

**AMLODIPINE 5MG TABLETS  
PL 20897/0003**

**AMLODIPINE 10MG TABLETS  
PL 20897/0004**

**UKPAR**

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**AMLODIPINE 5MG TABLETS**  
**PL 20897/0003**

**AMLODIPINE 10MG TABLETS**  
**PL 20897/0004**

**LAY SUMMARY**

The MHRA granted HELM AG Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg Tablets (PL 20897/0003) and Amlodipine 10mg Tablets (PL 20897/0004). These are prescription only medicines (POM) for the treatment of high blood pressure and angina.

Amlodipine Tablets contain the active ingredient amlodipine besilate, which acts as a calcium-channel blocker for the treatment of high blood pressure and angina.

The test product was considered to provide the same benefit as the original products Istin Tablets 5mg and 10mg (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 20897/0003**

**AMLODIPINE 10MG TABLETS  
PL 20897/0004**

**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 20897/0003) and Amlodipine 10mg Tablets (PL 20897/0004) on 25<sup>th</sup> September 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, and have been shown to be generic medicinal products of the original products Istin Tablets 5mg and 10mg (Pfizer Limited, UK).

The products contain the active ingredient amlodipine besilate, a calcium channel blocker and are indicated for the treatment of essential hypertension, prophylaxis of chronic stable angina pectoris and Prinzmetal's (variant) angina when diagnosed by a cardiologist.

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

## PHARMACEUTICAL ASSESSMENT

### DRUG SUBSTANCE

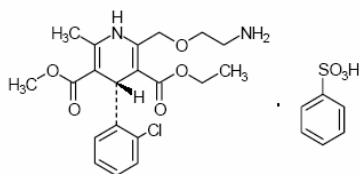
#### Amlodipine besilate

INN: Amlodipine Besilate

Chemical Name: 2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethyl 5-methyl ester benzenesulphonate ( $\pm$ )-2-[(2-Aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine benzenesulphonate 3-Ethyl 5-methyl (4RS)-2-[(2-aminoethyl)oxy]methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydro pyridine-3,5-dicarboxylate benzenesulphonate

CAS No: 111470-99-6

Structural Formula:



Molecular formula:  $C_{26}H_{31}ClN_2O_8S$

Molecular weight: 567.1 g/mol

Physical form: White to off-white powder.

Solubility: Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

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

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

The applicant has demonstrated that the active ingredient from this source is adequately controlled in accordance with the European Pharmacopoeia monograph for Amlodipine Besilate.

Active amlodipine besilate is stored in double low density polyethylene bags as a primary package, the outer bag is black and inner is transparent. The bag is stored in a fibre drum. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification. Certificates of analysis have been provided for any working standards used.

Appropriate stability data have been generated supporting a retest period of two years.

## **DRUG PRODUCT**

### **Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, calcium hydrogen phosphate anhydrous, sodium starch glycollate type A and magnesium stearate. All excipients used comply with their respective Ph Eur 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**

Satisfactory pharmaceutical development studies have been conducted and support the suitability of the product composition proposed for its intended use.

### **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. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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**

Both strengths of tablet are packed in blister strips of PVC/PVDC (made opaque with titanium dioxide) backed onto an aluminium sheet. 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 24 months has been set, which is satisfactory. The precaution 'Keep your medicine in a dry place' has been included.

### **Conclusion**

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

The drug product corresponds to the current EU definition of a generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of active substance, the same pharmaceutical form and bioequivalence has been demonstrated to a suitable reference product.

**PRECLINICAL ASSESSMENT**

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

## **CLINICAL ASSESSMENT**

### **INTRODUCTION AND BACKGROUND**

ATC Code: C08C A01 (Calcium channel blockers)

These applications of generic medicinal products refer to Istin, currently licensed in the UK as 5mg and 10mg tablets (PL 00057/0297 – 0298). The medicinal product used for bioequivalence study was Istin Tablets 10mg authorised in the UK.

Amlodipine besilate is well established for use in the requested indication. The early development was with maleate salt although later studies and marketing was for amlodipine besilate.

