

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

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

**UKPAR**

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

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

**LAY SUMMARY**

The MHRA today granted MR Pharma GmbH Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg Tablets (PL 20223/0011) and Amlodipine 10mg Tablets (PL 20223/0012). These are prescription only medicines (POM) for the treatment of high blood pressure and angina.

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

The test product was considered the same as the original products Istin Tablets 5 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 20223/0011**

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

**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 20223/0011) and Amlodipine 10mg Tablets (PL 20223/0012) on 20<sup>th</sup> November 2006. The products are prescription only medicines.

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

The products contain the active ingredient amlodipine maleate, a calcium channel blocker of the 1,4-dihydropyridine type that is structurally related to nifedipine, felodipine and nitrendipine. However, amlodipine exhibits favourable properties compared to these - the amino group and the corresponding pKa of 8.6 (90% ionisation at physiological pH) seems to be responsible for the long half-life enabling once daily dosing, and the replacement of the aromatic nitro group by chlorine enhances photostability. Unlike other calcium channel blockers amlodipine is not subject to first-pass metabolism. Amlodipine 5mg and 10mg Tablets are indicated for the treatment of hypertension, prophylaxis of chronic stable angina pectoris and Prinzmetal's (variant) angina when diagnosed by a cardiologist.

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

## **PHARMACEUTICAL ASSESSMENT**

### **DRUG SUBSTANCE**

#### **Amlodipine maleate**

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.

The structure has been confirmed by IR, UV, NMR and MS.

An appropriate specification based on the Ph Eur is provided for the active substance amlodipine maleate.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Amlodipine maleate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and appear to be satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated supporting a retest period of 2 years when stored in the packaging proposed for marketing.

### **DRUG PRODUCT**

#### **Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, calcium hydrogen phosphate dihydrate, sodium starch glycollate 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.

#### **Dissolution profiles**

Dissolution profiles for both strengths of drug product were found to be similar to the originator products marketed in various European countries. The data demonstrate that the dissolution specification is acceptable.

#### **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**

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 36 months has been set, which is satisfactory. The precaution 'Do not store above 25°C' has been included.

**Conclusion**

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

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

## **PRECLINICAL ASSESSMENT**

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

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

## **CLINICAL ASSESSMENT**

### **1 INTRODUCTION**

#### **1.1 GCP ASPECTS**

There are no apparent concerns regarding adherence to GCP/CPMP guidelines.

#### **1.2 THERAPEUTIC CLASS**

Amlodipine is a Calcium Channel Blocker. ATC code: CO8C A01

#### **1.3 BACKGROUND**

These are two abridged applications for amlodipine maleate for the treatment of essential hypertension and angina pectoris. The applicant under article 10.1 claims essential similarity to Istin (amlodipine besylate, Pfizer UK) which has been licensed in the EU for more than 10 years and is currently licensed in the UK (PL 00057/0297-8). The base active substance (amlodipine) is well established for use in the requested indications.

#### **1.4 REGULATORY STATUS**

The current product has not been authorised either within or outside the EU at the time of writing this report.

#### **1.5 INDICATIONS, DOSAGE AND DOSAGE REGIMEN.**

The indications as proposed in the SPC are similar to the innovator product, Istin (PL 00057/0297-8) and are therefore acceptable.

The dose and regimen as proposed in the SPC are identical to the innovator product, Istin (PL 00057/0297-8) and are therefore acceptable.

#### **1.6 CONSIDERATION FOR PAEDIATRIC USE**

Amlodipine is not recommended for use in children and this is in accordance with the brand leader's marketing authorisation. Neither the current applicant nor the brand leaders, have a paediatric development project for this product.

#### **1.7 ASSESSOR'S COMMENT**

The basis of the application, indications sought (with some modifications), dose and dosage regimens are appropriate and acceptable.

