Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

AMLODIPINE 5MG TABLETS
AMLODIPINE 10MG TABLETS

Procedure No: UK/H/2746 and 3018/001-2/DC

UK Licence No: PL 20154/0010-3

Ivowen Limited

LAY SUMMARY

On 19th February 2010, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Sweden and the UK agreed to grant a Marketing Authorisation to Ivowen Limited for the medicinal products Amlodipine 5mg and 10mg Tablets (PL 20154/0010-3; UK/H/2746 and 3018/001-2/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, Marketing Authorisations were granted in the UK on 19th March 2010.

Amlodipine belongs to a group of medicines known as calcium-channel blockers (calcium antagonists). Calcium-channel blockers lower blood pressure by relaxing the blood vessel walls so that blood passes through them more easily. They also have an effect on the heart, so that they can be used for angina (angina pectoris). They improve blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented.

Amlodipine is used for:

- High blood pressure
- Various types of angina except for unstable angina

Amlodipine may be used to treat angina on its own or together with other medicines.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Amlodipine 5mg and 10mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1

Product Name	Amlodipine 5 and 10mg Tablets
Type of Application	Generic, Article 10.1
Active Substances	Amlodipine besilate
Form	Tablet
Strength	5 and 10mg Tablets
MA Holder	Ivowen Ltd., 3 Anglesea Street, Clonmel, County Tipperary, Ireland
Reference Member State (RMS)	UK
CMS	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic and Sweden
Procedure Number	UK/H/2746 and 3018/001-2/DC
Timetable	Day 210 – 19th February 2010

Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 5 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg of amlodipine (as amlodipine besilate).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
5 mg tablet
White coloured, round biconvex tablets debossed with "5" on one side and scored on other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
- Essential hypertension
- Chronic stable and vasospastic angina pectoris

4.2 Posology and method of administration
For oral use
The tablets should be taken with a glass of water.

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 a single dose), depending on the individual patient's response. Amlodipine may be used either as monotherapy or in combination with other antianginal drugs in patients with angina.

Children with hypertension from 6 years to 17 years of age.
The recommended antihypertensive oral dose in pediatric 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 pediatric 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

Elderly patients
Normal dosage regimens are recommended in the elderly, but caution should be exercised when increasing the dosage (see section 5.2).

Patients with renal impairment
In these patients amlodipine can be used at the normal dosage (see section 5.2). Amlodipine should be administered with particular caution in patients undergoing dialysis. Amlodipine is not dialysable.

Patients with hepatic impairment
A dosage regimen for patients with hepatic impairment has not been established and therefore amlodipine should be administered with caution (see section 4.4).

4.3 Contraindications
Amlodipine is contra-indicated in patients with:
- hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients
- severe hypotension
- shock (including cardiogenic shock)
- obstruction of the outflow tract of the left ventricle (e.g. high-grade aortic stenosis)
- haemodynamically unstable heart failure after acute myocardial infarction

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure:
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class 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 associated with worsening of the heart failure (see section 5.1).

Use in patients with impaired hepatic function:
The half life of amlodipine 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).

Use in patients with renal failure:
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on amlodipine
CYP3A4 inhibitors: With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of amlodipine increased by 22% and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (i.e. rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

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

Effects of amlodipine on other medicinal products
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other antihypertensive agents.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, ethanol (alcohol), warfarin or cyclosporin.

There is no effect of amlodipine on laboratory parameters.

4.6 Pregnancy and lactation

Pregnancy
The safety of amlodipine in human pregnancy has not been established.

Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans.

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.

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 benefit of amlodipine therapy to the mother.

4.7 Effects on ability to drive and use machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with amlodipine 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)

Blood and the lymphatic system disorders:
Very rare: Leukocytopenia, thrombocytopenia

Immune system disorders:
Very rare: Allergic reactions

Metabolism and nutrition disorders:
Very rare: Hyperglycaemia

Psychiatric disorders:
Uncommon: Insomnia, mood changes (including anxiety), depression
Rare: Confusion

Nervous system disorders:
Common: Somnolence, dizziness, headache (especially at the beginning of the treatment)
Uncommon: Tremor, dysgeusia, syncope, hypoesthesia, paresthesia
Very rare: Hypertonia, peripheral neuropathy

