10 DATE OF REVISION OF THE TEXT**

July 2020