SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Amlotan 5 and 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amlotan 5 mg tablets: Each tablet contains 5 mg amlodipine (as amlodipine mesilate monohydrate).
Amlotan 10 mg tablets: Each tablet contains 10 mg amlodipine (as amlodipine mesilate monohydrate).

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet
Amlotan 5 mg tablets: The tablets are white to off-white, round biconvex and embossed with "5" on one side.

Amlotan 10 mg tablets: The tablets are white to off-white, round biconvex and scored and embossed with "10" on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Essential hypertension.
Chronic stable and vasospastic angina pectoris.

4.2. Posology and method of administration

In adults
For treatment of both hypertension and angina pectoris the usual initial dose is 5 mg once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks this dose may be increased to a maximum dose of 10 mg daily (as single dose) depending on the individual patient's response.

Children with hypertension from 6 years to 17 years of age.
The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients (see section 5.1 "Pharmacodynamic Properties" and section 5.2 "Pharmacokinetic Properties)". The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

The 2.5 mg dose cannot be obtained with Amlodipine 5 mg tablets as these tablets are not manufactured to break into two equal halves. The 2.5 mg dose cannot be obtained with Amlodipine 10 mg tablets.

In the elderly
Normal dosage regimens are recommended in the elderly, however, increase of the dosage should take place with care (see Section 5.2 "Pharmacokinetic properties").

In patients with renal impairment
Amlodipine is not dialysable. In these patients amlodipine can be used in the normal dosage (see Section 5.2 "Pharmacokinetic properties")

In patients with hepatic impairment
A dosage regimen for patients with hepatic impairment has not been established, therefore amlodipine should be administered with caution (see Section 4.4 "Special warnings and precautions for use").

The tablets should be taken with a glass of water independently from meals.

4.3. Contraindications

Amlodipine is contra-indicated in patients with:

- severe hypotension
- shock, including cardiogenic shock
- hypersensitivity to dihydropyridine derivatives, amlodipine or any of the excipients
- heart failure after acute myocardial infarction (during the first 28 days)
- obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis)
- unstable angina pectoris (excluding Prinzmetal's angina)
- Pregnancy and lactation

4.4. Special warnings and special precautions for use

Amlodipine should be administered with caution to patients with low cardiac reserve. There are no data to support the use of amlodipine alone, during or within one month of myocardial infarction. The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure
Patients with cardiac failure should be treated with caution. In a long-term study including patients suffering from severe heart failure (NYHA grade III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group, but this was not indicating an aggravation of heart failure (see Section 5.1 Pharmacodynamic properties).

Use in patients with impaired hepatic function
Amlodipine's half-life is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution in these patients.

Use in elderly patients
In the elderly, increase of the dosage should take place with care (see Section 5.2 Pharmacokinetic properties).

4.5. Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on amlodipine
CYP3A4 inhibitors: A study of elderly patients has shown that diltiazem inhibits metabolism of amlodipine, probably via CYP3A4, since plasma concentration increases by approx. 50% and the effect of amlodipine is increased. It cannot be excluded that stronger inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) increase the plasma concentration of amlodipine to a greater extent than diltiazem. Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors.

CYP3A4 inducers: There is no information available on the effect of CYP3A4 inducers (i.e. rifampicin, St. John's wort) on amlodipine. Co-administration may lead to reduced plasma concentration of amlodipine. Caution should be exercised in combination of amlodipine and CYP3A4 inducers.

Consumption of grapefruit/ grapefruit juice should be avoided while taking amlodipine. The intake of grapefruit juice may result in increased plasma amlodipine concentrations, which may enhance the blood pressure lowering effects of amlodipine. This interaction has been observed with other dihydropyridine calcium antagonists and represents a class effect.

In clinical interaction studies cimetidine, aluminium/magnesium (antacid) and sildenafil did not affect the pharmacokinetics of amlodipine.

Effects of amlodipine on other medicinal products
Amlodipine may potentiate the effect of other antihypertensive agents, such as beta-adrenoceptor blocking agents, ACE-inhibitors, alpha-1-blockers and diuretics. In patients with an increased risk (for example after myocardial infarction) the combination of a calcium channel blocker with a beta-adrenoceptor blocking agent may lead to heart failure, to hypotension and to a (new) myocardial infarction.

Amlodipine has been safely administered with long acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

Pharmacokinetic studies with ciclosporin hve demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

In vitro data from studies of human plasma, show that amlodipine has no effect on protein binding of phenytoin or indometacin. There is no effect of amlodipine on laboratory parameters.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of amlodipine in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see Section 5.3 "Preclinical safety data"). The potential risk for humans is unknown. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Lactation
It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the the benefit of amlodipine therapy to the woman.

4.7. Effect on ability to drive and use machines

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired. ***The medicinal product has minor or no moderate influence on the ability to drive and use machines.***

4.8. Undesirable effects

Very common: >1/10
Common: >1/100 and <1/10
Uncommon: >1/1000 and <1/100
Rare: >1/10 000 and <1/1000
Very rare: <1/10 000 including isolated cases

Blood and lymphatic system disorders:

Very rare: Leukocytopenia, thrombocytopenia.

Metabolism and nutrition disorders:

Very rare: Hyperglycaemia.

Nervous system disorders:

Common: Headache (especially at the beginning of the treatment), fatigue, dizziness, somnolence.

Uncommon: Dry mouth, taste perversion, syncope, tremor paraesthesia, hypoaesthesia.

Very rare: Peripheral neuropathy.

Eye disorders:

Uncommon: Visual disturbances.

Ear and labyrinth disorders

Uncommon: Tinnitus.

Psychiatric disorders:

Uncommon:	Sleep disorder, irritability, depression
Rare:	Confusion, mood changes including anxiety.

Cardiac disorders:

Common:	Palpitations
Uncommon:	Tachycardia, chest pain, at the beginning of treatment aggravation of angina pectoris may happen, isolated cases of myocardial infarction and arrhythmias (including extrasystole, ventricular tachycardia, bradycardia and atrial arrhythmias) and chest pain have been reported in patients with coronary artery disease, but a clear association with amlodipine has not been established.

Vascular disorders:

Common:	Flushing.
Uncommon:	Hypotension.
Very rare:	Vasculitis.

Respiratory, thoracic and mediastinal disorders:

Uncommon:	Dyspnoea, rhinitis.
Very rare:	Cough.

Gastrointestinal disorders:

Common:	Nausea, dyspepsia, abdominal pain.
Uncommon:	Vomiting, diarrhoea, constipation, dyspepsia, dry mouth.
Very rare:	Gastritis, gingival hyperplasia.

Hepato-biliary disorders:

Rare:	Elevated liver enzymes (mostly consistent with cholestasis), jaundice, hepatitis
Very rare:	Pancreatitis.

Skin and subcutaneous tissue disorders:

Very common:	Ankle swelling.
Common:	Facial flushing with heat sensation, especially at the beginning of the treatment.
Uncommon:	Exanthema, pruritus, alopecia, skin discolouration, purpura, increased sweating, rash.
Very rare:	Angioedema, isolated cases of allergic reactions including pruritus, urticaria, angioedema and erythema exsudativum multiforme, exfoliative dermatitis, Stevens Johnson syndrome, Quincke oedema have been reported.

Musculoskeletal, connective tissue and bone disorders:

Uncommon:	Muscle cramps, back pain, myalgia and arthralgia.

Renal and urinary disorders:

Uncommon:	Increased micturition frequency, nocturia.

Reproductive system and breast disorders:

Uncommon:	Impotence, gynaecomastia.

General disorders and administration site conditions:

Common	Oedema, fatigue
Uncommon:	Chest pain, asthenia, pain, malaise.

Investigations

Uncommon:	Increase or decrease of weight.

4.9. Overdose

In humans, experience with intentional overdose is limited. Available data suggest that large overdoses (> 100mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Dihydropyridine derivatives
ATC code: C08CA01

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but the following two actions play a role:

1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. The mechanism of action also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilation increases the supply of oxygen to myocardiac muscle in patients with Prinzmetal anginal attack.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) throughout the 24 hour interval.

In patients with angina, once daily administration of amlodipine increases total exercise time, the delay of occurrence of anginal attack and the delay of the occurrence of a 1-mm ST interval. Amlodipine decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Patients with cardiac failure
Haemodynamic studies and exercise based clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure patients receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or a combined risk of mortality and morbidity with heart failure.

A follow-up study (PRAISE 2) showed that amlodipine did not have an effect on the total or cardiovascular mortality of decompensatio cordis Class III-IV patients without ischaemic origin. In this study treatment with amlodipine was associated with an increase in pulmonary oedema, although this could not be related to an increase in symptoms.

Children
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2. Pharmacokinetic properties

Absorption/Distribution
After oral administration of therapeutic doses, amlodipine is slowly absorbed. Absorption of amlodipine is not influenced by concomitant food intake. Absolute bioavailability of the unchanged active substance is estimated to be 64-80%. Peak plasma levels are reached 6-12 hours after administration. The volume of distribution is approximately 21 l/kg. The pKa of amlodipine is 8.6. *In vitro* studies have shown that amlodipine is bound to plasmatic proteins up to 97.5%.

Metabolism/Elimination
The plasma elimination half-life is about 35-50 hours. Steady-state plasma levels are reached after 7-8 consecutive days. Amlodipine is extensively metabolised to inactive metabolites. About 60% of the administered dose is excreted in the urine, of which 10% is as unchanged amlodipine.

In the elderly
The time to reach peak plasma concentrations is similar in elderly and younger patients. The clearance tends to be decreased with resulting increases in "area under the curve" (AUC) and terminal elimination half-life. The recommended dosage regimen for the elderly is the same, although increasing the dose should take place with caution.

In patients with renal failure
Amlodipine is extensively metabolised to inactive metabolites. 10% of the parent compound is excreted unchanged in urine. Changes in amlodipine concentration are not correlated with degree of renal impairment. Therefore the normal dosage is recommended. Amlodipine is not dialysable.

Patients with hepatic impairment:
The half-life of amlodipine is prolonged in patients with impaired hepatic function.

Children
A population PK study has been conducted in 74 hypertensive children aged from 12 months to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 l/hr respectively in males and 16.4 and 21.3 l/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In animal studies with respect to reproduction in rats at high doses delayed parturition, difficult labour and impaired foetal and pup survival were seen.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose
Anhydrous calcium hydrogen phosphate
Sodium starch glycollate type A
Magnesium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5. Nature and contents of container

White opaque PVC/PVDC-aluminium blister.
Pack sizes: 10, 14, 20, 28, 30, 50, 98, 100 and 200 tablets
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

Athlone Laboratories Ltd.,
Ballymurray,
Co. Roscommon,
Ireland

8. MARKETING AUTHORISATION NUMBER

Amlotan 5 mg tablets: PA 298/15/1
Amlotan 10 mg tablets: PA 298/15/2

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th August 2006

Date of last renewal: 11th May 2011.

10. DATE OF REVISION OF THE TEXT

June 2012