Eye disorders:
Uncommon: Visual disturbance (including diplopia)

Ear and labyrinth disorders:
Uncommon: Tinnitus

Cardiac disorders:
Uncommon: Palpitations
Very rare: Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)

Vascular disorders:
Common: Flushing
Uncommon: Hypotension
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea, rhinitis
Very rare: Cough

Gastrointestinal disorders:
Common: Abdominal pain, nausea
Uncommon: Vomiting, dyspepsia, altered bowel habits (including diarrohea and constipation), dry mouth
Very rare: Pancreatitis, gastritis, gingival hypeplasia

Hepatobiliary disorders:
Very rare: Hepatitis, jaundice, hepatic enzymes increased*

Skin and subcutaneous tissue disorders:
Uncommon: Alopecia, purpura, skin discolouration, hyperhydrosis, pruritus, rash, exanthema
Very rare: Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity

Musculoskeletal, connective tissue disorders:
Common: Ankle swelling
Uncommon: Arthralgia, myalgia, muscle cramps, back pain

Renal and urinary disorders:
Uncommon: Micturition disorder, nocturia, increased urinary frequency

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: Weight increase, weight decrease

*mostly consistent with cholestatis

4.9 Overdose

In humans experience with intentional overdose is limited

Symptoms:
Available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment:
Clinically significant hypotension due to amlodipine overdose 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 10 mg 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: Calcium antagonists. Dihydropyridine derivatives, ATC code: C08 CA01

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

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

2. Dilatation of the main coronary arteries and the coronary arterioles also probably plays a role in its action. This dilatation increases the supply of oxygen to myocardiac muscle in patients with Prinzmetal's angina.

In patients with hypertension, once daily dosing provides a clinically significant reduction of blood pressure (in both the supine and standing position) that persists for 24 hours.

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

Use in children from 6 years to 17 years of age.
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.

Use in Patients with Heart Failure
Haemodynamic studies and exercise based controlled 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 receiving digoxin, diuretics and angiotensin-converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity in patients with heart failure.

In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

5.2 Pharmacokinetic properties

Absorption/Distribution
After oral administration of therapeutic doses, amlodipine is slowly absorbed from the gastrointestinal tract. The absorption of amlodipine is unaffected by the concomitant intake of food. The absolute bioavailability of the unchanged compound is estimated to be 64-80%. Peak plasma levels are reached 6 to 12 hours post-dose. The volume of distribution is about 20 l/kg. The pKa of amlodipine is 8.6. Plasma protein binding in vitro is approximately 98%.

Metabolism/Elimination
The plasma elimination half-life varies from 35 to 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, about 10% of which in the form of unchanged amlodipine.

Use in children from 6 years to 17 years of age.
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 21.3L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

Use in Elderly
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly patients. Increases in AUC and elimination half life in patients with congestive heart failure were as expected for the patient age group study (See Section 4.4).

Patients with impaired renal function
Amlodipine is extensively metabolised to inactive metabolites. Ten percent of the substance is excreted unchanged in the urine. Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients, amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

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

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 reproduction toxicity studies in rats, delayed parturition, difficult labour and reduced fetal and pup survival were seen at high doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Calcium hydrogen phosphate anhydrous
Cellulose microcrystalline
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package in order to protect from light.

6.5 Nature and contents of container
Amlodipine tablets may be presented in:
- PVC/PVdC/Al blister packs containing 10, 14, 28, 30, 50, 56, 60, 100, 180 tablets
- HDPE bottle with HDPE screw cap containing 28, 30, 56, 100, 180, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Ivowen Limited, 3 Anglesea Street, Clonmel, County Tipperary, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 20154/0010
PL 20154/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/03/2010

10 DATE OF REVISION OF THE TEXT
19/03/2010

1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension
- Chronic stable and vasospastic angina pectoris

4.2 Posology and method of administration

For oral use
The tablets should be taken with a glass of water.

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 a single dose), depending on the individual patient's response. Amlodipine may be used either as monotherapy or in combination with other antianginal drugs in patients with angina.

Children with hypertension from 6 years to 17 years of age.
The recommended antihypertensive oral dose in pediatric 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 pediatric 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

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Patients with renal impairment
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A dosage regimen for patients with hepatic impairment has not been established and therefore amlodipine should be administered with caution (see section 4.4).

