Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atenetic 50 mg/12.5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active constituents	mg/tablet
Atenolol	50
Chlortalidone	12.5

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, biconvex, film-coated tablet, embossed with 'AC 62' 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 who do not respond adequately to Atenetic 50mg/12.5mg, the dosage maybe increased to one tablet of Atenetic 100mg/25mg.
Where necessary, another anti hypertensive drug, such as a vasodilator, can be added.

Special populations:

Paediatric population (children and adolescents < 18 years of age)
The safety and efficacy of atenolol/chlortalidone in children less than 18 years has 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, Ateneticshas reduced efficacyin 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.
- Severe bradycardia.
- Hypotension
- Uncontrolled or digitalis/diuretic refractory heart failure.
- Cardiogenic shock.
- Severe peripheral arterial circulatory disturbances.
- Severe renal failure.
- Metabolic acidosis.
- Sick sinus syndrome.
- Untreated phaeochromocytoma.
- Treatment with intravenous verapamil within the previous 48 hours.
- Hypokalaemia.
- Precoma associated with hepatic, renal or Addison's disease.
- Digitalis intoxication.

Atenetic must not be given during pregnancy or 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. Evidence of worsening heart failure should be regarded as a signal to discontinue therapy.

• 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.

• 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$_1$-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 (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.

• 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.

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

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, diltiazemcan lead toan exaggeration of these effects particularly in patients with impaired ventricular function and/or sino-atrial oratrio-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.

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

Digitalis glycosides, in association with beta-blockers, may increase atrioventricular 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, eg adrenaline (epinephrine), nor adrenaline (no repinephrine) 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 there fore be necessary.
Adjustment of the dosage of hypoglycaemic agents may be necessary if given with uncontrolled or brittle diabetes mellitus.

Due to the combination product:

Concomitant therapy with dihydropyridineseg, 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 hypotensive action of the drug.

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 or 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 1/1000), 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 andmediastinaldisorders:
Rare: Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints.

Gastrointestinaldisorders:
Common: Gastrointestinal disturbances (including nausea related to chlortalidone).
Rare: Dry mouth.
Not known: Constipation

Hepatobiliarydisorders:
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 andbreast disorders:
Rare: Impotence.

General disordersand 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.

4.9 Overdose

The symptoms of overdosage may include bradycardia, hypotension, acutecardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastriclavage, activated charcoal and alaxative to prevent absorption of any drug still present in the gastro intestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock. The possible use of haemodialysis or haemoperfusion maybe considered.

Excessive bradycardia can be countered with atropine 1-2mg 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 in otropic 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 anti hypertensive activity of two agents: a beta-blocker (atenolol) and a diuretic (chlortalidone).

Mechanism of action

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

Atenolol is without intrinsic sympathomimetic activity and membrane stabilising properties 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 of atenolol in the treatment of hypertension is unclear.

It is unlikely that any additional ancillliary 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 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.
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

5.2 Pharmacokinetic properties

Atenolol
Absorption
Absorption of atenolol following oral dosing is consistent but incomplete (approximately 35-50%) with peak plasma concentrations occurring 2-4 hours after dosing. The atenolol blood levels are consistent and subject to little variability.

Distribution
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 %).

Biotransformation
There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

Elimination
The plasma half- life of about 6 hours but this may rise in severe renal impairment since the kidney is the major rote of elimination.

Chlortalidone

Absorption

Following oral dosing chlortalidone is consistently absorbed from the gastrointestinal tract (approximately 60%) with peak plasma concentrations occurring about 12 hours after dosing. The chlortalidone blood levels are consistent and subject to little variability.

Distribution
Its plasma half-life is about 50 hours has been reported to be due to its strong binding to red blood cells, of approximately 75%.

Biotransformation
There is no significant hepatic metabolism of chlortalidone.

Elimination
During long-term administration 30 to 60% has been reported to be excreted unchanged in urine.

Pharmacokinetic relationship
Co-administration of chlortalidone and atenolol has little effect on the pharmacokinetics of either.

Atenolol/Chlortalidone
Atenetic are 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

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
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Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/194/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 21st May 2006

10 DATE OF REVISION OF THE TEXT

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