### **2 CLINICAL PHARMACOLOGY**

#### **2.1 PHARMACOKINETICS & PHARMACODYNAMICS**

##### **2.1.1 Summary:**

No new data are submitted and none are required for this type of application. As the pharmacology including kinetics of amlodipine are well established in clinical practice, this is acceptable, for an application under EC article 10.1.

## 2.2 BIOAVAILABILITY & BIOEQUIVALENCE

### 2.2.1 Bioavailability

Usually, the salt, the pharmaceutical preparation and absorption, are likely to influence bioavailability of a medicinal product. However, for amlodipine, only the base is absorbed while the ester is hydrolysed in the GUT. Therefore, the differences in salt are not expected to affect bioavailability greatly. The applicant has provided a bioequivalence study comparing the two products, which is discussed below.

### 2.2.2 Bioequivalence study.

This is a single-dose, two-way crossover, block- randomised study comparing the test product (Amlodipine 10mg Tablets) versus Norvasc 10mg Tablets (Pfizer Germany).

#### Results:

Parameter	Test Amlod	Ref Prod (Norvasc)	90% CI Ratio
AUC <sub>t</sub> (pg./ml*h)	150580.0 ± 49351	147740.0 ± 51699.0	1.014 (0.863 to 1.203)
AUC <sub>∞</sub> (pg./ml*h)	160670.0 ± 51501.0	157910.0 ± 55249.0	1.01 (0.864 to 1.198)
C <sub>max</sub> (pg./ml)	3682.6 ± 1355.30	3489.4 ± 1239.20	1.065 (0.89 to 1.23)
T <sub>max</sub> (h)	5.667 ± 2.22	5.708 ± 2.29	

*Data are expressed as pg./ml or pg./ml\*hr*

The assay methodology and LLOQ (Lower limit of quantification) for the assay appear to be acceptable. The AUC<sub>t</sub> is >80% of the AUC<sub>inf</sub> suggesting an appropriate point of extrapolation to infinity. The 90% Confidence intervals lie within the limits of acceptability (80-125%) for all three parameters.

As the kinetics are linear, the BE study has been conducted with the higher dose. This is acceptable so far as the compositions of the two strengths are identical (or the active/excipient ratio is unchanged).

**Comment:** Based the above study results, the applicant and the expert have both concluded that the two products are bioequivalent. As the parameters are within the acceptability criteria set out by the CPMP (BE guideline CPMP/EWP/1408/01), the assessor concurs that bioequivalence between the innovator (Norvasc, Pfizer A/S, Germany) and the generic product (Amlodipine, MR Pharma) may be concluded.

The applicant has also provided evidence that Norvasc and Istin (marketed in the UK) are comparable in terms of composition and dissolution profiles as required by the CPMP guideline (CPMP/EWP/QWP/1401/98).

## 3 CLINICAL EFFICACY

No new data are submitted and none are required for this type of application. The efficacy of amlodipine has been well established for use in the indications sought and sufficient published literature has been submitted in support of this.

## 4 CLINICAL SAFETY

No new data are submitted and none are required for this type of application. The safety of amlodipine has been well established for use in the indications sought and sufficient published literature has been submitted in support of this. The bioequivalence studies did not raise any new safety concerns.

## **5 CLINICAL EXPERT REPORT**

The clinical expert report has been written by an appropriately qualified medic. It is an adequate summary of the clinical data provided in the dossier.

## **6 PRODUCT LITERATURE**

### **6.1 SPC: SUMMARY OF PRODUCT CHARACTERISTICS**

The proposed SPC is satisfactory.

### **6.2 PIL: PATIENT INFORMATION LEAFLET**

The proposed PIL is satisfactory.

### **6.3 LABELS**

The proposed labelling is satisfactory.

### **6.4 COMMENTS ON APPLICATION FORM**

The application form has been correctly completed

## **7 CONCLUSIONS**

### **7.1 PHARMACODYNAMICS & PHARMACOKINETICS**

In this application based on essential similarity, the applicant has not submitted any new pharmacological (kinetic or dynamic) data. This is acceptable, once the bioequivalence is demonstrated.

