Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Amlodipine 5 and 10 mg Tablets

UK/H/862/01-02/DC

Arrow Generics Limited

Medicines and Healthcare products Regulatory Agency

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Arrow Generics Limited Marketing Authorisations (licences) for the medicinal products Amlodipine 5 mg and 10 mg Tablets (Product Licence numbers: 18909/0173-4). These medicines are available on prescription only.

Amlodipine 5 mg and 10 mg Tablets treat high blood pressure (hypertension) by relaxing the blood vessels so that blood passes through them more easily. These tablets are also used in the treatment of a type of chest pain known as angina. Angina occurs when not enough blood reaches the heart and amlodipine helps prevent this by increasing the blood supply to the heart.

The data submitted in support of the application for Amlodipine 5 mg and 10 mg Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Amlodipine 5 mg Tablets Amlodipine 10 mg Tablets
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 10.1 Level 4 Chemical substance Level 5 Prescription only
Name(s) of the active substance(s) (INN)	Amlodipine besilate
Pharmacotherapeutic classification (ATC code)	Calcium channel blockers – dihydropyridine derivatives (C08 CA01)
Pharmaceutical form and strength(s)	Tablet, 6.94 mg or 13.88 mg amlodipine besilate/tablet (equivalent to 5 or 10 mg amlodipine base/tablet)
Reference numbers for the Mutual Recognition Procedure	UK/H/862/01-02/DC
Reference Member State	United Kingdom
Member States concerned	BE, CZ, DE, DK, HU, IT, MT, NL, NO, PL, PT, SE, SI, SK
Date of start of the procedure	7 April 2006
End date of decentralised procedure	7 March 2007
Marketing Authorisation Number(s)	PL 18909/0173 PL 18909/0174
Name and address of the authorisation holder	Arrow Generics Ltd Unit 2, Eastman Way Stevenage, Hertfordshire SG1 4SZ, United Kingdom

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

PL 18909/0173:

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.

White to off-white, elongated octagon-shaped tablets, embossed with 'AM 5' on one side and '>' on the other 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. Amlodipine may be used either as monotherapy or in combination with other antianginal drugs in patients with angina.

In children and adolescents (less than 18 years of age)
Amlodipine is not recommended in children and adolescents due to insufficient data on safety and efficacy.

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

In patients with renal impairment
In these patients amlodipine can be used in the normal dosage (see section 5.2). Amlodipine is not dialyzable.

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).

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

4.3 Contraindications

Amlodipine is contra-indicated in patients with:

- hypersensitivity to amlodipine, dihydropyridine derivatives or to any of the excipients
- severe hypotension
- shock, including cardiogenic shock
- 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

4.4 Special warnings and precautions for use

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.

Amlodipine should be administered with caution to patients with low cardiac reserve.

Patients with heart 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 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).

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.

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

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.

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

There is no effect of amlodipine on laboratory parameters.

4.6 Pregnancy and lactation

There are no adequate data from the use of amlodipine in pregnant women.

In animal studies effects on reproduction were found at high dosages (see section 5.3). The potential risk for humans is unknown. Accordingly amlodipine should not be used during pregnancy unless clearly needed.

It is not known whether amlodipine is excreted in breast milk. It is advised to stop breastfeeding during treatment with amlodipine.

4.7 Effects on ability to drive and use machines

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

The following convention has been utilised for the classification of 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
Not known: Cannot be established from the available data

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

Endocrine disorders:
Uncommon: Gynaecomastia.

Metabolism and nutrition disorders:
Very rare: Hyperglycaemia.

Nervous system disorders:
Common: Headache (especially at the beginning of the treatment), Fatigue, dizziness, asthenia
Uncommon: Malaise, dry mouth, tremor, paraesthesia, increased sweating
Rare: Taste changes
Very rare: Peripheral neuropathy

Eye disorders:
Uncommon: Visual disturbances.

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

Ear and labyrinth disorders:
Rare: Tinnitus

Cardiac disorders:
Common: Palpitations

Uncommon: Syncope, 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:
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, gingival hyperplasia
Very rare: Gastritis.

Hepato-biliary disorders:
Rare: Elevated liver enzymes, 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, urticaria, alopecia, skin discolouration
Very rare: Angioedema, isolated cases of allergic reactions including pruritus, rash, angioedema and erythema exsudativum multiforme, exfoliative dermatitis and Stevens Johnson syndrome and 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.

Reproductive system and breast disorders:
Uncommon: Impotence.

General disorders and administration site conditions:
Uncommon: Increase or decrease of weight.

4.9 Overdose

In humans, experience with intentional overdose is limited. Available data suggest that overdose (>100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension.