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Amlodipine is contra-indicated in patients with:
- hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients
- severe hypotension
- shock (including cardiogenic shock)
- obstruction of the outflow tract of the left ventricle (e.g. high-grade aortic stenosis)
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In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, ethanol (alcohol), warfarin or cyclosporin.

There is no effect of amlodipine on laboratory parameters.

4.6 Pregnancy and lactation

Pregnancy
The safety of amlodipine in human pregnancy has not been established.

Reproductive studies in rats have shown no toxicity except for delayed date of delivery and prolonged duration of labour at dosages 50 times greater than the maximum recommended dosage for humans.

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.

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 benefit of amlodipine therapy to the mother.

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Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

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The following undesirable effects have been observed and reported during treatment with amlodipine with the following frequencies:

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Uncommon: Insomnia, mood changes (including anxiety), depression
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Very rare: Hypertonia, peripheral neuropathy

Eye disorders:
Uncommon: Visual disturbance (including diplopia)

Ear and labyrinth disorders:
Uncommon: Tinnitus

Cardiac disorders:
Uncommon: Palpitations
Very rare: Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)

Vascular disorders:
Common: Flushing
Uncommon: Hypotension
Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea, rhinitis
Very rare: Cough

Gastrointestinal disorders:
Common: Abdominal pain, nausea
Uncommon: Vomiting, dyspepsia, altered bowel habits (including diarrohea and constipation), dry mouth
Very rare: Pancreatitis, gastritis, gingival hypeplasia

Hepatobiliary disorders:
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Skin and subcutaneous tissue disorders:
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4.9 Overdose

In humans experience with intentional overdose is limited

Symptoms:
Available data suggest that gross overdose could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment:
Clinically significant hypotension due to amlodipine overdose 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 10 mg 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: Calcium antagonists. Dihydropyridine derivatives, ATC code: C08 CA01

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

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2. Dilatation of the main coronary arteries and the coronary arterioles also probably plays a role in its action. This dilatation increases the supply of oxygen to myocardiac muscle in patients with Prinzmetal's angina.

In patients with hypertension, once daily dosing provides a clinically significant reduction of blood pressure (in both the supine and standing position) that persists for 24 hours.

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

Use in children from 6 years to 17 years of age.
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.

Use in Patients with Heart Failure
Haemodynamic studies and exercise based controlled 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 receiving digoxin, diuretics and angiotensin-converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity in patients with heart failure.

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5.2 Pharmacokinetic properties

Absorption/Distribution
After oral administration of therapeutic doses, amlodipine is slowly absorbed from the gastrointestinal tract. The absorption of amlodipine is unaffected by the concomitant intake of food. The absolute bioavailability of the unchanged compound is estimated to be 64-80%. Peak plasma levels are reached 6 to 12 hours post-dose. The volume of distribution is about 20 l/kg. The pKa of amlodipine is 8.6. Plasma protein binding in vitro is approximately 98%.

Metabolism/Elimination
The plasma elimination half-life varies from 35 to 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, about 10% of which in the form of unchanged amlodipine.

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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 21.3L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

Use in Elderly
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly patients. Increases in AUC and elimination half life in patients with congestive heart failure were as expected for the patient age group study (See Section 4.4).

Patients with impaired renal function
Amlodipine is extensively metabolised to inactive metabolites. Ten percent of the substance is excreted unchanged in the urine. Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients, amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

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

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 reproduction toxicity studies in rats, delayed parturition, difficult labour and reduced fetal and pup survival were seen at high doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Calcium hydrogen phosphate anhydrous
Cellulose microcrystalline
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package in order to protect from light.

6.5 Nature and contents of container
Amlodipine tablets may be presented in:
- PVC/PVdC/Al blister packs containing 10, 14, 28, 30, 50, 56, 60, 100, 180 tablets
- HDPE bottle with HDPE screw cap containing 28, 30, 56, 100, 180, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Ivowen Limited, 3 Anglesea Street, Clonmel, County Tipperary, Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 20154/0011
PL 20154/0013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/03/2010

10 DATE OF REVISION OF THE TEXT
19/03/2010

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

AMLODIPINE 5 MG TABLETS
AMLODIPINE 10 MG TABLETS
(Amlodipine)

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START TAKING THIS MEDICINE.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1. WHAT AMLODIPINE IS AND WHAT IT IS USED FOR

Amlodipine belongs to a group of medicines known as calcium-channel blockers (calcium antagonists). Calcium-channel blockers lower blood pressure by relaxing the blood vessel walls so that blood passes through them more easily. They also have an effect on the heart, so that they can be used for angina (angina pectoris). They improve blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented.