### **7.2 BIOEQUIVALENCE**

As required, the applicant has provided a bioequivalence study where bioequivalence between the test and innovator products may be concluded despite differing salts (maleate and besylate, respectively). This is satisfactory and acceptable.

The applicant has also provided evidence that Norvasc (reference product used in bioequivalence study) and Istin (Innovator product in the UK) are of similar composition and dissolution profile.

### **7.3 EFFICACY & SAFETY**

The applicant has no provided no new safety or efficacy data. This is acceptable for an application based on essential similarity, as no new indication or posology is claimed.

### **7.4 RISK – BENEFIT**

This is considered favourable and is therefore acceptable.

## **8 CLINICAL AND PRE-CLINICAL ASSESSORS' CONCLUSIONS**

There are no preclinical issues related to these applications for amlodipine, as it has been well established in clinical use for over 10 years. The applicant has demonstrated

satisfactory bioequivalence with the innovator product (Norvasc, Pfizer Germany), despite the differences in the two salts.

The product literature is satisfactory.

## OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

### QUALITY

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

### PRECLINICAL

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

### EFFICACY

Bioequivalence has been demonstrated between the applicant's Amlodipine 10mg Tablets and Istin 10mg Tablets (Pfizer Germany). Given that linear kinetics apply between the 5 and 10mg tablets, that proportional formulae for the capsules have been used 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 20223/0011**

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

**STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation applications on 6 <sup>th</sup> February 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 20 <sup>th</sup> February 2004
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 7 <sup>th</sup> September 2004, and further information relating to the quality dossiers on 30 <sup>th</sup> September 2004, 6 <sup>th</sup> April 2005, 29 <sup>th</sup> March 2006, 4 <sup>th</sup> May 2006 and 18 <sup>th</sup> October 2006.
4	The applicant responded to the MHRA's requests, providing further information on 14 <sup>th</sup> January 2005 for the clinical sections, and again on 14 <sup>th</sup> January 2005, 21 <sup>st</sup> March 2006, 4 <sup>th</sup> May 2006, 19 <sup>th</sup> May 2006 and 7 <sup>th</sup> November 2006 for the quality sections.
5	The applications were determined on 20 <sup>th</sup> November 2006

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**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

Active Ingredient: Amlodipine.

Each tablet contains Amlodipine Maleate (equivalent to 5mg Amlodipine).

For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet for oral administration.

5mg tablets: white, round (8 mm diameter) flat uncoated tablets, scored on one side and other side with "AM5" marking

### 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, alpha blocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor.

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 once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response.

For angina, Amlodipine 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.

No dose adjustment of Amlodipine 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, 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 is contraindicated in patients with known hypersensitivity to Amlodipine, other dihydropyridines or any excipient in the tablet.
- 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 (PRAISE-2) of Amlodipine 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.

#### *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 a single oral dose of Amlodipine 10mg in 20 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 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 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 Cyclosporin.

**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 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.

#### 4.8 Undesirable effects

- *Very common:* >1/10
- *Common:* >1/100 and <1/10
- *Uncommon:* >1/1000 and <1/100
- *Rare:* >1/10,000 and <1/1000
- *Very rare:* < 1/10,000, including isolated reports.

*Blood and the lymphatic  
system disorders:*

Very rare: thrombocytopenia

*Immune system disorder:*

Very rare: Allergic reaction.

*Metabolism and nutrition  
disorders:*

Very rare: Hyperglycaemia.

*Nervous system disorders:*

Common: Headache, somnolence, dizziness.