### **INDICATIONS**

- Hypertension.
- Prophylaxis of chronic stable angina pectoris.
- Prinzmetal's (variant) angina when diagnosed by a cardiologist.
- In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alphablocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor.
- For angina, Amlodipine Tablets may be used as monotherapy or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.
- Amlodipine is well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.

### **DOSE & DOSE SCHEDULE**

#### *In adults*

For both hypertension and angina the usual initial dose is 5mg Amlodipine Tablets once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response. No dose adjustment of Amlodipine Tablets is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

#### *Use in children*

Not recommended.

#### *Use in the elderly*

Amlodipine Tablets, 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.

## CLINICAL PHARMACOLOGY

A single bioequivalence study is presented in support of this application. The comparator product in this study is Istin 10mg tablets (Pfizer, UK).

This was a monocentric, open, randomised, single dose, two-period cross-over study in 24, male caucasian healthy volunteers. A total of 28 subjects were enrolled and 24 completed. The test product was 10mg Amlodipine besilate tablet (Eczacibasi Pharmaceuticals Co. Istanbul, Turkey). The washout period was 21 days.

A total of 28 patients were screened, 24 were enrolled, randomised and completed par protocol. The tablets were administered under fasting conditions.

### Summary of comparative PK data of Amlodipine. Each point represents the arithmetic mean $\pm$ SD (n=24)

PK parameters	Test (arithm. Mean)	Reference (arithm. Mean)	Point estimate	CI
C <sub>max</sub> (ng/ml)	5.2 (1.04)	5.4 (0.84)	0.96	0.93-1.00*
AUC (0-tlast) (ng.h/ml)	228.3 (54.99)	238 (58.34)	0.96*	0.92-1.00*
AUC (0-inf) (ng.h/ml)	259.6 (68.83)	274.1 (82.18)		
T <sub>max</sub> (h)	6.29 (1.73)	5.75 (1.15)	0.01	0.00-1.00**

\*ANOVA-log confidence interval

\*\* non-parametric confidence interval

### Assessor's comments on bioequivalence

The reference product used and the washout period was appropriate. The applicant has justified a sampling period of 144 hours (corresponding to approximately 4 average half-lives) based on the long half-life of amlodipine (30–50 hours). There were no female subjects in the study.

The bioequivalence of the test product has been shown.

## EFFICACY

The efficacy of amlodipine in the proposed indications is well known as it has been in clinical use for many years. No new data has been submitted and none is required.

## SAFETY

No new data except from the single study with limited number of patients mentioned earlier were submitted and none are required for this type of application.

**EXPERT REPORT**

A satisfactory Clinical Expert Report has been submitted with appropriate CV.

**PATIENT INFORMATION LEAFLET (PIL)**

This is satisfactory.

**LABELLING**

This is satisfactory.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

This is satisfactory. The text of the SPC is essentially the same as that of the cross-reference product licence.

**DISCUSSION**

The bioequivalence of the product has been shown in a study which used an appropriate reference product. The washout period and the sampling periods were acceptable.

The efficacy and safety of amlodipine in the proposed indications is well known. The applicant has not provided any new data and none is required.

**CONCLUSION**

Marketing authorisations should be granted for these products.

## OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

### QUALITY

The important quality characteristics of Amlodipine 5mg 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, UK). Given that linear kinetics apply between the 5mg and 10mg tablets, that the formulae for the tablets are proportional and that similar dissolution results have been shown for the two strengths, a separate bioequivalence study using the 5mg tablets is not considered necessary.

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  
PL 20897/0003**

**AMLODIPINE 10MG TABLETS  
PL 20897/0004**

**STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the marketing authorisation applications on 30 <sup>th</sup> July 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 9 <sup>th</sup> August 2004
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 4 <sup>th</sup> March 2005, and further information relating to the quality dossiers on 10 <sup>th</sup> March 2005, 17 <sup>th</sup> March 2005, 13 <sup>th</sup> October 2006 and 12 <sup>th</sup> March 2007.
4	The applicant responded to the MHRA's requests, providing further information on 26 <sup>th</sup> August 2005 for the clinical sections, and again on 10 <sup>th</sup> April 2006, 8 <sup>th</sup> November 2006, 8 <sup>th</sup> February 2007 and 30 <sup>th</sup> March 2007 for the quality sections.
5	The applications were determined on 25 <sup>th</sup> September 2007.