Amlodipine is used for:
- High blood pressure
- Various types of angina except for unstable angina

Amlodipine may be used to treat angina on its own or together with other medicines.

2. BEFORE YOU TAKE AMLODIPINE TABLETS

Do not take Amlodipine Tablets
- If you are allergic (hypersensitive) to amlodipine or similar calcium-channel blockers (the so-called dihydropyridine derivatives), or to any of the other ingredients of Amlodipine Tablets.
- If you have very low blood pressure.
- If you are suffering from shock (a very severe lowering of blood pressure by which you become unconscious).
- If you have heart failure following an acute heart attack.
- If the blood flow from the left side of your heart is obstructed.

If you are not sure whether any of the above applies to you, ask your pharmacist or your doctor.

Take special care with Amlodipine Tablets
- If you have heart failure.
- If you have kidney problems.

- If you have liver problems; amlodipine must be used very carefully because the required dosage is not known exactly in this situation.

Taking other medicines

- Diltiazem (a medicine to treat high blood pressure and problems with heartbeat rhythm): concomitant use can increase the effect of amlodipine. Concomitant use of other medicines, such as ketoconazole, itraconazole (medicines for fungal infections), HIV-protease-inhibitors such as ritonavir (a medicines for HIV/AIDS), clarithromycin, erythromycin, telithromycin (antibiotics) and nefazodone (medicine to treat depression) can also increase the effect of amlodipine. Ketoconazol, itraconazol or ritonavir may increase the effect of amlodipine even more than diltiazem.
- The effect of amlodipine may be reduced by medicines that increase the breakdown of amlodipine, such as rifampicin and rifabutin (antibiotics used for certain infections), St. John's wort (a product for depression that can be bought without a prescription), dexamethasone (cortisone), phenobarbital, phenytoin, carbamazepine (medicines for epilepsy) and nevirapine (antiviral medicine).
- Amlodipine may increase the effect of other medicines used to lower blood pressure (such as beta-blockers, ACE inhibitors, alpha-blockers and water tablets). In patients at risk (for example, people who have recently had a heart attack), the combination of a calcium antagonist with a beta-blocker can cause heart failure, low blood pressure, and a (new) heart attack.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Amlodipine Tablets with food and drink
Amlodipine can be taken with or without food.

Pregnancy and breastfeeding
There is very little information on whether it is harmful to take amlodipine during pregnancy. Amlodipine should only be used during pregnancy if your doctor decides that it is absolutely necessary.

There is no information on the use of amlodipine while breast-feeding. You are advised not to breastfeed when using amlodipine. Ask your doctor or pharmacist for advice before taking any medicine.

Children
Safety and effectiveness have been studied in 6-17 year old boys and in girls. Amlodipine has not been studied in children under the age of 6 years. For more information, talk to your doctor.

Driving and using machines
Amlodipine may cause dizziness, tiredness, or make you feel sick. These side effects are more likely to occur after initiation of treatment or after dosage increase. If you have any of these side effects, you should keep in mind that this can affect your ability to drive and/or use machinery.

3. HOW TO TAKE AMLODIPINE

Always take Amlodipine Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The dose is decided by your doctor.
Take the tablets by mouth with plenty of liquid, for example a glass of water. The tablets may be taken before, during or after a meal.

Adults
Starting dose for high blood pressure and angina: 5 mg once a day.

Maximum dose for high blood pressure and angina: if there has been insufficient effect after 2-4 weeks, the dose may be increased to a maximum of 10 mg once a day.

Elderly
There is no special dosage for the elderly; however, care must be taken when the dose is increased.

Children (6-17 years old)
For children (6 -17 years old), the recommended usual starting dose is 2.5 mg a day. The maximum recommended dose is 5 mg a day.

If you have kidney problems
If you have kidney problems, the dose does not need to be changed. Amlodipine cannot be removed from the blood by dialysis (artificial kidney).
If you go for kidney dialysis, amlodipine should be taken with particular caution.