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

Very rare:	Peripheral neuropathy.
<i>Eye disorders:</i>	
Uncommon:	Visual disturbances.
Ear and Labyrinth disorder:	
<i>Uncommon:</i>	Tinnitus.
<i>Psychiatric disorders:</i>	
Uncommon:	insomnia, mood changes.
<i>Cardiac disorders:</i>	
Common:	Palpitations.
Very rare:	myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation.
<i>Vascular disorders</i>	
Common:	Flushing
Uncommon:	Hypotension.
Very rare:	Vasculitis.
<i>Respiratory, thoracic and mediastinal disorders:</i>	
Uncommon:	Dyspnoea, rhinitis.
Very rare:	Coughing.
<i>Gastrointestinal disorders</i>	
Common:	Nausea, abdominal pain.
Uncommon:	Vomiting, dyspepsia, altered bowel habits, dry mouth.
Very rare:	Gastritis, pancreatitis, gingival hyperplasia
<i>Hepato- biliary disorders:</i>	
Very rare:	Hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)

*Skin and subcutaneous tissue disorders:*

Uncommon:	alopecia, purpura skin discolouration, increased sweating, pruritus, rash
Very rare:	angioedema, erythema multiforme, urticaria

*Musculoskeletal, connective tissue and bone disorders:*

Uncommon:	Muscle cramps, back pain, myalgia, arthralgia.
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*Renal- and urinary disorders:*

Uncommon:	Micturition disorder, nocturia, increased urinary frequency.
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*Reproductive system and breast disorders:*

Uncommon:	Impotence, gynaecomastia.
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*General disorders and administration site conditions:*

Common:	Oedema, fatigue
Uncommon:	chest pain, asthenia, pain, malaise.

*Investigations*

Uncommon:	weight increase, weight decrease.
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**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 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. 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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, dihydropyridine derivative.

ATC-code: C 08 CA 01

#### Mechanism of Action

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.

1) 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.

2) 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.

*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 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.

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: Amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.”

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke > 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI(0.90-1.07) p=0.65. Among Secondary Endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0mg dose of Amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of Amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of Amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

## 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,  
Calcium hydrogen Phosphate dihydrate,  
Sodium Starch Glycollate,  
Magnesium Stearate

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

36 months

**6.5 Nature and contents of container**

*Amlodipine 5 mg tablets*

Blister of PVC/PVCD/aluminium in a carton: 10 (also as sample), 28, 30, 50, 98, 100, 200 tablets

Unit dose blister of PVC/PVDC/aluminium in a carton: 50x1

Hospital pack, blister of PVC/PVCD/aluminium in a carton: 300 (10x30) tablets

HDPE bottle with LDPE closure: 100, 250, 500 tablets

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

M.R. Pharma

Waldstr. 30

D- 22889 Tangstedt

Germany

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 20223/0011

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

21/11/2006

**10 DATE OF REVISION OF THE TEXT**

21/11/2006

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: Amlodipine.

Each tablet contains Amlodipine maleate (equivalent to 10mg Amlodipine).

For a full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Tablet for oral administration.

10mg tablets: white, round (10 mm diameter), flat uncoated tablets, scored on one side and other side with "AM10" marking

### 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, alpha blocker, beta-adrenoceptor blocking agent, or an angiotensin converting enzyme inhibitor.

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 once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response.

For angina, Amlodipine 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.

No dose adjustment of Amlodipine 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, 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 is contraindicated in patients with known hypersensitivity to amlodipine, other dihydropyridines or any excipient in the tablet.
- 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 (PRAISE-2) of Amlodipine 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.

*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 a single oral dose of Amlodipine 10mg in 20 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 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 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 Cyclosporin.

*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 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.

**4.8 Undesirable effects**

- *Very common:* >1/10
- *Common:* >1/100 and <1/10
- *Uncommon:* >1/1000 and <1/100
- *Rare:* >1/10,000 and <1/1000
- *Very rare:* < 1/10,000, including isolated reports.

*Blood and the lymphatic  
system disorders:*

Very rare: thrombocytopenia

*Immune system disorder:*

Very rare: Allergic reaction.

*Metabolism and nutrition  
disorders:*

Very rare: Hyperglycaemia.

*Nervous system disorders:*

Common: Headache, somnolence, dizziness.

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

Very rare: Peripheral neuropathy.

*Eye disorders:*

Uncommon: Visual disturbances.

Ear and Labyrinth disorder:

*Uncommon:* Tinnitus.

*Psychiatric disorders:*

Uncommon: insomnia, mood changes.

*Cardiac disorders:*

Common: Palpitations.

Very rare: myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation.

*Vascular disorders*

Common: Flushing

Uncommon: Hypotension.

Very rare: Vasculitis.

*Respiratory, thoracic and mediastinal disorders:*

Uncommon: Dyspnoea, rhinitis.

Very rare: Coughing.

*Gastrointestinal disorders*

Common: Nausea, abdominal pain.

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

Very rare: Gastritis, pancreatitis, gingival hyperplasia

*Hepato- biliary disorders:*

Very rare: Hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)

*Skin and subcutaneous tissue disorders:*

Uncommon: alopecia, purpura skin discolouration,

Very rare:	increased sweating, pruritus, rash angioedema, erythema multiforme, urticaria
<i>Musculoskeletal, connective tissue and bone disorders:</i>	
Uncommon:	Muscle cramps, back pain, myalgia, arthralgia.
<i>Renal- and urinary disorders:</i>	
Uncommon:	Micturition disorder, nocturia, increased urinary frequency.
<i>Reproductive system and breast disorders:</i>	
Uncommon:	Impotence, gynaecomastia.
<i>General disorders and administration site conditions:</i>	
Common:	Oedema, fatigue
Uncommon:	chest pain, asthenia, pain, malaise.
<i>Investigations</i>	
Uncommon:	weight increase, weight decrease.

#### 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 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. 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: Calcium channel blockers, dihydropyridine derivative.

ATC-code: C 08 CA 01

#### Mechanism of Action

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.

1) 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.

2) 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.

***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 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.

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: Amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.”

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke > 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI(0.90-1.07) p=0.65. Among Secondary Endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the Amlodipine group as compared to the chlorthalidone group (10.2% vs 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0mg dose of Amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of Amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

## 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,  
Calcium hydrogen Phosphate dihydrate,  
Sodium Starch Glycollate,  
Magnesium Stearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

36 months

**6.4 Special precautions for storage**

Do not store above 25°C.

**6.5 Nature and contents of container**

*Amlodipine 10 mg tablets*

Blister of PVC/PVCD/aluminium in a carton: 20 (also as sample), 30, 50, 98, 100 tablets

Unit dose blister of PVC/PVDC/aluminium in a carton: 50x1 tablets

Hospital pack, blister of PVC/PVCD/aluminium in a carton: 300 (10x30) tablets

HDPE bottle with LDPE closure: 100, 250, 500 tablets

**6.6 Special precautions for disposal**

No special requirements.

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PL 20223/0012

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

21/11/2006

**10 DATE OF REVISION OF THE TEXT**

21/11/2006

**PACKAGE LEAFLET: INFORMATION FOR THE USER****AMLODIPINE**  
**5mg and 10mg tablets****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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

**In this leaflet:**

1. What Amlodipine is and what it is used for
2. Before you take Amlodipine
3. How to take Amlodipine
4. Possible side effects
5. How to store Amlodipine
6. Further information

**1. WHAT AMLODIPINE IS AND WHAT IT IS USED FOR**

Amlodipine is one of a group of medicines called calcium antagonists. Amlodipine is used to treat high blood pressure (hypertension) or a certain type of chest pain called angina, a rare form of which is 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 does not provide immediate relief of chest pain from angina.

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

**2. BEFORE YOU TAKE AMLODIPINE****Do not take Amlodipine if:**

- you are hypersensitive (allergic) to Amlodipine, other calcium antagonists or any of the other ingredients of Amlodipine.
- you are in a cardiogenic shock
- you have aortic stenosis
- you have unstable angina
- you have low blood pressure
- you are pregnant or breast feeding
- you are a women of child-bearing potential effective contraception is advised.

**Take special care with Amlodipine:**

- if you have had a heart attack during or are in hypertensive crisis?
- when you have a liver disease
- if you are under 18 years of age

**Taking other medicines:**

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 fluid (e.g. 1 glass of water), and can be taken on an empty stomach, between meals or with a meal. The simultaneous intake of food does not affect the uptake of Amlodipine.

**Pregnancy and Breast-feeding**

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

*Pregnancy*

Amlodipine should not be used during pregnancy.

*Breast-feeding*

Amlodipine should not be used when breast-feeding.

**Driving and using machines:**

In patients suffering from dizziness, headache, fatigue or nausea, the ability to react may be impaired, which may influence the ability to drive and use machines.

**3. HOW TO TAKE AMLODIPINE**

Always take Amlodipine exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

If you have the impression that the effect of Amlodipine is too strong or too weak, talk to your doctor or pharmacist.

The initial dose is 5 mg once daily. If this dose is insufficient, it may be increased to a maximum dose of 10 mg daily. The tablets should be taken with a glass of water independently of meals.

Take your tablet as your doctor told you and as written on the label on the pack. Continue to take your tablet each day following the days and arrows on the pack. 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 tablets.

**If you take more Amlodipine than you should:**

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. You should take remaining tablets in the packaging with you so that your doctor knows exactly what and how many tablets have been taken.

**If you forget to take Amlodipine:**

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

**If you stop taking Amlodipine:**

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.

*Common (occur in more than 1 in 100 patients but in less than 1 in 10 patients):*  
headache, oedema (for example ankle swelling), skin rash, feeling tired, feeling sick, flushing, dizziness and swelling or soreness of the gums.

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

*Uncommon (occur in more than 1 in 1,000 patients but in less than 1 in 100 patients):*  
itchy skin, hair loss, palpitations (a quicker or irregular heart beat), shortness of breath, abdominal pain, back pain, indigestion, muscle cramps, weakness, sleepiness, sleeplessness, altered bowel habit, muscle or joint pain, mood changes, increased need to urinate especially during the night, excess sugar in blood, dry mouth, loss of pain sensation, inflamed pancreas, increased sweating, fainting, red blood cell damage (unusual bruising and bleeding), red patches on skin, inability to obtain an erection, visual disturbances, weight increase or decrease, increased sensitivity particularly of the skin, pins and needles, trembling, bruising more easily or purplish marks on the skin, coughing, taste abnormalities, ringing in the ears, sneezing/ running nose and hives.

*Very rare (occur less than 1 in 10,000 including isolated reports)*  
abnormal liver function, inflammation of the liver, yellowing of the skin, severe skin reactions and enlarging of the male breasts

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

All medicines can cause allergic reactions. Serious allergic reactions are very rare and seldom life-threatening. Any sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body) should be reported to a doctor immediately.

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 store above 25°C.

Do not use Amlodipine after expiry date which is stated on the carton.

## 6. FURTHER INFORMATION

### What Amlodipine contains

The active substance is Amlodipine Maleate.

The other ingredients are Microcrystalline Cellulose, Calcium hydrogen Phosphate dihydrate, Sodium Starch Glycollate, and Magnesium Stearate.

### What Amlodipine looks like and contents of the pack

Amlodipine tablets come in two strengths, 5 mg and 10 mg.

*Amlodipine 5 mg tablets* are white, round (8 diameter) flat uncoated tablets, scored on one side and other side with "AM5" marking.

Amlodipine 5 mg tablets are available in:

Blister of PVC/PVCD/aluminium in a carton: 10, 28, 30, 50, 98, 100, 200 tablets

Unit dose blister of PVC/PVDC/aluminium in a carton: 50x1

HDPE bottle with LDPE closure: 100, 250, 500 tablets

*Amlodipine 10 mg tablets* are white, round (10 mm diameter) flat uncoated tablets, scored on one side and other side with "AM10" marking.

Amlodipine 10 mg tablets are available in:

Blister of PVC/PVCD/aluminium in a carton: 20, 30, 50, 98, 100 tablets

Unit dose blister of PVC/PVDC/aluminium in a carton: 50x1 tablets

HDPE bottle with LDPE closure: 100, 250, 500 tablets

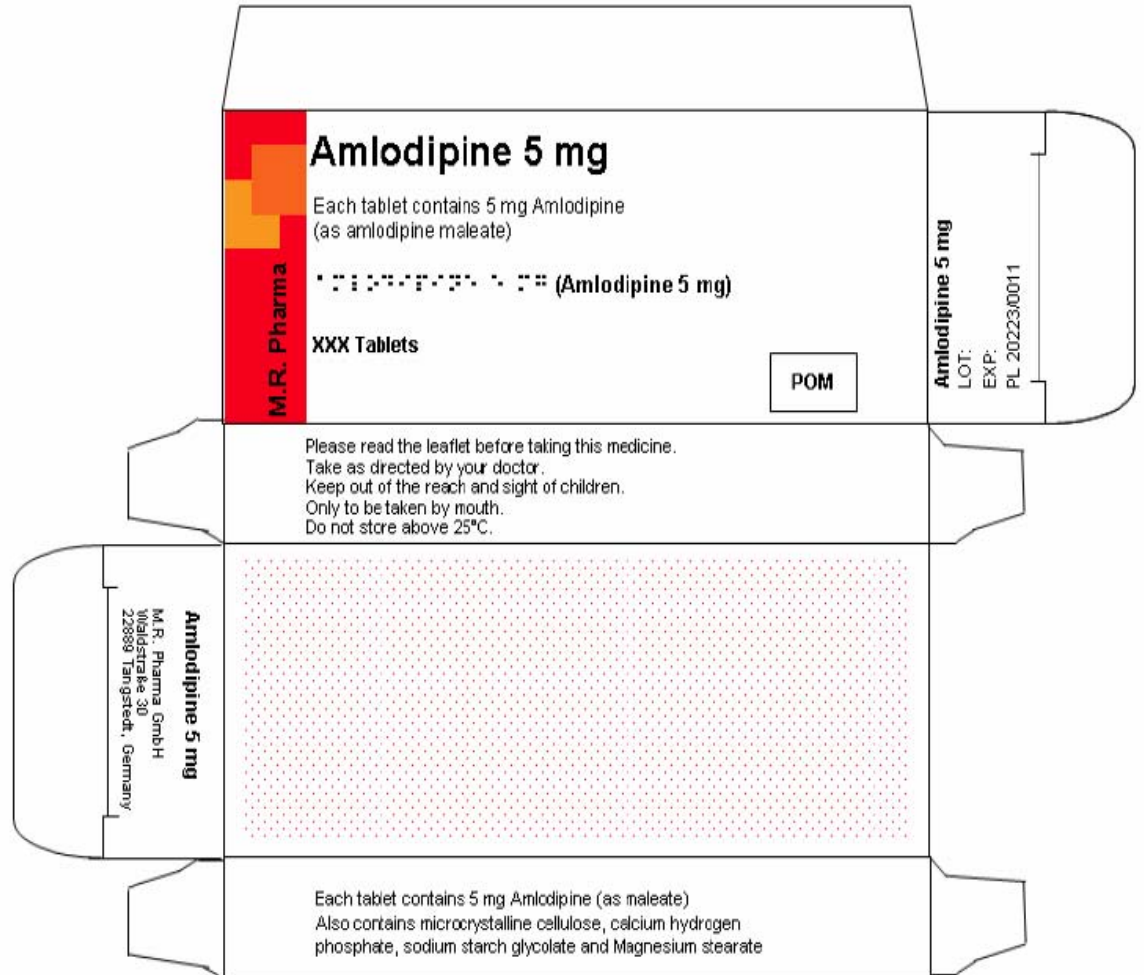
### Marketing Authorisation Holder and Manufacturer

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Germany

Actavis hf.  
Kopavogur  
Iceland

**This leaflet was last approved on 02/2006**

Amlodipine 5 mg tablets



Amlodipine 10 mg tablets

