Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atenetic 100 mg/25 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active constituents	mg/tablet
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:

*Useinolder 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).

Usein patientswithhepatic impairment:
Dose adjustments are not required in patients with hepatic impairment.

Method of administration
For oral use

4.3 Contraindications

Atenetic shouldnotbe used in patients with anyof thefollowing:

- 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-blockercomponent:

• although contra-indicated in uncontrolled heart failure (see section 4.3) Atenetic maybe used in patients whose signs ofheart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

• Atenetic mayincrease the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alphareceptor mediated coronary artery vasoconstriction. Atenolol is a beta-1 selective beta-blocker; consequently the use of Atenetic maybe 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-cardio selective beta-blockers.

• will reduce heart rate, asa result of its pharmacological action. In the rareinstances when a treated patient develops symptoms which maybe attributable to a slow heart rate, the dose maybe 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 maybe unresponsive to the usual doses of adrenaline used to treat the allergicreactions.

• patients with bronchospastic disease should, in general, not receive beta blockers due to increasing in airways resistance. Atenolol is a $beta_1$-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(egsalbutamol) 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 reflextachycardia 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 inpotassium) diet or those suffering from gastrointestinal complaints. Hypokalaemia may predispose to arrhythmiasin 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. Onlya minor increase in serum uric acid usually occurs but in cases of prolonge delevation, 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 100mg/25 mg Film-coated Tablets, 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.

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.

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, diltiazemcan lead toan exaggeration of these effects particularly in patients with impaired ventricular function and/or sino-atrial oratrio-ventricular conduction abnormalities. This may resultin 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 chlortalidonecomponent 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 dihydropyridineseg. nifedipine, may increase the risk of hypotension, and cardiac failure ma yoccur 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 concombitant 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 (≥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):

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: Dryeyes, visual disturbances.

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

Vascular disorders:
Common: Cold extremities.
Rare: Postural hypotension which maybe associated with syncope, intermittent claudication maybe increased if already present, insusceptible 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: Drymouth.
Not known: Constipation

Hepatobiliarydisorders:
Rare: Hepatictoxicity 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 andbreast disorders:
Rare: Impotence.

General disordersand administration site conditions:
Common: Fatigue.

Investigations:
Common (related to chlortalidone): Hyperuricaemia, hyponatraemia, hypokalaemia, impaired glucosetolerance.
Uncommon: Elevations of transaminase levels.
Veryrare: An increase in ANA (AntinuclearAntibodies) 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

General treatment shouldi nclude: close supervision, treatment in an intensive care ward, the use of gastric lavage,a ctivated charcoal and alaxative to prevent absorption of any drug still present in the gastrointestinal tract, the use of plasma orplasma substitutes to treat hypotension and shock. The possible use of haemodialysis or haemoperfusion maybe 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 beused to treat hypotension and acutecardiac insufficiency. It is likely that these doses would be inadequateto 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 there quired response according to the clinical condition of the patient.

Bronchospasm can usually bereversed 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$_1$-selective (i.e. acts preferentially on beta$_1$-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$_2$-effects. In addition, and in contrast to the non-selective agents, atenolol preserves the beta$_2$-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 ancilliary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Chlortalidone
Chlortalidone is a monosufonyl 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 lines 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 chlortalidonedoes 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: 21st May 1991
Date of last renewal: 21st May 2006

10 DATE OF REVISION OF THE TEXT

December 2018