Clinically significant hypotension due to amlodipine overdose calls for active cardio-vascular 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 2h 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: C08C A01

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle cells. The mechanism of the antihypertensive action is due to the direct relaxant 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 total 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 dilation increases the supply in 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) that persist for 24 hours.

In *patients with angina pectoris*, 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 attack frequency and glyceryl trinitrate tablet consumption.

In haemodynamic studies *in patients with heart failure* and in clinical studies based on exercise tests in patients with NYHA class II-IV heart failure, amlodipine was found not

to cause any clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction and clinical signs and symptoms.

In a placebo-controlled study (PRAISE) designed to evaluate patients with NYHA class III-IV heart failure treated with digoxin, diuretics and ACE inhibitors, amlodipine was shown not to cause any increase in the risk of death or in the combined risk of mortality and morbidity in patients with heart failure.

A follow-up study (PRAISE 2) showed that amlodipine did not have an effect on the total or cardiovascular mortality in class III-IV heart failure 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.

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 active substance is estimated as 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 is about 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.

In the elderly
The time to reach peak plasma concentrations is the same in elderly and younger patients. Clearance may be reduced in elderly patients so that the area under the curve (AUC) and the terminal elimination half-life are increased. The recommended dosage regimen for elderly patients is however the same, although caution should be exercised when increasing the dosage.

In patients with impaired renal function
Amlodipine is extensively biotransformed 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 repeated dose toxicity, genotoxicity and carcinogenic potential. In reproductive toxicity studies in rats at high doses, delayed parturition, difficult labour and reduced foetal and pup survival were seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
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 below 25^{o}C.

6.5 Nature and contents of container

PVC/Aclar/Aluminium Foil Blister Packs.

*Pack sizes 10, 20, 28, 30, 50, 56, 60, 98, 100, 300 tablets.

* Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 18909/0173

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/03/2007

10 DATE OF REVISION OF THE TEXT

07/03/2007

PL 18909/0173:

1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of amlodipine (as amlodipine besilate).

For a full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White to off-white, elongated octagon-shaped tablets, embossed with ‘AM 10’ on one side and ‘>’ on the other 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. Amlodipine may be used either as monotherapy or in combination with other antianginal drugs in patients with angina.

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

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Amlodipine is contra-indicated in patients with:

- hypersensitivity to amlodipine, dihydropyridine derivatives or to any of the excipients
- severe hypotension
- shock, including cardiogenic shock
- 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

4.4 Special warnings and precautions for use

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.

Amlodipine should be administered with caution to patients with low cardiac reserve.

Patients with heart 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 the heart failure (see Section 5.1).

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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.

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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.

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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.

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

There is no effect of amlodipine on laboratory parameters.

4.6 Pregnancy and lactation

There are no adequate data from the use of amlodipine in pregnant women.

In animal studies effects on reproduction were found at high dosages (see section 5.3). The potential risk for humans is unknown. Accordingly amlodipine should not be used during pregnancy unless clearly needed.

It is not known whether amlodipine is excreted in breast milk. It is advised to stop breastfeeding during treatment with amlodipine.

4.7 Effects on ability to drive and use machines

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

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The following convention has been utilised for the classification of 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
Not known: Cannot be established from the available data.

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

Endocrine disorders:
Uncommon: Gynaecomastia.

Metabolism and nutrition disorders:

Very rare: Hyperglycaemia.

Nervous system disorders:
Common: Headache (especially at the beginning of the treatment), Fatigue, dizziness, asthenia
Uncommon: Malaise, dry mouth, tremor, paraesthesia, increased sweating
Rare: Taste changes
Very rare: Peripheral neuropathy

Eye disorders:
Uncommon: Visual disturbances.

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

Ear and labyrinth disorders:
Rare: Tinnitus

Cardiac disorders:
Common: Palpitations
Uncommon: Syncope, 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:
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, gingival hyperplasia
Very rare: Gastritis.

Hepato-biliary disorders:
Rare: Elevated liver enzymes, 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, urticaria, alopecia, skin discolouration
Very rare: Angioedema, isolated cases of allergic reactions including pruritus, rash, angioedema and erythema exsudativum multiforme, exfoliative dermatitis and Stevens Johnson syndrome and 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.

Reproductive system and breast disorders:
Uncommon: Impotence.

General disorders and administration site conditions:
Uncommon: Increase or decrease of weight.

4.9 Overdose

In humans, experience with intentional overdose is limited. Available data suggest that overdose (>100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension.

Clinically significant hypotension due to amlodipine overdose calls for active cardio-vascular 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 2h 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: C08C A01

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle cells. The mechanism of the antihypertensive action is due to

the direct relaxant 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 total 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 dilation increases the supply in 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) that persist for 24 hours.