**AMLODIPINE 5MG TABLETS  
PL 20223/0011**

**AMLODIPINE 10MG TABLETS  
PL 20223/0012**

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 5 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains amlodipine besilate equivalent to 5mg of amlodipine.

For excipients see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

- Hypertension.
- Prophylaxis of chronic stable angina pectoris.
- Prinzmetal's (variant) angina when diagnosed by a cardiologist.
- In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alphablocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor.
- For angina, Amlodipine Tablets may be used as monotherapy or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.
- Amlodipine is well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.

#### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

##### *In adults*

For both hypertension and angina the usual initial dose is 5mg Amlodipine Tablets once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response. No dose adjustment of Amlodipine Tablets is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

##### *Use in children*

Not recommended.

##### *Use in the elderly*

Amlodipine Tablets, 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

- Amlodipine Tablets are contra-indicated in patients with a known sensitivity to dihydropyridines, amlodipine or any of the excipients.
- Amlodipine Tablets 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

In a long term, placebo-controlled study, in patients with NYHA III and IV heart failure of non-ischaeamic 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.

##### *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 Tablets alone, during or within one month of a myocardial infarction. The safety and efficacy of Amlodipine Tablets 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: Effects 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 a single oral dose of amlodipine 10mg in healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

*Sildenafil:* When sildenafil and amlodipine 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 10mg 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 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.

*Ciclosporin:* Pharmacokinetic studies with ciclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

*Drug/Laboratory test interactions:* None known.

#### 4.6 PREGNANCY AND 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 pregnancy or lactation. Accordingly, Amlodipine Tablets should not be administered during pregnancy, or lactation, or to women of childbearing potential unless effective contraception is used.

#### 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

Adverse events that have been reported in amlodipine trials are categorised below, according to system organ class and frequency. Frequencies are defined as: very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%) and very rare (<0.01%).

<i>Blood and the Lymphatic System Disorders</i>	thrombocytopenia	Very Rare
<i>Immune System Disorders</i>	allergic reaction	Very Rare
<i>Metabolism and Nutrition Disorders</i>	hyperglycaemia	Very Rare
<i>Psychiatric Disorders</i>	insomnia, mood changes	Uncommon
<i>Nervous System Disorders</i>	somnolence, dizziness, headache	Common
	tremor, taste perversion, syncope, hypoaesthesia, paraesthesia	Uncommon
	peripheral neuropathy	Very Rare
<i>Eye Disorders</i>	visual disturbances	Uncommon
<i>Ear and Labyrinth Disorders</i>	tinnitus	Uncommon



<i>Cardiac Disorders</i>	palpitations	Common
	myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation)	Very rare
<i>Vascular Disorders</i>	flushing	Common
	hypotension	Uncommon
	vasculitis	Very Rare
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	dyspnoea, rhinitis coughing	Uncommon Very Rare
<i>Gastrointestinal Disorders</i>	abdominal pain, nausea	Common
	vomiting, dyspepsia, altered bowel habits, dry mouth	Uncommon
	pancreatitis, gastritis, gingival hyperplasia	Very Rare
<i>Hepato-biliary Disorders</i>	hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)	Very Rare
<i>Skin and Subcutaneous Tissue Disorders</i>	alopecia, purpura, skin discolouration, increased sweating, pruritus, rash	Uncommon
	angioedema, erythema multiforme, urticaria	Very Rare
<i>Musculoskeletal and Connective Tissue Disorders</i>	arthralgia, myalgia, muscle cramps, back pain	Uncommon
<i>Renal and Urinary Disorders</i>	micturition disorder, nocturia, increased urinary frequency	Uncommon
<i>Reproductive System and Breast Disorders</i>	impotence, gynaecomastia	Uncommon
<i>General Disorders and Administration Site Conditions</i>	oedema, fatigue	Common
	chest pain, asthenia, pain, malaise	Uncommon
<i>Investigations</i>	weight increase, weight decrease	Uncommon

#### 4.9 OVERDOSE

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. 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. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antihypertensive agents. Calcium antagonist.