If you have liver problems
The exact dose needed for patients with liver problems has not been determined. If you have liver problems, amlodipine should be used very carefully (see also the section Take special care with Amlodipine Tablets).
If you think that Amlodipine Tablets do not work or have a too strong effect, discuss this with your doctor or pharmacist.

If you take more Amlodipine Tablets than you should
If you or someone else has taken too much amlodipine, contact your doctor or hospital emergency department immediately. The person concerned should be made to lie down with their arms and legs up (resting on a couple of cushions, for example). Symptoms of an overdose are: extreme dizziness and/or feeling very light-headed, problems with breathing, having to urinate very often.

If you forget to take Amlodipine Tablets
If you have forgotten to take a tablet, you can still take it up to 12 hours after you usually take your tablet. If it is more than 12 hours after the time that you should have taken the tablet, you should not take the missed dose and you should take the next tablet at the usual time. Do not take a double dose to make up for at forgotten dose.

If you stop taking Amlodipine Tablets
Your doctor has told you for how long you should take amlodipine. If you stop the treatment suddenly, your symptoms may come back. Do not stop the treatment earlier than agreed without discussing this with your doctor or pharmacist. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Amlodipine Tablets can cause side effects, although not everybody gets them. A list of possible side effects is given below.

Very common means	1 or more than 1 in 10 patients
Common means	1 or more than 1 in 100 but less than 1 in 10 patients
Uncommon means	1 or more than 1 in 1000 but less than 1 in 100 patients
Rare means	1 or more than 1 in 10.000 but less than 1 in 1000 patients
Very rare means	less than 1 in 10.000 patients including isolated reports

You should stop taking Amlodipine Tablets and see your doctor immediately if you experience symptoms of angioedema, such as

- swollen face, tongue or throat
- difficulty to swallow
- hives and difficulty breathing

Possible side effects are:

common:

- feeling weak or tired, sleepiness, dizziness, headache (especially at the start of treatment)
- flushing of the face (especially at the start of treatment)
- feeling sick, stomach ache
- swelling of the ankles and other parts of the body

uncommon:

- difficulty sleeping, changes in mood (including anxiety), depression
- uncontrolled shaking (tremor), taste disturbance or loss of taste, fainting, decreased feeling or sensitivity (especially in the skin),burning or itching sensation in the skin
- disturbed vision (including double vision)
- ringing in the ears (tinnitus)
- low blood pressure, an irregular heart rhythm or missed beats (palpitations)
- breathlessness, difficulty breathing, itchy runny nose
- being sick, indigestion (dyspepsia), changes in bowel habits (including diarrhoea and constipation), dry mouth
- hair-loss
- reddish spots on the skin, change in skin colour, excessive sweating, itchy skin, skin rash
- muscle cramps, backache, muscle pain, joint pain
- increased need to urinate
- impotence, enlargement of male breasts (Gynaecomastia)
- chest pain, general pain, feeling of weakness, tiredness, lack of energy
- increase or decrease in weight

rare:

- feeling confused

very rare:

- low numbers of white blood cells giving a higher risk of infections (leucopenia), low numbers of platelets with the risk of bruising (thrombocytopaenia)
- allergic reactions
- high blood sugar level (hyperglycaemia)
- unusual muscle stiffness causing poor control of movement, a burning sensation or numbness or weakness of the hands and feet (peripheral neuropathy)
- heart attack, severe chest pain, unusual or abnormal heart beat.
- inflammation of the blood or lymphatic vessels, often with skin rash (vasculitis)
- cough
- inflammation of the pancreas which causes severe pain in the abdomen and back (pancreatitis)
- inflammation of the stomach (symptoms include: pain, feeling sick, being sick, blood in your vomit, blood in the bowel motions)
- bleeding, tender or enlarged gums
- dark urine, pale stools, yellowing of the skin or whites of the eyes (jaundice), nausea, fever (hepatitis)
- increase of liver enzymes in the blood indicating abnormal liver function
- serious allergic reaction which causes swelling of the face or the throat
- severe skin reaction, hives, flaking or peeling of the skin, serious allergic reaction with fever, red patches, joint pain and/or eye problems (Stevens Johnson syndrome), swelling of the lips, eyelids and genitals (Quincke oedema)
- sensitivity to light

if any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

5. HOW TO STORE AMLODIPINE TABLETS

Keep out of reach and sight of children.

