AMLODIPINE 5MG TABLETS (AMLODIPINE BESILATE) PL 19156/0039

AMLODIPINE 10MG TABLETS (AMLODIPINE BESILATE) PL 19156/0040

UKPAR

TABLE OF CONTENTS

AMLODIPINE 5MG TABLETS
(AMLODIPINE BESILATE)
PL 19156/0039

AMLODIPINE 10MG TABLETS
(AMLODIPINE BESILATE)
PL 19156/0040

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Pharmaceutical Services Incorporated (PSI) N.V. Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg Tablets (PL 19156/0039) and Amlodipine 10mg Tablets (PL 19156/0040) on 10th December 2007. These are prescription-only medicines (POM) used for the treatment of high blood pressure and angina (chest pain).

The active ingredient, amlodipine, is one of a group of medicines known as calcium antagonists. Amlodipine is authorised to treat high blood pressure, which it achieves by relaxing blood vessels so blood can pass through them more easily. Amlodipine is also used to treat 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). It does this by improving blood supply, and thus oxygen supply, to the heart muscle.

These applications are duplicates of previously granted applications for Amlodipine 5mg Tablets (PL 19156/0033) and Amlodipine 10mg Tablets (PL 19156/0034), held by Pharmaceutical Services Incorporated (PSI) N.V. The test and reference products are identical.

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

AMLODIPINE 5MG TABLETS
(AMLODIPINE BESILATE)
PL 19156/0039

AMLODIPINE 10MG TABLETS
(AMLODIPINE BESILATE)
PL 19156/0040

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

The UK granted Pharmaceutical Services Incorporated (PSI) N.V. Marketing Authorisations for the medicinal products Amlodipine 5mg Tablets (PL 19156/0039) and Amlodipine 10mg Tablets (PL 19156/0040) on 10th December 2007. The products are prescription-only medicines.

These applications were submitted as simple abridged 'informed consent' applications according to article 10c of Directive 2001/83/EC (as amended), cross-referring to the Marketing Authorisations Amlodipine 5mg Tablets (PL 19156/0033) and Amlodipine 10mg Tablets (PL 19156/0034), granted to Pharmaceutical Services Incorporated (PSI) N.V. on 21st May 2007. A PAR has been written and published for these reference products. These abridged applications had been approved as generic medicinal products of Istin Tablets 5mg (PL 00057/0297) and Istin Tablets 10mg (PL 00057/0298) respectively, granted to Pfizer Limited on 18th September 1989.

No new data was submitted nor was it necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products.

Amlodipine 5mg Tablets and Amlodipine 10mg Tablets contain the active ingredient amlodipine, as the besilate. Amlodipine is one of a group of medicines known as calcium antagonists and is indicated for the treatment of essential hypertension, and both chronic stable, and vasospastic, anginal pectoris. Amlodipine 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.

These applications for Amlodipine 5mg Tablets and Amlodipine 10mg Tablets were submitted at the same time and were assessed concurrently. Consequently, all sections of this Scientific Discussion refer to both products.

PHARMACEUTICAL ASSESSMENT

LICENCE NUMBERS:	PL 19156/0039 & 0040
PROPRIETARY NAME:	Amlodipine 5mg & 10mg Tablets
ACTIVE INGREDIENTS:	Amlodipine besilate
COMPANY NAME:	Pharmaceutical Services Incorporated (PSI) N.V.
E.C. ARTICLE:	Article 10c of Directive 2001/83/EC (as amended)
LEGAL STATUS:	POM

1. INTRODUCTION

These are simple abridged applications, submitted under Article 10c of Directive 2001/83/EC (as amended) for Amlodipine 5mg Tablets and Amlodipine 10mg Tablets. The proposed MA holder is 'PSI N.V., Kraanlei 27, 9000 Ghent, Belgium'.

The reference products are Amlodipine 5mg Tablets (PL 19156/0033) and Amlodipine 10mg Tablets (PL 19156/0034), granted to PSI N.V. on 21st May 2007. The test and reference products are identical.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1 Name(s)

The proposed names of the products are Amlodipine 5mg Tablets and Amlodipine 10mg Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes

The products contain amlodipine besilate equivalent to 5mg and 10mg of amlodipine respectively. They are to be stored in blister packs (PVC (polyvinylchloride) or PVC / PVDC (polyvinylidine chloride) / aluminium) of 28 tablets.

The proposed shelf-life (3 years) and storage conditions (Store in the original package) are consistent with the details registered for the cross-reference products.