ATC-Code: C08CA01

Amlodipine Tablets 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 Tablets is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which Amlodipine Tablets relieves angina has not been fully determined but Amlodipine Tablets reduces total ischaemic burden by the following two actions.

- Amlodipine Tablets 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 Tablets 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.

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

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III - IV heart failure receiving digoxin, diuretics and 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) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE

inhibitors, digitalis and diuretics, amlodipine had no effect on total cardiovascular mortality. In the 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,  
Dibasic Calcium Phosphate Anhydrous,  
Sodium Starch Glycollate and  
Magnesium Stearate.

### 6.2 INCOMPATIBILITIES

None stated.

### 6.3 SHELF LIFE

24 months

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

None specified.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Amlodipine Tablets is available as:

Packs of 28 tablets. Aluminium/PVC/PVDC blister strips, 14 tablets/strip, 2 strips in a carton box.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Helm AG  
Nordkanalstrasse 28  
20097  
Hamburg  
Germany

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20897/0003

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

25/09/2007

**10 DATE OF REVISION OF THE TEXT**

25/09/2007

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains amlodipine besilate equivalent to 10 mg of amlodipine.

For excipients see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

- Hypertension.
- Prophylaxis of chronic stable angina pectoris.
- Prinzmetal's (variant) angina when diagnosed by a cardiologist.
- In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alphablocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor.
- For angina, Amlodipine Tablets may be used as monotherapy or in combination with other antianginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.
- Amlodipine is well tolerated in patients with heart failure and a history of hypertension or ischaemic heart disease.

#### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

##### *In adults*

For both hypertension and angina the usual initial dose is 5mg Amlodipine Tablets once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response. No dose adjustment of Amlodipine Tablets is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

##### *Use in children*

Not recommended.

##### *Use in the elderly*

Amlodipine Tablets, 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

Amlodipine Tablets are contra-indicated in patients with a known sensitivity to dihydropyridines, amlodipine or any of the excipients. Amlodipine Tablets 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

In a long term, placebo-controlled study, in patients with NYHA III and IV heart failure of non-ischaemic 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.

##### *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 Tablets alone, during or within one month of a myocardial infarction. The safety and efficacy of Amlodipine Tablets 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: Effects 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 a single oral dose of amlodipine 10mg in healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

*Sildenafil:* When sildenafil and amlodipine 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 10mg 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 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.

*Ciclosporin:* Pharmacokinetic studies with ciclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciclosporin.

*Drug/Laboratory test interactions:* None known.

#### 4.6 PREGNANCY AND 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 pregnancy or lactation.

Accordingly, Amlodipine Tablets should not be administered during pregnancy, or lactation, or to women of childbearing potential unless effective contraception is used.

#### 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

Adverse events that have been reported in amlodipine trials are categorised below, according to system organ class and frequency.

Frequencies are defined as: very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%) and very rare (<0.01%).

<i>Blood and the Lymphatic System Disorders</i>	thrombocytopenia	Very Rare
<i>Immune System Disorders</i>	allergic reaction	Very Rare
<i>Metabolism and Nutrition Disorders</i>	hyperglycaemia	Very Rare
<i>Psychiatric Disorders</i>	insomnia, mood changes	Uncommon
<i>Nervous System Disorders</i>	somnolence, dizziness, headache	Common
	tremor, taste perversion, syncope, hypoaesthesia, paraesthesia	Uncommon
	peripheral neuropathy	Very Rare
<i>Eye Disorders</i>	visual disturbances	Uncommon
<i>Ear and Labyrinth Disorders</i>	tinnitus	Uncommon
<i>Cardiac Disorders</i>	palpitations	Common
	myocardial infarction, arrhythmia,	Very rare

	ventricular tachycardia and atrial fibrillation)	
<i>Vascular Disorders</i>	flushing	Common
	hypotension	Uncommon
	vasculitis	Very Rare
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	dyspnoea, rhinitis coughing	Uncommon Very Rare
<i>Gastrointestinal Disorders</i>	abdominal pain, nausea	Common
	vomiting, dyspepsia, altered bowel habits, dry mouth	Uncommon
	pancreatitis, gastritis, gingival hyperplasia	Very Rare
<i>Hepato-biliary Disorders</i>	hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)	Very Rare
<i>Skin and Subcutaneous Tissue Disorders</i>	alopecia, purpura, skin discolouration, increased sweating, pruritus, rash	Uncommon
	angioedema, erythema multiforme, urticaria	Very Rare
<i>Musculoskeletal and Connective Tissue Disorders</i>	arthralgia, myalgia, muscle cramps, back pain	Uncommon
<i>Renal and Urinary Disorders</i>	micturition disorder, nocturia, increased urinary frequency	Uncommon
<i>Reproductive System and Breast Disorders</i>	impotence, gynaecomastia	Uncommon
<i>General Disorders and Administration Site Conditions</i>	oedema, fatigue	Common
	chest pain, asthenia, pain, malaise	Uncommon
<i>Investigations</i>	weight increase, weight decrease	Uncommon

#### 4.9 OVERDOSE

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. 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. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.



## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antihypertensive agents. Calcium antagonist.

ATC-Code: C08CA01

Amlodipine Tablets 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 Tablets is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which Amlodipine Tablets relieves angina has not been fully determined but Amlodipine Tablets reduces total ischaemic burden by the following two actions.

- Amlodipine Tablets 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 Tablets 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.

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

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III - IV heart failure receiving digoxin, diuretics and 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) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis and diuretics, amlodipine had no effect on total cardiovascular mortality. In the 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,  
Dibasic Calcium Phosphate Anhydrous,  
Sodium Starch Glycollate and  
Magnesium Stearate.

### 6.2 INCOMPATIBILITIES

None stated.

### 6.3 SHELF LIFE

24 months

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

None specified.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Amlodipine Tablets is available as:

Packs of 28 tablets. Aluminium/PVC/PVDC blister strips, 14 tablets/strip, 2 strips in a carton box.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Helm AG  
Nordkanalstrasse 28  
20097 Hamburg  
Germany

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20897/0004

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

25/09/2007

**10 DATE OF REVISION OF THE TEXT**

25/09/2007

**Patient Information Leaflet****AMLODIPINE 10 mg TABLETS  
(Amlodipine besilate)**

**Please read this leaflet before you start to take Amlodipine 10 mg Tablets. It will help you. If you do not understand or you want to know more, ask your doctor or pharmacist (chemist). Keep this leaflet, you may want to read it again.**

The name of this medicine is Amlodipine 10 mg Tablets.

The active ingredient is amlodipine besilate.

**WHAT DO AMLODIPINE 10 MG TABLETS CONTAIN?**

Amlodipine Tablets are available in two strengths, 5 mg and 10 mg.

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

Each tablet also contains the inactive ingredients: dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

Amlodipine 10 mg Tablets are available in packs of 28 tablets.

**Product Licence Holder and Manufacturer**

Helm AG, Nordkanalstraße 28,

20097 Hamburg, Germany

**WHAT ARE AMLODIPINE 10 MG TABLETS AND WHAT ARE THEY USED FOR?**

Amlodipine 10 mg Tablets belongs to a group of medicines called calcium antagonists.

Amlodipine 10 mg Tablets are used to treat;

- high blood pressure (hypertension)
- a certain type of chest pain called angina, including a rare form called Prinzmetal's or variant angina.

In patients with high blood pressure amlodipine works by relaxing blood vessels, so that blood passes through them more easily.

In patients with 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 Tablets do not provide immediate relief of chest pain from angina.

Amlodipine Tablets is well tolerated in patients with heart failure and a history of high blood pressure or angina.

**BEFORE YOU USE AMLODIPINE 10 MG TABLETS****Do not take Amlodipine Tablets if:**

- You are allergic (hypersensitive) to amlodipine, other calcium antagonists or to any of the other ingredients in Amlodipine 10mg Tablets. You may get itching, reddening of the skin or difficulty in breathing.

- You have heart problems such as cardiogenic shock, aortic stenosis (narrowing of the aortic heart valve) or unstable angina.
- You are pregnant during pregnancy or breast feeding. If you are a woman of child-bearing potential effective contraception is advised.

**Tell your doctor before taking Amlodipine Tablets** if the answer is **YES** to any of the questions below:

- Have you just had a heart attack or sudden, severe high blood pressure?
- Do you have liver disease?
- Are you under 18 years of age?

Your doctor may still want you to take the tablets.

#### **Can you take other medicines with Amlodipine Tablets?**

Tell your doctor or pharmacist before you take Amlodipine Tablets if you are taking any other medicines including those obtained without a prescription.

#### **Pregnancy and Breast feeding**

Amlodipine Tablets should not be taken if you are pregnant or breast feeding your baby. Women of childbearing age should not take Amlodipine 5mg Tablets unless effective contraception is used.

#### **Driving and using machinery**

Amlodipine Tablets are unlikely to affect your ability to drive or operate machinery. However, if you suffer from dizziness, headache, tiredness or feeling sick you must be careful when carrying out these tasks.

#### **HOW TO TAKE AMLODIPINE 10 MG TABLETS**

##### **Adults (including the elderly):**

- The usual initial dose is 5mg of Amlodipine once daily, which may be increased to 10mg Amlodipine daily.
- Take your tablet as your doctor told you and as written on the label on the pack.
- It is best to take Amlodipine 10 mg Tablets at the same time each day with a drink of water.
- Continue to take your tablet each day.
- If you are still not sure, ask your doctor or pharmacist.
- It is important to keep taking the tablets. They may help you to remain well.
- Do not wait until your tablets are finished before seeing your doctor. Your doctor may wish to give you more Amlodipine 10 mg Tablets.

#### **What if you take too many tablets?**

Too many tablets at once may make you unwell. If several tablets are taken it may be dangerous. Tell your doctor immediately or go to your nearest hospital casualty department.

#### **What if you miss a tablet?**

Do not worry. If you forget to take a tablet, leave out that dose completely and take your next dose at the usual time.

**DO AMLODIPINE 10 MG TABLETS CAUSE SIDE EFFECTS?**

Amlodipine 10 mg Tablets, like all medicines, may cause some side effects.

All medicines can cause allergic reactions. If you experience any of the following contact a doctor IMMEDIATELY:

- Any sudden wheeziness or difficulty in breathing
- Swelling of eyelids, face or lips
- Rash or itching (especially affecting the whole body)

Serious allergic reactions are very rare and seldom life-threatening.

**Common side effects:**

- |                                       |                 |   |
|---------------------------------------|-----------------|---|
| • headache                            | • feeling tired | • dizziness   |
| • oedema (for example ankle swelling) | • stomach pain  | • palpitations (a quicker or irregular heart beat). |
| • skin rash                           | • feeling sick  |   |
|                                       | • flushing      |   |

Tell your doctor if these effects cause you any problems or if they last for more than one week.

**Uncommon side effects:**

- |                        |   |  |
|------------------------|---|--|
| • itchy skin           | • increased need to urinate                             | • inability to obtain an erection                    |
| • hair loss            | • changes in taste                                      | • enlarging of the male breasts                      |
| • shortness of breath  | • dry mouth   | • visual disturbances                                |
| • abdominal pain       | • loss of pain sensation                                | • increased sensitivity particularly on the skin     |
| • back pain            | • ringing in the ears                                   | • pins and needles                                   |
| • chest pain           | • increased sweating                                    | • bruising more easily or purplish marks on the skin |
| • vomiting             | • fainting  | • sneezing or runny nose                             |
| • indigestion          | • low blood pressure                                    | • hives.   |
| • muscle cramps        | • red blood cell damage (unusual bruising and bleeding) |  |
| • weakness             | • red patches on skin                                   |  |
| • sleepiness           | • weight changes  |  |
| • difficulty sleeping  |   |  |
| • altered bowel habit  |   |  |
| • muscle or joint pain |   |  |
| • mood changes         |   |  |

**Very rare side effects:**

- |                             |                                     |                                    |
|-----------------------------|-------------------------------------|------------------------------------|
| • abnormal liver function   | • blood disorders                   | • excess sugar in blood, coughing  |
| • inflammation of the liver | • inflammation of the nerves        | • swelling or soreness of the gums |
| • yellowing of the skin     | • inflammation of the blood vessels | • inflamed pancreas and stomach    |
| • severe skin reactions     |                                     |                                    |

The following effects have occurred in patients but the relationship to treatment with Amlodipine Tablets or the disease state is uncertain: heart attack (myocardial infarction), irregular heart beat (arrhythmia) and chest pain.

**Tell your doctor or pharmacist if any of these side effects gets serious or if you notice any other unwanted effect not listed in this leaflet.**

**Look after your medicine**

This treatment is for **YOU**. **DO NOT** give it to others. It may not suit them. If your doctor stops your treatment return any remaining tablets to the pharmacist. Do not take this medicine after the expiry date stamped on the pack.

**Where to keep your medicine**

- Keep your medicine in a dry place.
- Keep all medicines out of the reach and sight of children.

**Further information**

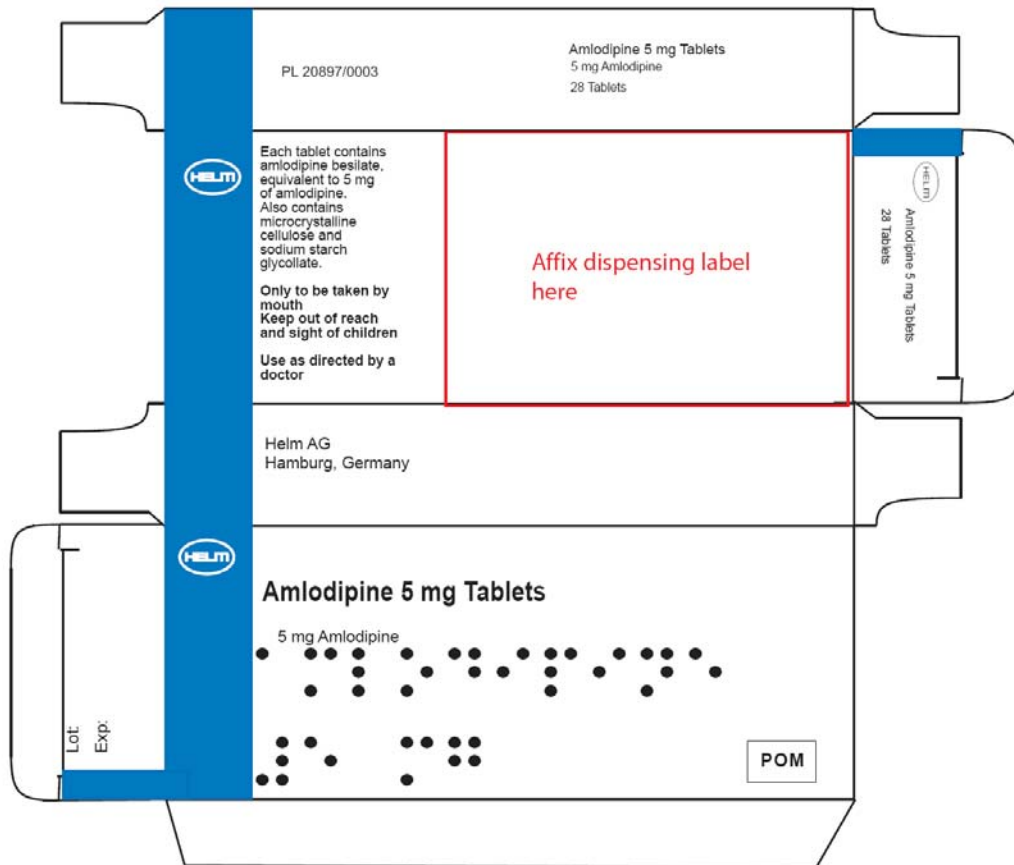
This leaflet does not contain all the information about this medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist. The information in this leaflet relates to Amlodipine 10 mg Tablets only.