Do not use Amlodipine Tablets after the expiry date which is stated on the carton and the bottle or blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.
Do not use if you notice any discolouration of the tablets.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What amlodipine tablets contain

- The active substance is amlodipine.
- Each tablet contains 5 mg or 10 mg of amlodipine (as amlodipine besilate)
- The other ingredients are calcium hydrogen phosphate anhydrous, cellulose microcrystalline, sodium starch glycolate (type A), magnesium stearate.

What Amlodipine Tablets looks like and contents of the pack

Amlodipine 5 mg Tablets are white to off-white, round tablets with "5" on one side and a score line on the other side. The tablet can be divided into equal halves.

Amlodipine 10 mg Tablets are white to off-white, round tablets with "10" on one side and a score line on the other side. The tablet can be divided into equal halves.

Amlodipine Tablets are packed in blisters containing 10, 14, 28, 30, 50, 56, 60, 100, 180 tablets per pack.

Amlodipine Tablets are packed in bottles containing 28, 30, 56, 100, 180, 500 tablets per pack.

Not all pack sizes may be marketed

Marketing authorisation holder and manufacturer:
<To be completed nationally>

For procedure UK/H/2746/001-002/DC:
Manufacturer:
McDermott Laboratories Limited trading as Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.
Mylan B.V, Dieselweg 25, 3752 LB Bunschoten, The Netherlands.
Mylan dura GmbH, Wittichstraße 6, D-64295 Darmstadt, Germany.
Tjoa Pack Hungary Ltd, 2040 Budaors, Vasut u. 13, Hungary

For procedure UK/H/3018/001-002/DC: Manufacturer:
McDermott Laboratories Limited trading as Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland.

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

<To be completed nationally>

This medicinal product is authorised in the Member States of the EEA under the following names:

Name of medicinal product	Member State
Amlodipinbesilat Arcana	Austria
Amlodipin Ivowen	Czech Republic, Denmark, Finland, Norway, Slovak Republic, Sweden
Amlodipina Ivowen	Portugal
Amlodipină Ivowen	Romania
Amlodipina Mylan	Italy
Amlodipinbesilat Ivowen	Germany
Amlodipine	Ireland, United Kingdom
Amlodipine (Als Besilaat) Ivowen	The Netherlands
Amlodipine Ivowen	Belgium, Poland, Greece
Amlodipino Ivowen	Spain
Amlogen	Bulgaria
Amloivowen	Belgium
Cardigen	Hungary

This leaflet was last approved in {MM/YYYY}.
<To be completed nationally>

Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Cardboard Carton for PVC/PVdC - Aluminium Blisters

1. NAME OF THE MEDICINAL PRODUCT

Amlodipine 5 mg tablets
Amlodipine

Amlodipine 10 mg tablets
Amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains amlodipine besilate equivalent to amlodipine 5 mg.

Each tablet contains amlodipine besilate equivalent to amlodipine 10 mg.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

10 tablets
14 tablets
28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
100 tablets
180 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Amlodipine 5 mg tablets
Amlodipine 10 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

HDPE bottle with HDPE screw cap

1. NAME OF THE MEDICINAL PRODUCT

Amlodipine 5 mg tablets
Amlodipine

Amlodipine 10 mg tablets
Amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains amlodipine besilate equivalent to amlodipine 5 mg.

Each tablet contains amlodipine besilate equivalent to amlodipine 10 mg.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
100 tablets
180 tablets
500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Amlodipine 5 mg tablets
Amlodipine 10 mg tablets

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

HDPE bottle with HDPE screw cap

1. NAME OF THE MEDICINAL PRODUCT

Amlodipine 5 mg tablets
Amlodipine

Amlodipine 10 mg tablets
Amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains amlodipine besilate equivalent to amlodipine 5 mg.

Each tablet contains amlodipine besilate equivalent to amlodipine 10 mg.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet
28 tablets
30 tablets
50 tablets
56 tablets
60 tablets
100 tablets
180 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use. Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Amlodipine 5 mg tablets
Amlodipine 10 mg tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PVdC/Aluminium Blister Strips

1. NAME OF THE MEDICINAL PRODUCT

Amlodipine 5 mg tablets
Amlodipine

Amlodipine 10 mg tablets
Amlodipine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MA Holder:

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Amlodipine 5mg and 10mg Tablets (PL 20154/0010-3; UK/H/2746 and 3018/001-2/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as reference member state (RMS), and Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic and Sweden as concerned member states (CMS).