In *patients with angina pectoris*, 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 attack frequency and glyceryl trinitrate tablet consumption.

In haemodynamic studies *in patients with heart failure* and in clinical studies based on exercise tests in patients with NYHA class II-IV heart failure, amlodipine was found not to cause any clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction and clinical signs and symptoms.

In a placebo-controlled study (PRAISE) designed to evaluate patients with NYHA class III-IV heart failure treated with digoxin, diuretics and ACE inhibitors, amlodipine was shown not to cause any increase in the risk of death or in the combined risk of mortality and morbidity in patients with heart failure.

A follow-up study (PRAISE 2) showed that amlodipine did not have an effect on the total or cardiovascular mortality in class III-IV heart failure 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.

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 active substance is estimated as 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 is about 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.

In the elderly
The time to reach peak plasma concentrations is the same in elderly and younger patients. Clearance may be reduced in elderly patients so that the area under the curve (AUC) and the terminal elimination half-life are increased. The recommended dosage regimen for elderly patients is however the same, although caution should be exercised when increasing the dosage.

In patients with impaired renal function
Amlodipine is extensively biotransformed 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 repeated dose toxicity, genotoxicity and carcinogenic potential. In reproductive toxicity studies in rats at high doses, delayed parturition, difficult labour and reduced foetal and pup survival were seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
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 below 25^{o}C.

6.5 Nature and contents of container

PVC/Aclar/Aluminium Foil Blister Packs.

*Pack sizes 10, 14, 20, 28, 30, 50, 56, 60, 98, 100 tablets.

* Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 18909/0174

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/03/2007

10 DATE OF REVISION OF THE TEXT

07/03/2007

Module 3

Product Information Leaflet

PACKAGE LEAFLET : INFORMATION FOR THE USER

Amlodipine 5 mg and 10 mg Tablets

(Amlodipine besilate)

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 TABLETS ARE AND WHAT THEY ARE USED FOR

Amlodipine Tablets are used to treat high blood pressure (hypertension) or a certain type of chest pain called angina, including Prinzmetal's (or variant) angina. Amlodipine is one of a group of medicines called calcium channel blockers.

If you have high blood pressure, amlodipine works by relaxing blood vessels, so that blood passes through them more easily.

If you have angina, you may get chest pains when your heart cannot get enough blood. This usually happens during exercise or stress. Amlodipine helps to prevent this by increasing the blood supply to the heart. Amlodipine Tablets do not work immediately to stop the chest pain from angina.

2. BEFORE YOU TAKE AMLODIPINE TABLETS

Do not take Amlodipine Tablets:
- if you are allergic (hypersensitive) to amlodipine, other calcium channel blockers or to any of the other ingredients in the tablets (these are listed in section 6, Further Information)
- if you have shock including cardiogenic shock (poor heart output caused by severe heart disease or a heart attack)
- if you have had a heart attack within the last 28 days
- if you are suffering from obstruction to the outflow of blood from the left main chamber of the heart
- if you are suffering from unstable angina (angina at rest or at night)
- if you are suffering from very low blood pressure (severe hypotension).

Take special care with Amlodipine Tablets

Before you take Amlodipine Tablets tell your doctor:
- if you have any liver problems
- if you have a history of heart failure or low cardiac reserve (your heart has difficulty pumping blood around your body especially when you exercise).

If any of the above apply to you, talk to your doctor who will decide what to do.

Taking other medicines

Tell your doctor if you are taking or have taken any of the following medicines as they may interact with your Amlodipine Tablets:
- medicines called antifungal agents (such as ketoconazole or itraconazole), which are used to treat infections caused by fungi or yeasts e.g. thrush and ringworm
- medicines used to treat infections caused by viruses (antiviral agents), such as ritonavir used in the treatment of HIV infections
- medicines used to treat infections caused by bacteria and yeasts (antibiotics), such as rifampicin used in the treatment of tuberculosis
- herbal medicines used to treat depression such as St. John's Wort
- diltiazem, another medicine used to treat high blood pressure and angina
- other medicines for the treatment of high blood pressure e.g. ACE inhibitors such as enalapril or captopril, alpha-1-blockers such as doxazosin or tamsulosin, beta-blockers such as bisoprolol or sotalol and diuretics (water tablets) such as furosemide or amiloride.

It may still be alright for you to take Amlodipine Tablets and your doctor will be able to decide what is suitable for you.

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

Pregnancy and breast-feeding

There is very little information on whether it is harmful to take amlodipine during pregnancy. Amlodipine must 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 breast-feed when using amlodipine.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

The tablets may make you feel dizzy, tired or nauseous. Therefore, care is recommended when driving or using machines.

3. HOW TO TAKE AMLODIPINE TABLETS

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 label on the carton will tell you how many tablets you should take and when. The tablets should be swallowed whole with plenty of water and not with your meals. Take your tablets at the same time each day.

Adults and the elderly

The usual dose of amlodipine is one tablet daily. Your doctor may start your treatment with Amlodipine 5 mg Tablets and increase your dosage to Amlodipine 10 mg Tablets depending on how you get on.

Amlodipine Tablets are not recommended for children or adolescents (under 18 years old).

If you take more Amlodipine Tablets than you should

If you have accidentally taken more than your prescribed dose, contact your nearest casualty department or tell your doctor or pharmacist immediately. Remember to take the pack and any remaining tablets with you.

If you forget to take Amlodipine Tablets

If you forget to take a tablet, simply leave out that dose completely and then take your next dose at the right time. Do not take a double dose to make up for a forgotten dose.

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 everyone gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. If you get any of the following symptoms after taking these tablets, contact your doctor immediately:
- **any sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat**
- **peeling and blistering of the skin, mouth, eyes and genitals**
- **rash affecting your whole body.**

The following side effects have also been reported:

Very common side effects (probably affecting more than 1 in 10 people)
- *swelling of the ankles*

Common side effects (probably affecting up to 1 in 10 people)
- *headache*
- *feeling tired*
- *dizziness*
- *weakness*
- *feeling sick*
- *stomach-ache*
- *indigestion*
- *flushing of the face*
- *palpitations (a quicker or irregular heart beat).*

Uncommon side effects (probably affecting fewer than 1 in 100 people)
- *feeling unwell*
- *dry mouth*
- *tremor (shaking)*
- *pins and needles*
- *increased sweating*
- *difficulty sleeping*
- *irritability*
- *depression*
- *shortness of breath*
- *rhinitis (runny nose)*
- *vomiting (being sick)*
- *diarrhoea or constipation*
- *swelling or soreness of the gums*
- *muscle cramps*
- *back pain*
- *muscle or joint pain*
- *increased need to urinate (pass water)*
- *changes in your weight*
- *inability to obtain an erection*
- *fainting*
- *chest pains*
- *increased heart rate*
- *low blood pressure*
- *skin rash*
- *itching*
- *local swelling causing wheals on the skin ("nettle rash")*
- *hair loss*
- *discolouration of the skin*
- *visual disturbances*
- *enlargement of male breasts.*

Rare side effects (probably affecting fewer than 1 in 1,000 people)
- *confusion*
- *mood changes including anxiety*
- *taste changes*
- *tinnitus (ringing in the ears)*
- *inflammation of the liver (hepatitis) or your liver doesn't work properly*
- *yellowing of the skin and eyes (jaundice).*

Very rare side effects (probably affecting fewer than 1 in 10,000 people)
- *excess sugar in the blood*
- *inflammation of the stomach*
- *vasculitis (inflammation of blood vessels, often with skin rash)*
- *certain blood disorders, which may increase the risk of bleeding, bruising or infections*
- *numbness in fingers or toes*
- *cough*
- *inflamed pancreas which causes severe pain in the abdomen and back*
- *allergic reactions (described above).*

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 the reach and sight of children

Store below 25ºC.

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

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

6. FURTHER INFORMATION

What Amlodipine Tablets contain:
- The active substance is amlodipine (as amlodipine besilate). Each tablet contains 5 mg or 10 mg of amlodipine.
- The other ingredients are calcium hydrogen phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate and magnesium stearate.

What Amlodipine Tablets look like and the contents of the pack

Amlodipine 5 mg Tablets are white to off-white, elongated octagonal tablets, marked 'AM5' on one side and '>' on the other side.

Amlodipine 10 mg Tablets are white to off-white, elongated octagonal tablets, marked 'AM10' on one side and '>' on the other side.

Your medicine is available in blisters containing 10, 20, 28, 30, 50, 56, 60, 98, 100 and 300 tablets (Amlodipine 5 mg Tablets) and 10, 14, 20, 28, 30, 50, 56, 60, 98 and 100 tablets (Amlodipine 10 mg Tablets). Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ

Manufacturer:

Arrow Pharm (Malta) Limited,
HF62, Hal Industrial Estate, Birzebbugia BBG06, Malta

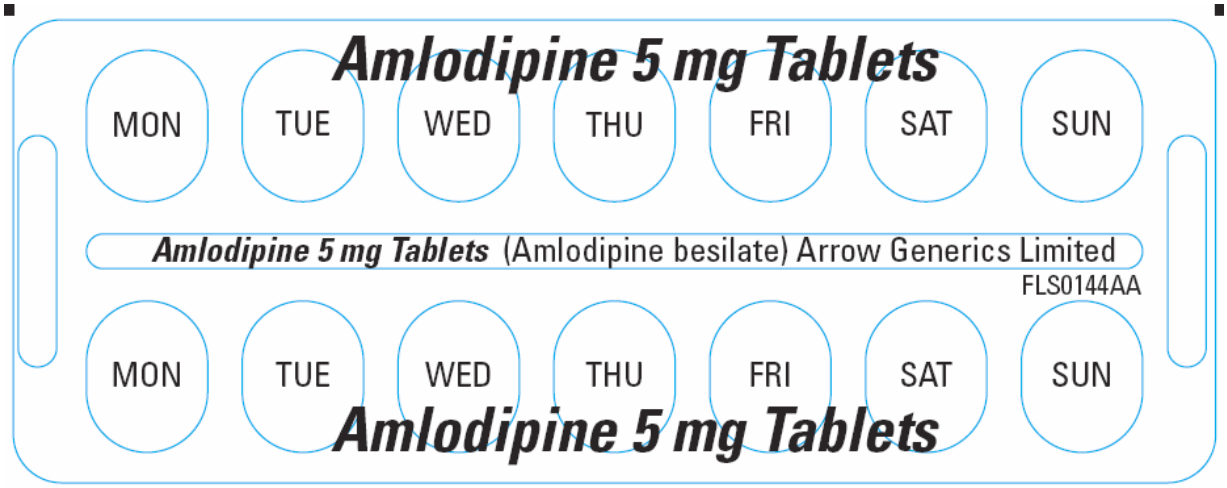
This leaflet was last approved in (MM/YYYY)

Module 4

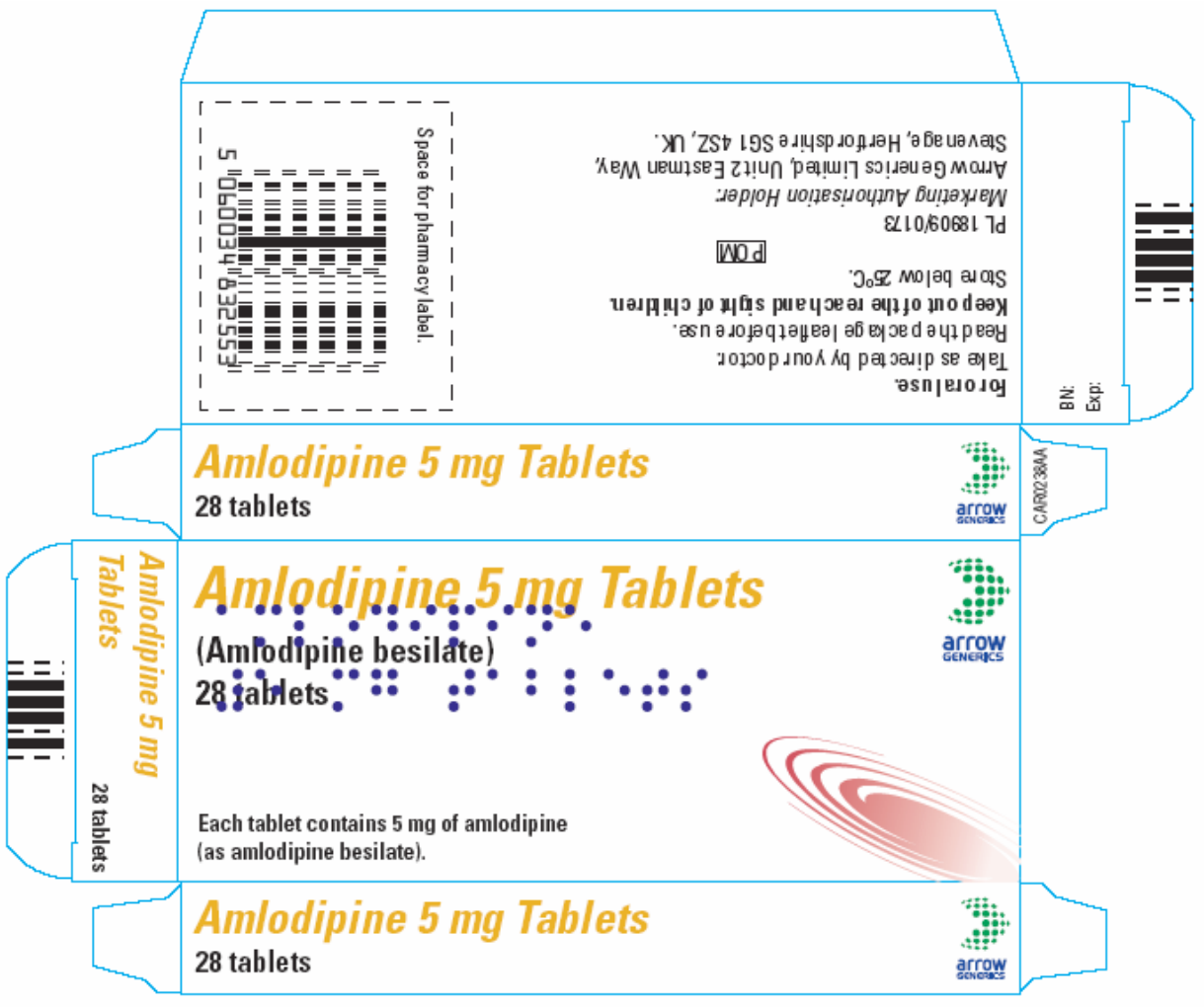
Labelling

5 mg:

Foil

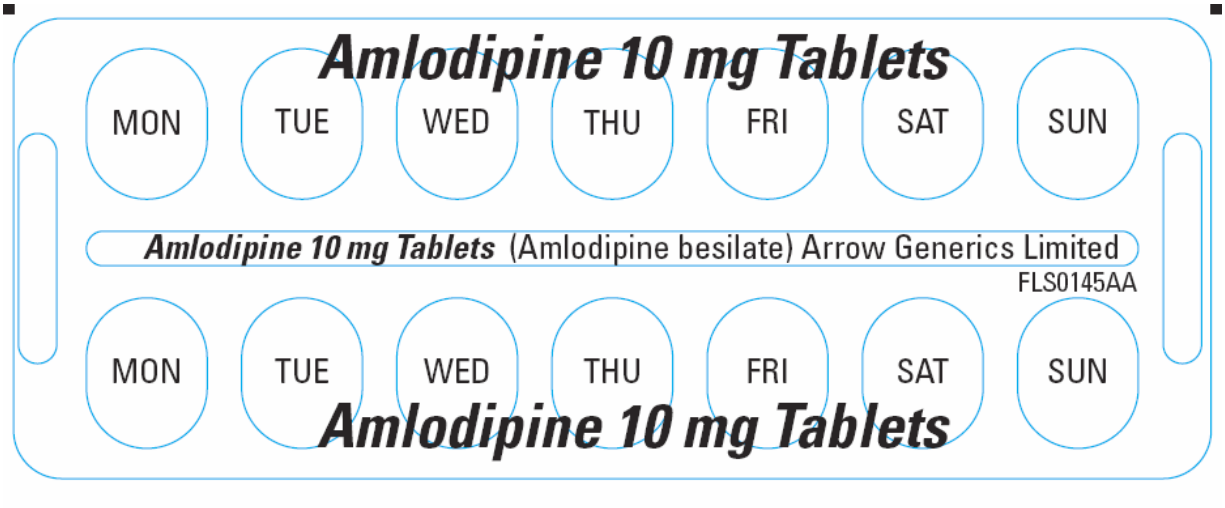


Carton

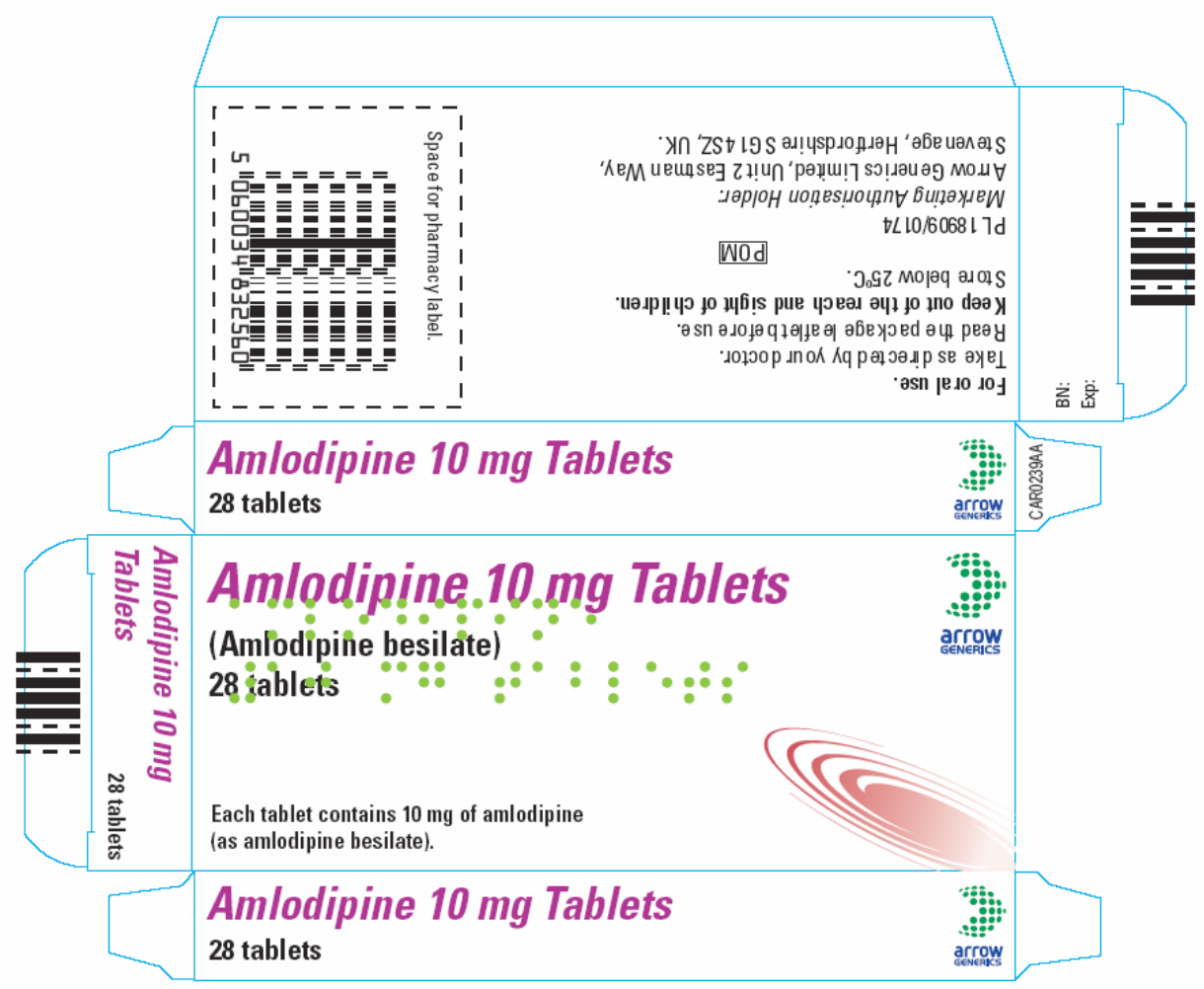

Amlodipine 5 mg Tablets
28 tablets
arrow GENERICS
CAR02384A
Amlodipine 5 mg Tablets
(Amlodipine besilate)
28 tablets
Each tablet contains 5 mg of amlodipine
(as amlodipine besilate).
Amlodipine 5 mg Tablets
28 tablets
For oral use.
Take as directed by your doctor.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store below 25°C.
PL 18909/0173
Marketing Authorisation Holder:
Arrow Generics Limited, Unit 2 Eastman Way,
Stevenage, Hertfordshire SG1 4SZ, UK.
BN:
Exp:
Space for pharmacy label.
5 060003 832553

10 mg:

Foil


Amlodipine 10 mg Tablets
MON
TUE
WED
THU
FRI
SAT
SUN
Amlodipine 10 mg Tablets (Amlodipine besilate) Arrow Generics Limited
FLS0145AA
MON
TUE
WED
THU
FRI
SAT
SUN
Amlodipine 10 mg Tablets

Carton


Space for pharmacy label.
5 050036 325500 9
For oral use.
Take as directed by your doctor.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store below 25°C.
POM
PL 18909/0174
Marketing Authorisation Holder:
Arrow Generics Limited, Unit 2 Eastman Way,
Stevenage, Hertfordshire SG1 4SZ, UK.
BN:
Exp:
Amlodipine 10 mg Tablets
28 tablets
arrow GENERICS
CAR0239AA
Amlodipine 10 mg Tablets
(Amlodipine besilate)
28 tablets
Each tablet contains 10 mg of amlodipine
(as amlodipine besilate).
Amlodipine 10 mg Tablets
28 tablets

Module 5

Scientific discussion during initial procedure

I. RECOMMENDATION

Based on the review of the data and the Applicant's responses to questions raised by the RMS and CMSs on quality, safety and efficacy, the RMS considered that the application for Amlodipine 5mg and 10mg Tablets in the treatment of essential hypertension and chronic stable and vasospastic anginal pectoris was approvable.

II. EXECUTIVE SUMMARY

II.1 Problem statement

Hypertension and ischaemic heart disease, including angina, remain major problems in the cardiovascular disease area. Pharmacotherapy remains the cornerstone of treatment. Calcium antagonists have been used for a long time for treatment of these conditions and have a good record of efficacy and safety through their extensive use in clinical practice.

II.2 About the product

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 cells and differs from nifedipine by way of its slow onset of action and recovery. It is well established for use in the proposed indications.

II.3 General comments on the submitted dossier

The dossier is of good quality. The applicant submitted the overviews and summaries in CTD format and these were found to be helpful.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

A current Certificate of GMP compliance for the finished product manufacturing site has been provided.