**UK Amlodipine 10 mg Tablets leaflet last revised:**  
March 2007

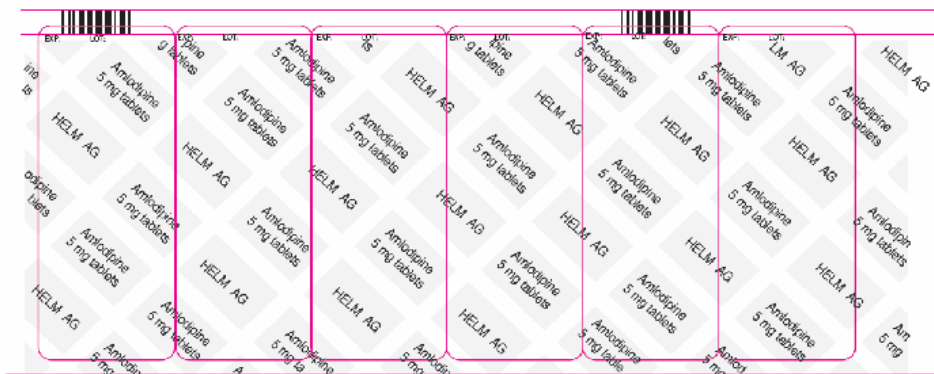
**AMLODIPINE 10MG TABLETS  
PL 20897/0003**

**LABELLING**

**CARTON**



**BLISTER**



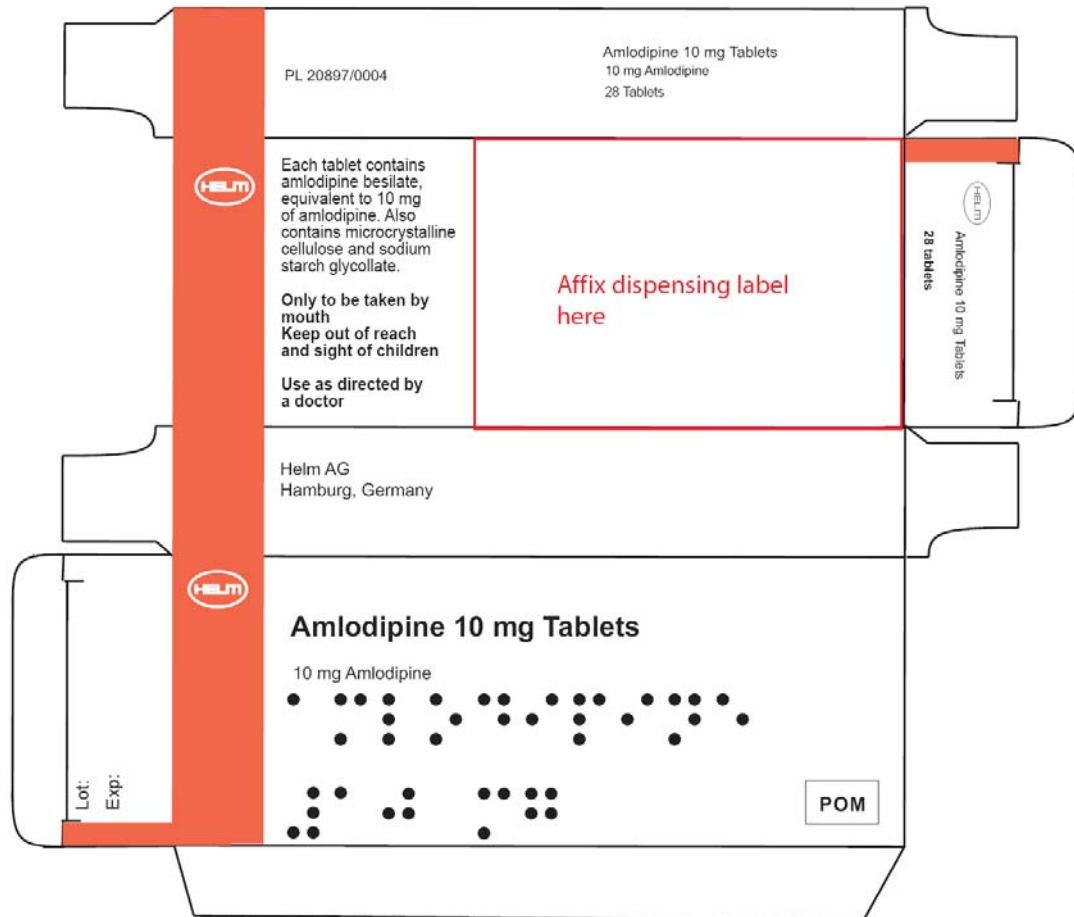


# AMLODIPINE 10MG TABELTS

## PL 20897/0004

### LABELLING

#### CARTON



#### BLISTER FOIL