The products are prescription-only medicines for the treatments of essential hypertension and chronic stable and vasospastic angina pectoris.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, claiming to be generic medicinal products of Istin 5 and 10mg Tablets, which were originally granted licences in 1995 to Pfizer Limited.

Amlodipine besilate is a long-acting, dihydropyridine calcium channel-blocking agent with vascular selectivity. It inhibits the influx of calcium ions into cardiac and smooth muscle cell and differs from nifedipine by way of slow onset of action and recovery. It is well-established for use in the proposed indications.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 19th February 2010. After a subsequent national phase, the licences were granted in the UK on 19th March 2010.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Amlodipine 5mg Tablets Amlodipine 10mg Tablets
Name(s) of the active substance(s) (INN)	Amlodipine besilate
Pharmacotherapeutic classification (ATC code)	Calcium channel blockers (C08CA01)
Pharmaceutical form and strength(s)	5 and 10mg Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/2746 and 3018/001-2/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic and Sweden
Marketing Authorisation Number(s)	PL 20154/0010-3
Name and address of the authorisation holder	Ivowen Limited, 3 Anglesea Street, Clonmel, County Tipperary, Ireland

III SCIENTIFIC OVERVIEW AND DISCUSSION

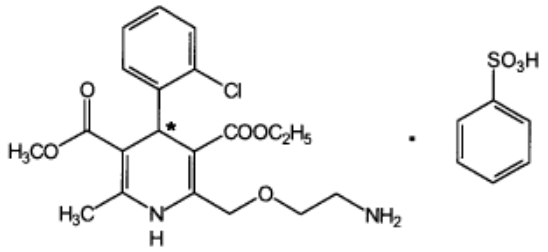
III.1 QUALITY ASPECTS

S. Active substance

INN: Amlodipine besilate

Chemical name: 3-Ethyl 5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate

Structure:



★ Asymetric carbon center

Molecular formula: $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$

Molecular weight: 567.1

Appearance: A white or almost white powder. Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

Amlodipine besilate is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients calcium hydrogen phosphate anhydrous, cellulose microcrystalline, sodium starch glycolate (type A) and magnesium stearate.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent tablet dosage form of Amlodipine Tablets, comparable to Istin Tablets (Pfizer, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System

All strengths of tablets are packaged in either:

- polyvinylchloride/aluminium/polyvinylidene chloride blisters in pack sizes of 10, 14, 28, 30, 50, 56, 60, 100, 180 tablets
- high-density polyethylene bottles with a screw cap containing 28, 30, 56, 100, 180, 500 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product

Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from

these studies support a shelf-life of 2 years, with the storage conditions “Store in the original package in order to protect from light”.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of amlodipine besilate are well-known, no further preclinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a preclinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Amlodipine Besilate 10mg Tablets versus the reference product Istin 10mg Tablets (Pfizer Limited, UK) in healthy adult male volunteers under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 216 hours post dose. The two treatment arms were separated by a 21-day washout period.

The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) are presented below:

Parameters (Units)	In-transformed Data			90% Confidence Interval (Parametric
	Geometric Least Squares Mean			
	Test Product-B	Reference Product-A	Ratio (B/A)%	
C_{max} (ng/mL)	4.228	4.101	103.1%	98.68 – 107.70%
AUC_{0-t} (ng.h/mL)	214.805	211.179	101.7%	96.20 – 107.56
$AUC_{0-\infty}$ (ng.h/mL)	241.346	239.728	100.7%	96.41 – 105.13%

The 90% confidence intervals for C_{max} and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

As the 5 and 10mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the extrapolation of results and conclusions from the bioequivalence study on the 10mg strength to the 5mg strength is justified.

Efficacy

No new data on the efficacy have been submitted and none are required for these types of applications.

Safety

No new or unexpected safety issues were raised by the bioequivalence data.

SPC, PIL, Labels

The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Amlodipine 5 and 10mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's 10mg Tablets and its respective reference product. As the 5mg and 10mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to the 5mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable, and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with amlodipine besilate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome