

**AMLODIPINE 5MG TABLETS
PL 19156/0033**

**AMLODIPINE 10MG TABLETS
PL 19156/0034**

UKPAR

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**AMLODIPINE 5MG TABLETS
PL 19156/0033**

**AMLODIPINE 10MG TABLETS
PL 19156/0034**

LAY SUMMARY

On 21st May 2007, the MHRA granted Pharmaceutical Services Incorporated (PSI) NV Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg Tablets (PL 19156/0033) and Amlodipine 10mg Tablets (PL 19156/0034). These are prescription only medicines (POM) for the treatment of high blood pressure (hypertension) or a certain type of chest pain called angina, a rare form of which is Prinzmetal's or variant angina.

Amlodipine Tablets contain the active ingredient amlodipine besilate, which is a type of medicine known as a calcium-channel blocker. It relieves heart problems by widening blood vessels to allow more blood through. This helps reduce blood pressure and relieve the strain on heart muscles.

The test products were considered to be generic medicinal products of the original products Istin 5mg and 10mg Tablets (Pfizer Limited, UK) based on the bioequivalence study submitted and no new safety issues arose as a result of this study. 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.

**AMLODIPINE 5MG TABLETS
PL 19156/0033**

**AMLODIPINE 10MG TABLETS
PL 19156/0034**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Amlodipine 5mg Tablets (PL 19156/0033) and Amlodipine 10mg Tablets (PL 19156/0034) on 21st May 2007. The products are prescription-only medicines.

These are two strengths of Amlodipine submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products Istin Tablets 5 and 10mg (Pfizer Limited, UK).

The products contain the active ingredient amlodipine besilate, a dihydropyridine calcium antagonist. Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. Amlodipine 5mg and 10mg Tablets are indicated for the treatment of essential hypertension and chronic stable and vasospastic angina pectoris.

These applications for Amlodipine 5 and 10mg Tablets were submitted at the same time and both depend on the bioequivalence study comparing the applicant's 10mg product with Norvasc 10mg Tablets (Pfizer Ltd, The Netherlands). Consequently, all sections of this Scientific Discussion refer to both products.

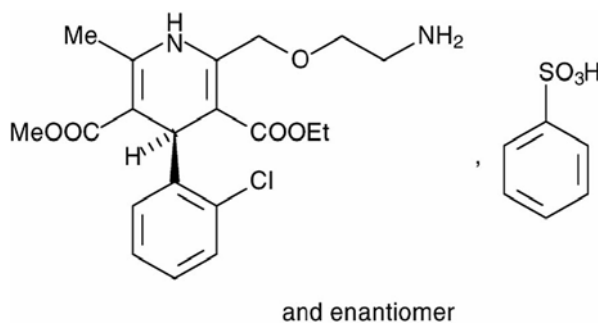
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Amlodipine besilate

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:



CAS registry number: 111470-99-6

Physical form: A white or almost white powder. Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol. No polymorphism has been encountered.

Molecular formula: $C_{20}H_{25}ClN_2O_6$, $C_6H_6O_3S$

Molecular weight: 567.1

Amlodipine besilate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of amlodipine besilate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of amlodipine besilate for inclusion in this medicinal product.

Appropriate stability data have been generated supporting a retest period of 36 months when stored in the proposed packaging. Suitable post approval commitments have been provided to perform follow-up stability studies.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, croscarmellose sodium, sodium starch glycollate, sodium acid citrate, crospovidone and magnesium stearate. All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of sodium acid citrate (which complies with a British Pharmacopoeia monograph). Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

Pharmaceutical development

The applicant has provided a suitable product development rationale and data.

Satisfactory impurity and dissolution data have been provided, showing that the proposed products are comparable to the comparator products (Istin 5mg and 10mg Tablets).

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is packaged in aluminium/polyvinylchloride/polyvinylidene chloride blisters in pack sizes of 28 tablets. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. The storage condition 'Store in original package' has been included.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution and impurity profiles have been provided for the proposed and reference products and bioequivalence has been demonstrated to a suitable reference product.

PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Istin 5 and 10mg Tablets (Pfizer Limited, UK), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Pharmacodynamics

No new data submitted. The pharmacodynamics of amlodipine are well-described. It is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The mechanism by which amlodipine relieves angina involves reduction of total peripheral resistance and dilatation of the main coronary arteries and coronary arterioles.

Pharmacokinetics

After oral administration of therapeutic doses, amlodipine is well-absorbed, with peak blood levels between 6-12 hours post dose. Pharmacokinetics over the therapeutic range are dose proportional. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Bioequivalence

A comparative, randomised, two-treatment, two-period, single-dose crossover study was performed on healthy fasted volunteers, comparing the applicant's 10mg test product versus Norvasc 10mg Tablets (Pfizer Limited, The Netherlands).

Blood samples were taken from subjects pre-dose and up to 168 hours post dose. There was a 21-day washout period between doses.

Bioequivalence results for log-transformed test/reference ratios (with 90% confidence intervals) are presented below:

AUC_t	0.992 (0.883-1.041)
AUC_{inf}	0.996 (0.900-1.067)
C_{max}	0.991 (0.914-1.053)

Based on the submitted bioequivalence data, it can be considered that the applicant's Amlodipine 10mg Tablets is a generic medicinal product to Istin 10mg Tablets and Norvasc 10mg Tablets.

As these products meet all the criteria as specified in the Note 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.

EFFICACY

No new data are submitted and none are required for this type of application.

SAFETY

No new data are submitted and none are required for this type of application.

EXPERT REPORTS

A clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

This is consistent with that for the reference products and is satisfactory.

LABELLING

These are satisfactory.

APPLICATION FORMS (MAA)

These are satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

These are consistent with those for the reference products and are satisfactory.

DISCUSSION

The applicant has satisfactorily demonstrated bioequivalence between the 10mg strengths of test and reference products. As these products meet all the criteria as specified in the Note 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.

MEDICAL CONCLUSION

The bioequivalence study submitted has shown that these products can be considered as generic medicinal products to the originator products Istin 5 and 10mg Tablets (Pfizer Limited, UK).

Marketing authorisations are recommended for these applications.

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 benefit/risk 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 Amlodipine 10mg Tablets and Istin 10mg Tablets (Pfizer Limited, UK). As these products meet all the criteria as specified in the Note 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. Thus, no separate bioequivalence study is necessary for the 5mg strength.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Istin tablets.

RISK BENEFIT ASSESSMENT

The quality of the product 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 innovator 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.

**AMLODIPINE 5MG TABLETS
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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 30 th June 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 20 th July 2004
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 24 th January 2005 and 27 th November 2006, and further information relating to the quality dossiers on 2 nd March 2005 and 28 th March 2006.
4	The applicant responded to the MHRA's requests, providing further information on 16 th May 2007 for the clinical sections, and again on 27 th March 2006 for the quality sections.
5	The applications were determined on 21 st May 2007

**AMLODIPINE 5MG TABLETS
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: amlodipine.

One tablet contains amlodipine besilate equivalent to 5 mg amlodipine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablets are white, circular, biconvex and plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension
- Chronic stable and vasospastic anginal pectoris

4.2 Posology and method of administration

In adults

For both hypertension and angina the usual initial dose is 5 mg amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Use in children and adolescents (less than 18 years of age)

Not recommended.

Use in the elderly

Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

Patients with hepatic impairment

See section 4.4 "Special warnings and special precautions for use".

Patients with renal impairment

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

4.3 Contraindications

Hypersensitivity to dihydropyridines, amlodipine or to any of the excipients.

Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Use in patients with heart failure

In a long term, placebo controlled study, in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1 (Pharmacodynamic Properties).

Use in patients with impaired hepatic function

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

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

4.5 Interaction with other medicinal products and other forms of interaction

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

In vitro data from studies with human plasma, indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.

Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors and CYP3A4 inducers.

Special Studies: Effect of other agents on amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration of 240ml of grapefruit juice with single oral dose of amlodipine 10mg in healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of amlodipine on other agents

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin: In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporin: Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporine.

Drug/Laboratory test interactions: None known.

4.6 **Pregnancy and lactation**

Pregnancy

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy. Accordingly, amlodipine should not be administered during pregnancy or to women of childbearing potential unless effective contraception is used (see section 4.3).

Lactation

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in lactation. Accordingly, amlodipine should not be administered during lactation (see section 4.3).

4.7 **Effects on ability to drive and use machines**

Clinical experience with amlodipine indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

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

4.8 **Undesirable effects**

The frequencies mentioned are subdivided on categories according to following percentages:

Very common: more than 10%

Common: 10% or less, but more than 1%

Uncommon: 1%, or less, but more than 0,1%,

Rare: 0,1 % or less, but more than 0,01%

Very rare: 0,01% and less (this includes isolated reports).

The most commonly reported side effects of amlodipine are headache, oedema, rash, fatigue, nausea, flushing and dizziness.

Other reported side effects are:

Blood and the lymphatic system disorders

Very rare: thrombocytopenia, leucocytopenia

Immune system disorders

Very rare: allergic reaction

Metabolic and nutrition disorders

Very rare: hyperglycaemia

Psychiatric disorders

Uncommon: mood changes, insomnia

Nervous system disorders

Common: somnolence

Uncommon: tremor, taste perversion, syncope, hypoaesthesia, paraesthesia

Very rare: peripheral neuropathy

Eye disorders

Uncommon: visual disturbances

Ear and Labyrinth disorders

Uncommon: tinnitus

Cardiac disorders

Common: Palpitations

Rare: syncope

Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation

Vascular disorders

Uncommon: hypotension

Very rare: vasculitis

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea, rhinitis

Very rare: coughing

Gastrointestinal disorders

Common: Abdominal pain

Uncommon: Vomiting, dyspepsia, altered bowel habits, dry mouth

Very rare: pancreatitis, gastritis, gingival hyperplasia

Hepato-biliary disorders

Very rare: abnormal liver function tests, hepatitis, jaundice,

Skin and subcutaneous tissue disorders

Uncommon: alopecia, pruritus, peripura, skin discolouration, increased sweating

Very rare: erythema multiforme, angioedema and urticaria

Musculoskeletal, connective tissue and bone disorders

Uncommon: myalgia, arthralgia, muscle cramps and back pain

Renal and urinary disorders

Uncommon: increased urinary frequency, micturition disorder, nocturia

Reproductive system and breast disorders

Uncommon: impotence, gynaecomastia

General disorders and administration site conditions

Uncommon: chest pain, asthenia, pain, malaise, increase or decrease in weight

4.9 Overdose

In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. Available data suggest that gross overdosage (> 100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. In healthy volunteers, the use of charcoal up to 2h 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 channel blockers – Dihydropyridine derivatives.

ATC code: C08CA01.

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has

not been fully determined but amlodipine reduces total ischaemic burden by the following two actions.

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

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 ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo-controlled study (PRAISE-2) 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 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, plasma protein binding

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation/elimination

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in the 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 studied.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Microcrystalline cellulose (E460)
Sodium starch glycollate
Sodium acid citrate (E331)
Magnesium stearate (E572)
Croscarmellose sodium
Crospovidone

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.
Store in the original packaging.

6.5 Nature and contents of container

Blisters made of aluminium foil with VMCH coating (a carboxyl modified vinyl copolymer) on one side and amber coloured PVC foil. Packs of 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

PSI NV
Kraanlei 27
9000 Ghent
Belgium

8 MARKETING AUTHORISATION NUMBER(S)

PL 19156/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/05/2007

10 DATE OF REVISION OF THE TEXT

21/05/2007

1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: amlodipine.