The bioequivalence study was conducted in compliance with GCP and in accordance with the Declaration of Helsinki and the US code of Federal Regulations.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The applicant refers to the AIM's Certificate of Suitability.

The drug substance is a well known pharmaceutical active substance and its synthesis and control are satisfactory. The drug substance specification is in line with the Ph Eur monograph. Stability studies support the proposed retest interval.

It has been stated that the drug substance manufacturer has collaborated with the Pharmacopoeia regarding the revision of the amlodipine besilate monograph.

Drug Product
The finished products are formulated as immediate release tablets using conventional pharmaceutical ingredients. The development studies carried out were appropriate for these generic products. The manufacturing process is supported by pilot data and the applicant has committed to conduct further process validation studies in accordance with the protocol agreed in the dossier on consecutive production scale batches. The product specification includes relevant controls for a product of this nature. Stability studies of the final packaged product have been conducted appropriately in accordance with relevant guidelines and results support the proposed shelf-life (2 years) and label storage conditions (store below 25°C).

III.2 Non-clinical aspects

Pharmacology
The pharmacology of amlodipine is well known. No new data have been submitted and none are required.

Pharmacokinetics
The pharmacokinetics of amlodpine are well known. No new data have been submitted and none are required.

Toxicology
The toxicological properties of amlodipine besilate are well known.

III.3 Clinical aspects

The clinical pharmacology of amlodipine is well known.

Pharmacokinetics
The bioequivalence of Arrow's Amlodipine 10mg tablets to Istin 10 mg tablets was evaluated in a single dose, randomised, crossover, comparative study. The study was conducted in healthy male and female volunteers and complied with the Declaration of Helsinki, the US Code of Federal Regulations and GCP.

A total of 28 subjects were enrolled in the study, of which 25 completed. Out of the three withdrawals one was due to withdrawal of consent, one was due to an adverse reaction (hypersensitivity) and one for inappropriate concomitant medication administration. Subjects received study medication in a fasted state. The sampling period was 192 hours and the wash out period was at least 21 days.

Data from 24 subjects were analysed as per protocol.

Summary pharmacokinetic data for amlodipine: mean (CV)

Parameter	Arrow Amlodipine 10 mg (test)	Istin 10mg (reference)	Relative mean ratio** (%)	90% confidence interval
C_{max} (pg/ml)	6737.3 (28.9)	6791.6 (32.4)	99.70	95.15 – 104.47
AUC $_{0-t}$ (pg.hr/ml)	331184.3 (29.4)	338245.4 (30.3)	98.02	94.07 – 102.13
AUC $_{0-\infty}$ (pg.hr/ml)	348074.5 (30.1)	355047.9 (30.4)	98.06	94.18 – 102.10
t_{max} (hr)*	7.50 (19.4)	7.50 (14.2)	-	-
$t_{½}$ (hr)	43.42 (15.6)	43.15 (14.9)	-	-

* t_{max} values are median ** based on geometric LS means

Assessor's comments on bioequivalence

When 25 subjects completed the study in its entirety, data from all 25 subjects should have been included in the final analysis. However, the confidence interval was narrow and exclusion of a single subject would not affect the data significantly. The protocol clearly defined the criteria for inclusion of the first 24 completers for analysis. Bioequivalence between the test product and Istin has been shown.

Pharmacodynamics

No new data have been submitted. The pharmacodynamics of amlodipine are well known.

Clinical efficacy

No new data have been submitted and none are required. The efficacy of amlodipine is well established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for this type of application. The safety profile of amlodipine is well known.

IV. BENEFIT RISK ASSESSMENT

The clinical efficacy and safety of amlodipine is well known from its extensive use in clinical practice. No new data were submitted and this is acceptable. Bioeqivalence between the product and Istin tablets has been shown. The risk:benefit ratio of the product is considered favourable

A marketing authorisation is recommended.

Overall conclusion

QUALITY

The important quality characteristics of Amlodipine 5 and 10 mg 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 benefit/risk balance.

PRECLINICAL

The pharmacological and pharmacokinetic data submitted are satisfactory for an application of this type.

Results of the toxicology studies did not identify any properties likely to cause toxicity in humans when the product is used as directed in the SPC.

EFFICACY

Clinical studies have demonstrated the efficacy of Amlodipine 5 mg and 10 mg Tablets in the treatment of essential hypertension and chronic stable and vasospastic angina pectoris.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.

Module 6

Steps taken after initial procedure

Following grant of marketing authorisation on 7 March 2007, a Type 1A variation was granted to register an updated Certificate of Suitability for the drug substance on 16 March 2007.

A type 1B variation was granted to amend one of the analytical procedures used on the finished product on 10 April 2007.