2.3 Legal status

The products are available by supply through pharmacies, subject to a medical prescription.

2.4 Marketing authorisation holder / Contact Persons/Company

The proposed Marketing Authorisation holder is 'PSI N.V., Kraanlei 27, 9000 Ghent, Belgium'.

The QP responsible for pharmacovigilance is stated and their CV is included.

2.5 Manufacturers

The proposed manufacturing site is consistent with that registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

2.8 Finished product / shelf-life specification

The proposed finished product specifications are in line with the details registered for the cross-reference products.

2.9 Drug substance specification

The proposed drug substance specifications are consistent with the details registered for the cross-reference products.

2.10 TSE Compliance

No materials of animal or human origin are included in the products.

3. EXPERT REPORTS

Satisfactory expert reports and curriculum vitae of experts are provided.

4. PRODUCT NAME & APPEARANCE

See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS

The approved SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL) / CARTON

PIL

The patient information leaflet has been prepared in the user tested format and in line with the details registered for the cross-reference products. The approved PIL is satisfactory.

Cartons

The approved artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In line with current legislation the applicant has included the name of the products in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS

The grounds for these applications are considered adequate. It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

The applications were submitted as simple abridged applications according to article 10c of Directive 2001/83/EC (as amended).

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

CLINICAL ASSESSMENT

The applications were submitted as simple abridged applications according to article 10c of Directive 2001/83/EC (as amended).

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

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The data for these applications are consistent with that previously assessed for the cross-reference products and as such has been judged to be satisfactory.

PRECLINICAL

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

EFFICACY

Medicinal products containing amlodipine have been available in the UK for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

These applications are identical to the cross-reference products Amlodipine 5mg Tablets (PL 19156/0033) and Amlodipine 10mg Tablets (PL 19156/0034), which were demonstrated to be generic medicinal products of the innovator products Istin Tablets 5mg (PL 00057/0297) and Istin Tablets 10mg (PL 00057/0298) respectively, granted to Pfizer Limited on 18th September 1989

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The approved SPCs, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

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

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products which, in turn, have been shown to be interchangeable with the innovator products. Extensive clinical experience with amlodipine besilate is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

AMLODIPINE 5MG TABLETS (AMLODIPINE BESILATE) PL 19156/0039

AMLODIPINE 10MG TABLETS (AMLODIPINE BESILATE) PL 19156/0040

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation applications on 8th October 2007

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 11th November 2007

3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 29th November 2007

4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 3rd December 2007

5 The applications were determined on 10th December 2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Amlodipine 5 mg tablets is as follows:

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 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 then 10%

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

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

Rare: 0,1 % or less, but more then 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, perpura, 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 19156/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/12/2007

10 DATE OF REVISION OF THE TEXT

10/12/2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Amlodipine 10mg Tablets is as follows:

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 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 then 10%

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

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

Rare: 0,1 % or less, but more then 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, perpura, 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 19156/0040

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/12/2007

10 DATE OF REVISION OF THE TEXT

10/12/2007

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Amlodipine 5 mg tablets
Amlodipine 10 mg tablets

Amlodipine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT AMLODIPINE IS AND WHAT IT IS USED FOR

Amlodipine belongs to a group of medicines 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.

- **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 Amlodipin.
- **Phenobarbital, phenytoin and carbamazepin (medicines for epilepsy)** may reduce the effect of Amlodipin.
- **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.

2. BEFORE YOU TAKE AMLODIPINE

Do not take Amlodipine
- if you are **allergic** to amlodipine or similar calcium channel blockers (the so-called dihydropyridine derivates) 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-proteinase-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.

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

In isolated cases allergic skin rash with irregular red spots, caused by medicines (erythema exsudativum 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 glycollate, sodium acid citrate (E331), magnesium stearate (E572), croscarmellose sodium, crospovidone.

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 occured, 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: pricking 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.

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 glycollate, 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.

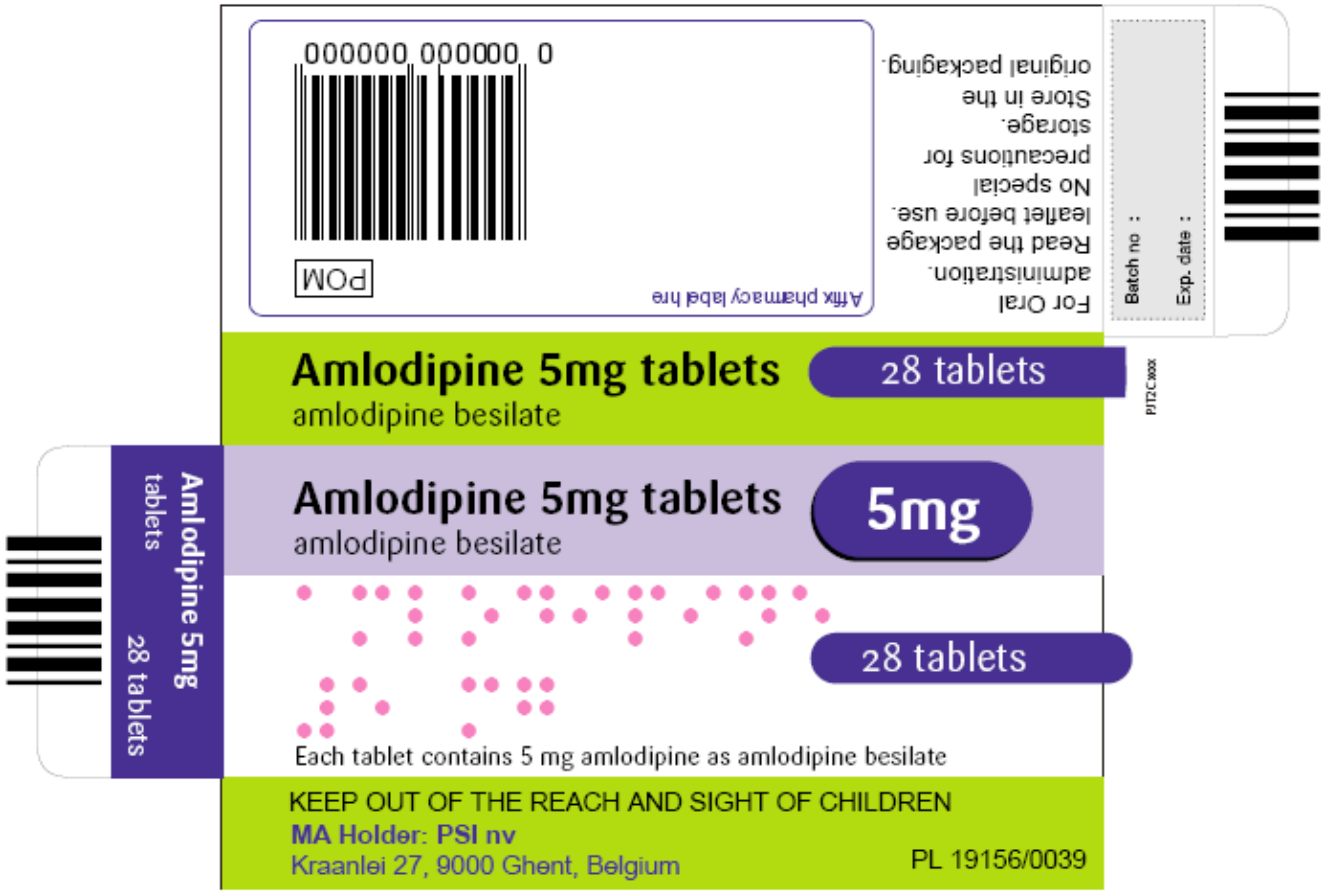
Your tablets come in:
- Blister packs of 28 tablets.

Marketing Authorisation Holder and Manufacturer

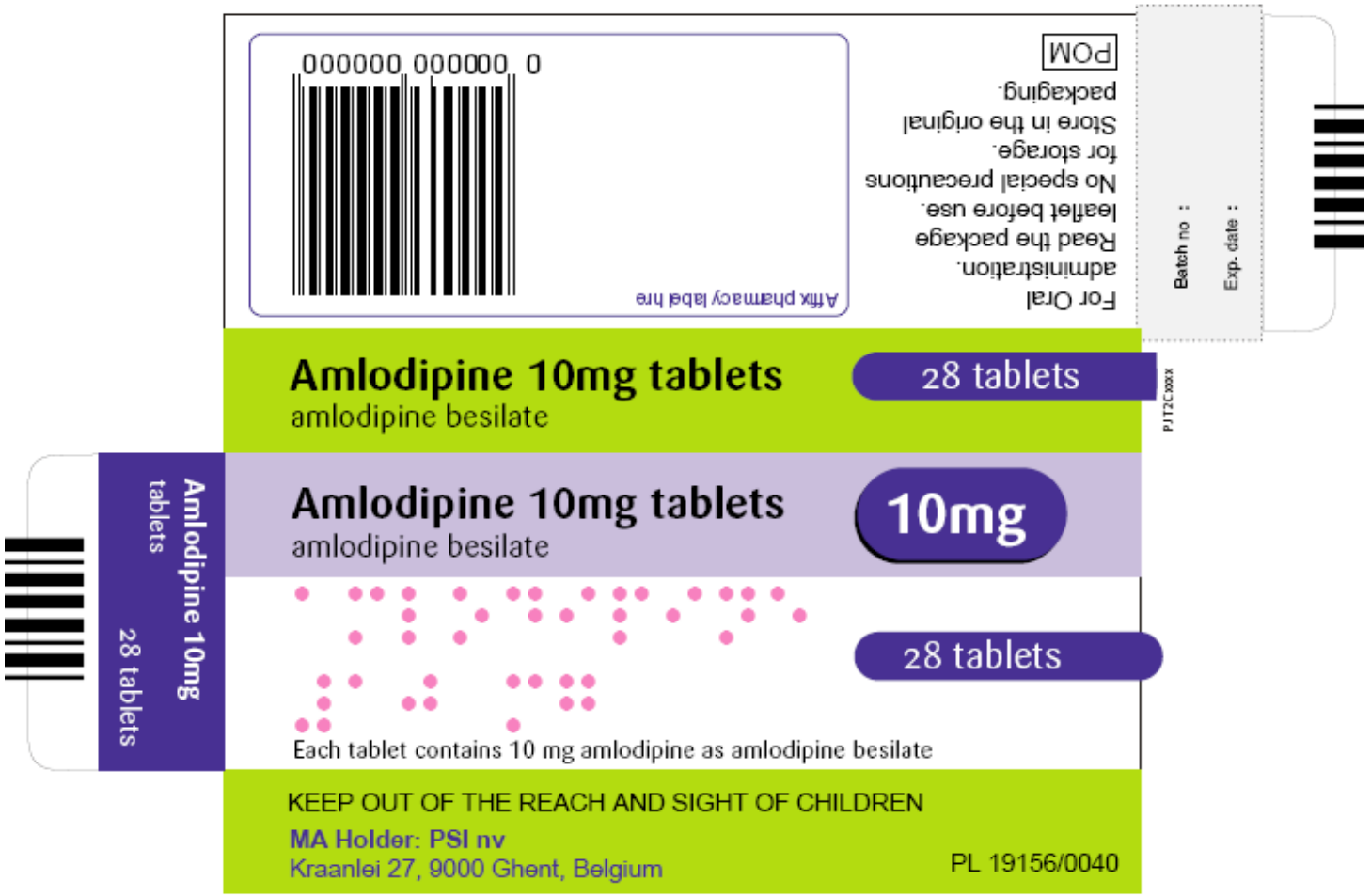
PSI nv	PSI supply nv
Kraanlei 27	Kraanlei 27
9000 Ghent	9000 Ghent
Belgium	Belgium

This leaflet was last approved in

LABELLING
Amlodipine 5mg Tablets
Carton for blisters, with braille

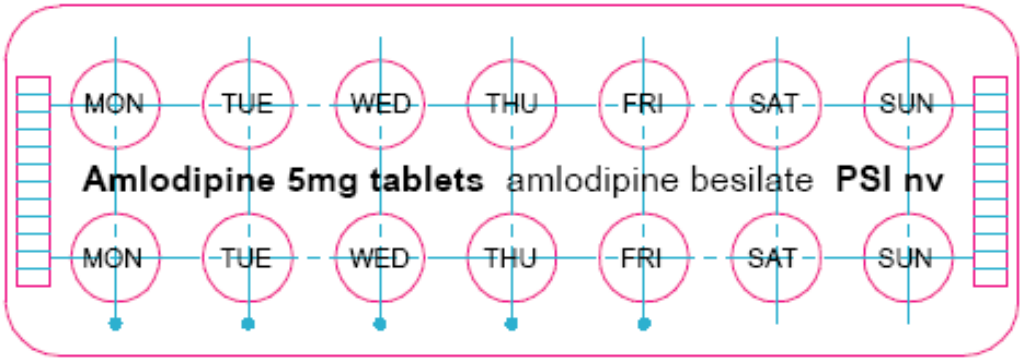


Amlodipine 10mg Tablets
Carton for blisters, with braille



Blister foils

Amlodipine 5mg Tablets



Amlodipine 10mg Tablets