One tablet contains amlodipine besilate equivalent to 10 mg amlodipine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablets are white, circular, biconvex and plain on both sides.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

- Essential hypertension
- Chronic stable and vasospastic anginal pectoris

4.2 Posology and method of administration***In adults***

For both hypertension and angina the usual initial dose is 5 mg amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.

No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Use in children and adolescents (less than 18 years of age)

Not recommended.

Use in the elderly

Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

Patients with hepatic impairment

See section 4.4 "Special warnings and special precautions for use".

Patients with renal impairment

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

4.3 Contraindications

Hypersensitivity to dihydropyridines, amlodipine or to any of the excipients.

Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Use in patients with heart failure

In a long term, placebo controlled study, in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1 (Pharmacodynamic Properties).

Use in patients with impaired hepatic function

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

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

4.5 Interaction with other medicinal products and other forms of interaction

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

In vitro data from studies with human plasma, indicate that amlodipine has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.

Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors and CYP3A4 inducers.

Special Studies: Effect of other agents on amlodipine

Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration of 240ml of grapefruit juice with single oral dose of amlodipine 10mg in healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of amlodipine on other agents

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin: In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporin: Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporine.

Drug/Laboratory test interactions: None known.

4.6 **Pregnancy and lactation**

Pregnancy

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy. Accordingly, amlodipine should not be administered during pregnancy or to women of childbearing potential unless effective contraception is used (see section 4.3).

Lactation

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in lactation. Accordingly, amlodipine should not be administered during lactation (see section 4.3).

4.7 **Effects on ability to drive and use machines**

Clinical experience with amlodipine indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

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

4.8 **Undesirable effects**

The frequencies mentioned are subdivided on categories according to following percentages:

Very common: more than 10%

Common: 10% or less, but more than 1%

Uncommon: 1%, or less, but more than 0,1%,

Rare: 0,1 % or less, but more than 0,01%

Very rare: 0,01% and less (this includes isolated reports).

The most commonly reported side effects of amlodipine are headache, oedema, rash, fatigue, nausea, flushing and dizziness.

Other reported side effects are:

Blood and the lymphatic system disorders

Very rare: thrombocytopenia, leucocytopenia

Immune system disorders

Very rare: allergic reaction

Metabolic and nutrition disorders

Very rare: hyperglycaemia

Psychiatric disorders

Uncommon: mood changes, insomnia

Nervous system disorders

Common: somnolence

Uncommon: tremor, taste perversion, syncope, hypoaesthesia, paraesthesia

Very rare: peripheral neuropathy

Eye disorders

Uncommon: visual disturbances

Ear and Labyrinth disorders

Uncommon: tinnitus

Cardiac disorders

Common: Palpitations

Rare: syncope

Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation

Vascular disorders

Uncommon: hypotension

Very rare: vasculitis

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea, rhinitis

Very rare: coughing

Gastrointestinal disorders

Common: Abdominal pain

Uncommon: Vomiting, dyspepsia, altered bowel habits, dry mouth

Very rare: pancreatitis, gastritis, gingival hyperplasia

Hepato-biliary disorders

Very rare: abnormal liver function tests, hepatitis, jaundice,

Skin and subcutaneous tissue disorders

Uncommon: alopecia, pruritus, peripura, skin discolouration, increased sweating

Very rare: erythema multiforme, angioedema and urticaria

Musculoskeletal, connective tissue and bone disorders

Uncommon: myalgia, arthralgia, muscle cramps and back pain

Renal and urinary disorders

Uncommon: increased urinary frequency, micturition disorder, nocturia

Reproductive system and breast disorders

Uncommon: impotence, gynaecomastia

General disorders and administration site conditions

Uncommon: chest pain, asthenia, pain, malaise, increase or decrease in weight

4.9 Overdose

In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. Available data suggest that gross overdosage (> 100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. In healthy volunteers, the use of charcoal up to 2h 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 channel blockers – Dihydropyridine derivatives.

ATC code: C08CA01.

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has

not been fully determined but amlodipine reduces total ischaemic burden by the following two actions.

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

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 ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo-controlled study (PRAISE-2) 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 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, plasma protein binding

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation/elimination

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in the 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 studied.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Microcrystalline cellulose (E460)
Sodium starch glycollate
Sodium acid citrate (E331)
Magnesium stearate (E572)
Croscarmellose sodium
Crospovidone

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.
Store in the original packaging.

6.5 Nature and contents of container

Blisters made of aluminium foil with VMCH coating (a carboxyl modified vinyl copolymer) on one side and amber coloured PVC foil. Packs of 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

PSI NV
Kraanlei 27
9000 Ghent
Belgium

8 MARKETING AUTHORISATION NUMBER(S)

PL 19156/0034

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/05/2007

10 DATE OF REVISION OF THE TEXT

21/05/2007

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.
2. Before you take Amlodipine.
3. How to take Amlodipine.
4. Possible side effects.
5. How to store Amlodipine.
6. Further information.

1. WHAT AMLODIPINE IS AND WHAT IT IS USED FOR

Amlodipine belongs to a group of medicines called calcium antagonists.

Amlodipine is used to treat:

- high blood pressure
- chest pain due to narrowing of the coronary arteries of the heart muscle (angina pectoris) or the more rare form of chest pain caused by cramping of the coronary arteries of the heart muscle (vasospastic angina).

If you suffer from high blood pressure, Amlodipine works by relaxing blood vessels, so that blood passes through them more easily.

If you suffer from angina, Amlodipine works by improving blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented. Amlodipine does not provide immediate relief of chest pain from angina.

2. BEFORE YOU TAKE AMLODIPINE

Do not take Amlodipine

- if you are **allergic** to amlodipine or similar calcium channel blockers (the so-called dihydropyridine derivatives) or to any of the other ingredients (for a full list of ingredients, see section 6)
- if you have very **low blood pressure**
- if you are suffering from **insufficient blood supply** to your tissues with symptoms like e.g. low blood pressure, low pulse, fast heartbeat (shock, including cardiogenic shock). Cardiogenic shock means shock due to severe heart troubles.
- if you have **heart failure** after a heart attack within the last four weeks
- if you are suffering from **narrowing of the aorta** (aortic stenosis)
- if you get heart-associated **chest pain** also at rest or with minimal effort (unstable angina pectoris)
- if you are pregnant or breast-feeding

Take special care with Amlodipine

Tell your doctor before you start treatment:

- if you have **heart failure**
- if you have reduced **liver function**
- if you have reduced **kidney function**.

Elderly

The dose should be increased with caution.

Children and adolescents (below 18 years)

Amlodipine should not be used in children and adolescents because of insufficient experience.

Taking other medicines

Some medicines (including medicines obtained without prescription, herbal medications or natural products) may interact with Amlodipine. This means that the action of both medicines can be changed.

It is therefore important to tell your doctor if you take any of the following medicines:

- **Medicines that can lower blood pressure**, e.g. beta-blockers, ACE-inhibitors, alpha-1-blockers and diuretics. Amlodipine may enhance the blood pressure lowering effects of these medicines.
- **Diltiazem (cardiac medicine)** may intensify the effect of Amlodipine.
- **Ketoconazole and itraconazole (antifungal medicines)** may intensify the effect of Amlodipine.
- **HIV-protease-inhibitors (antiviral medicines to treat HIV infections, e.g. ritonavir)** may intensify the effect of Amlodipine.
- **Clarithromycin, erythromycin and telithromycin (antibiotics)** may intensify the effect of Amlodipine.
- **Nefazodon (medicine to treat depression)** may intensify the effect of Amlodipine.

- **Rifampicin and rifabutin (antibiotics)** may reduce the effect of Amlodipine.
- **St. John's wort (Hypericum perforatum; herbal medicine for depression)** may reduce the effect of Amlodipine.
- **Dexamethason (cortisone)** may reduce the effect of Amlodipine.
- **Phenobarbital, phenytoin and carbamazepin (medicines for epilepsy)** may reduce the effect of Amlodipine.
- **Nevirapine (antiviral medicine)** may reduce the effect of Amlodipine.

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 with food and drink

Amlodipine should be taken with a glass of liquid (e.g. a glass of water) with or without food.

Simultaneous intake of grapefruit or grapefruit juice has no influence on the effect of amlodipine.

Pregnancy and breast-feeding

If you are pregnant or become pregnant during treatment, do not take Amlodipine unless specifically prescribed by your doctor.

There are insufficient data to evaluate the risk for the baby when you take amlodipine during pregnancy.

If you are breast-feeding, do not take Amlodipine. Please contact your doctor.

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

Driving and using machines

Be careful if you drive or operate machinery if you take this medicine. Amlodipine may not directly affect your ability to drive or operate machinery. However, some patients experience side effects such as dizziness or sleepiness related to the fall in the blood pressure (see section 4 of this leaflet). Such side effects are more likely to occur after beginning to take Amlodipine or after dose increases. If you experience these side effects, you should refrain from driving and other activities requiring alertness.

3. HOW TO TAKE AMLODIPINE

Dosage

Always take Amlodipine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Adults

The usual starting dose is 5 mg once daily. If necessary, your doctor may increase the dose to 10 mg once daily.

Children and adolescents (younger than 18 years)

Amlodipine should not be given to children and adolescents.

Elderly patients

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

If you have kidney problems

The normal dosage is recommended. Amlodipine cannot be removed from the blood by dialysis (artificial kidney). Amlodipine should be administered with particular caution to patients undergoing dialysis.

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").

Methods and routes of administration

Swallow the tablets with a glass of water. Do not chew. You can take them with or without food.

If you take more Amlodipine than you should

If you or someone else has taken too much Amlodipine, contact your doctor, an emergency department or a poisoning center 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. Never take a double dose of Amlodipine tablets to make up for the dose that you have missed.

If you stop taking Amlodipine tablets

Your doctor has told you 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.

Amlodipine is usually used for longterm treatment.

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 can cause side effects, although not everybody gets them.

For the assessment of side effects, the following descriptions of frequency have been used:

Very common	in more than 1 in 10 patients treated
Common	in less than 1 in 10, but more than 1 in 100 patients treated
Uncommon	in less than 1 in 100, but more than 1 in 1000 patients treated
Rare	in less than 1 in 1000, but more than 1 in 10 000 patients treated
Very rare	in less than 1 in 10 000 patients treated, including isolated cases

The following side effects have been observed during treatment with Amlodipine:

Blood and lymph (blood and lymphatic system disorders)

Very rare:

reduced number of white blood cells, which may cause unexplained fever, sore throat, and flu-like symptoms (leukopenia)

- reduced number of blood platelets in blood, which may cause easy bruising or nasal bleeding (thrombocytopenia)

Hormone system (endocrine disorders)

Uncommon: enlarged breasts in men

Metabolism disorders

Very rare: increase of the blood sugar level

Mind (psychiatric disorders)

Uncommon: sleep disorders, irritability, depression

Rare: confusion, mood changes including anxiety

Nerves (nervous system disorders)

Common: headache (especially at the beginning of treatment), sleepiness, dizziness, weakness

Uncommon: feeling unwell, dry mouth, uncontrolled shaking (tremor), pins and needles (paraesthesia), increased sweating

Rare: change in taste

Very rare: pain or numbness in hands and feet (peripheral neuropathy)

Eyes (eye disorders)

Uncommon: problems with your eye-sight (visual disturbances)

Ears (ear and labyrinth disorders)

Uncommon: ringing or buzzing in the ears (tinnitus)

Heart (cardiac disorders)

Common: a quicker or irregular heart beat (palpitations)

Uncommon: fainting, increased heart rate (tachycardia), chest pain, aggravation of angina may occur at the beginning of the treatment
In isolated cases the following side effects have occurred, but the relationship to treatment with Amlodipine is uncertain: heart attack (myocardial infarction), irregular heartbeat and chest pain (angina pectoris)

Circulation (vascular disorders)

Uncommon: low blood pressure, inflammation of the blood vessels

Lungs, breathing and chest (respiratory, thoracic and mediastinal disorders)

Uncommon: breathing difficulties, inflammation of the nasal mucosa (rhinitis), cough

Stomach and bowel (gastrointestinal disorders)

Common: nausea, digestive problems, stomach pain

Uncommon: vomiting, diarrhoea, constipation, swollen gums (gingival hyperplasia)

Very rare: inflammation of the stomach lining (gastritis), inflammation of the pancreas (pancreatitis)

Liver and bile (hepatobiliary disorders)

Rare: increase of certain liver enzymes; yellowing of the skin or whites of the eyes, this could be the result of abnormal liver function or inflammation of the liver

Skin (skin and subcutaneous tissue disorders)

Very common: swollen ankles

Common: facial redness and feeling hot (especially at the beginning of treatment)

Uncommon: prickling and tingling sensation of the skin (exanthema), itching, nettle rash, hair loss, discolouration of the skin

Very rare: allergic reaction with swelling of the skin of face or extremities, swelling of lips or tongue, swelling of the mucous membranes in the mouth and throat, resulting in shortness of breath and difficulty to swallow (angioedema). Contact an emergency room or a doctor immediately if this occurs.

In isolated cases allergic skin rash with irregular red spots, caused by medicines (erythema exudativum multiforme) or severe allergic reactions with blistering eruptions of the skin and mucous membranes (exfoliative dermatitis, Stevens-Johnson-Syndrome) have been observed.

Muscles and bones (musculoskeletal and bone disorders)

Uncommon: muscle cramps, back pain, muscle and joint pain

Kidneys (renal and urinary disorders)

Uncommon: increased need to urinate (increased micturition frequency)

Sexual organs and breast (reproductive system and breast disorders)

Uncommon: impotence

General disorders

Uncommon: increase or decrease in weight

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

Keep out of the reach and sight of children.

Do not use Amlodipine after the expiry date „EXP“ which is stated on the packaging. The expiry date refers to the last day of that month.

This medicine requires no special precautions for storage.

Keep the tablets in the original packaging.

Medicinal 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 to protect the environment.

6. FURTHER INFORMATION

What Amlodipine contains

Amlodipine 5 mg tablets

- The active substance is amlodipine. Each tablet contains 5 mg of amlodipine (as besilate).
- The other ingredients are microcrystalline cellulose (E460), sodium starch glycolate, sodium acid citrate (E331), magnesium stearate (E572), croscarmellose sodium, crospovidone.

Amlodipine 10 mg tablets

- The active substance is amlodipine. Each tablet contains 10 mg of amlodipine (as besilate).
- The other ingredients are microcrystalline cellulose (E460), sodium starch glycolate, sodium acid citrate (E331), magnesium stearate (E572), croscarmellose sodium, crospovidone.

What Amlodipine looks like and contents of the pack

Amlodipine 5 mg tablets

A white, circular tablet, smooth on both sides.

Amlodipine 10 mg tablets

A white, circular tablet, smooth on both sides.

Your tablets come in:

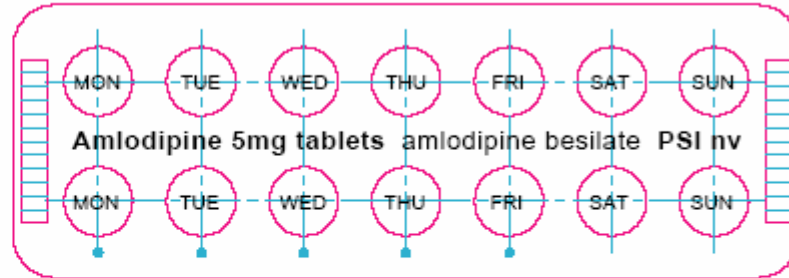
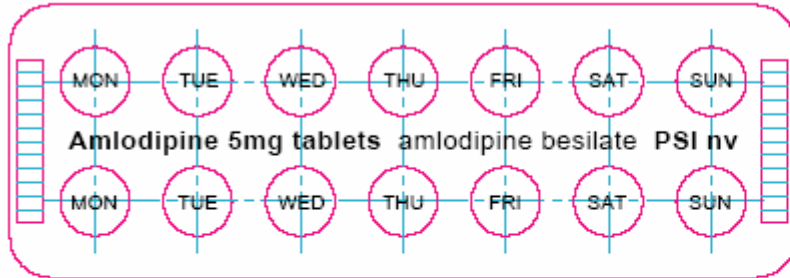
- Blister packs of 28 tablets.

Marketing Authorisation Holder and Manufacturer

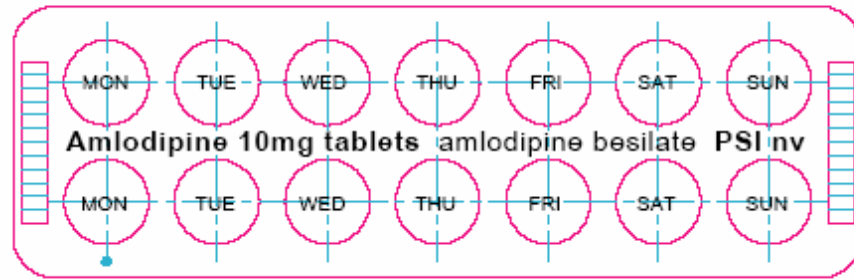
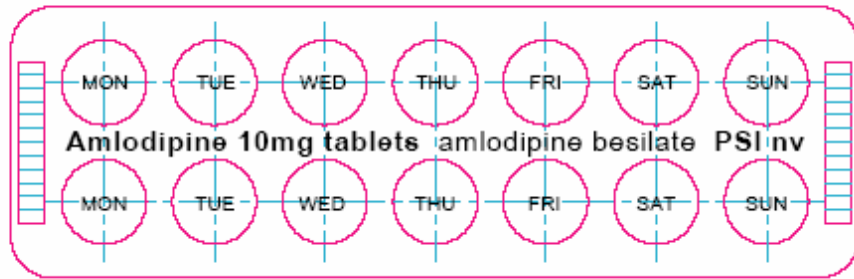
PSI nv	PSI supply nv
Kraanlei 27	Kraanlei 27
9000 Ghent	9000 Ghent
Belgium	Belgium

This leaflet was last approved in

LABELS



Batch and Exp will be embossed on ends as manufacturers template



Batch and Exp will be embossed on ends as manufacturers template

000000 000000 0

POM

Affix pharmacy label here

For Oral administration. Read the package leaflet before use. No special precautions for storage. Store in the original packaging.

Batch no :
Exp. date :

P/TzC xxx

Amlodipine 5mg tablets 28 tablets

amlodipine besilate

Amlodipine 5mg tablets 5mg

amlodipine besilate

28 tablets

Each tablet contains 5 mg amlodipine as amlodipine besilate

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
MA Holder: PSI nv
Kraanlei 27, 9000 Ghent, Belgium

PL 19156/0033

Amlodipine 5mg tablets
28 tablets

000000 000000 0

Affix pharmacy label here

POM

For Oral administration.
Read the package leaflet before use.
No special precautions for storage.
Store in the original packaging.

Batch no :
Exp. date :

Amlodipine 10mg tablets
amlodipine besilate

28 tablets

PJT2Cxxx

Amlodipine 10mg tablets
amlodipine besilate

10mg

Amlodipine 10mg tablets
28 tablets

28 tablets

Each tablet contains 10 mg amlodipine as amlodipine besilate

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

MA Holder: PSI nv
Kraanlei 27, 9000 Ghent, Belgium

PL 19156/0034