AMLODIPINE 5MG TABLETS
PL 20765/0007
PL 20765/0014
PL 20765/0016
PL 20765/0018

AMLODIPINE 10MG TABLETS
PL 20765/0008
PL 20765/0015
PL 20765/0017
PL 20765/0019

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Product Information Leaflet
Labelling
The MHRA today granted Stichting Parkpharma Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg Tablets (PL 20765/0007, 0014, 0016 and 0018) and Amlodipine 10mg Tablets (PL 20765/0008, 0015, 0017, 0019). 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.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Amlodipine Tablets outweigh the risks, hence Marketing Authorisations have been granted.
AMLODIPINE 5MG TABLETS
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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 5 and 10mg Tablets to Stichting Parkpharma (PL 20765/0007-8, 0014-19) on 13\textsuperscript{th} January 2006. The products are prescription only medicines.

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

The products contain the active ingredient amlodipine besilate, a calcium channel blocker, and are indicated for the treatment of essential hypertension and angina pectoris.

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

DRUG SUBSTANCE
Amlodipine besilate Ph Eur
Amlodipine besilate is a white or almost white powder, slightly soluble in water.

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 UV, IR, H1 NMR, MS and elemental 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.

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

Appropriate stability data have been generated supporting a retest period of 1 year and a shelf life of 2 years when stored in original packaging and protected from light.

DRUG PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, lactose anhydrous, maize starch dried, talc, colloidal anhydrous silica 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
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 full-scale batches of each strength (including the biobatch). The results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.
Container Closure System
Specifications, Certificates of Analysis with accompanying spectra/thermograms of the primary packaging material 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 precautions ‘Store in the original packaging’ and ‘store below 25°C’ have been included.

Suitable post-approval commitments have been made for the product packaged in Al/Aclar.

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. In addition, similar dissolution profiles have been demonstrated for the proposed and reference products.
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

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

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

Background
These are four sets of 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.

The basis of the application is acceptable and the salt is identical to the innovator product. The indications sought and the SPC are expected to be identical to the innovator.

Indications, dosage and dosage regimen.
The indications are similar to those of the reference product (hypertension, prophylaxis of chronic stable angina pectoris, Prinzmetal’s angina when diagnosed by a cardiologist).

The dose and regimen as proposed are identical to the reference product.

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.

No dose adjustment 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.

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.
**Assessor’s Comment**

The basis of the application, indications sought, and dose and dosage regimen are appropriate and acceptable.

2 CLINICAL PHARMACOLOGY

Pharmacokinetics & Pharmacodynamics

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.

Bioavailability & Bioequivalence

**Bioavailability**

The salt, the pharmaceutical preparation and absorption, may influence bioavailability of amlodipine. The generic product has the same salt as the innovator product and is thus acceptable. The applicant has further provided a bioequivalence study comparing the two products, which is discussed below.

**Bioequivalence study.**

This is a single-dose, two way crossover, open randomised study comparing the test product (Amlodipine 10mg Tablets) with the reference product (Istin 10mg Tablets).

Results:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test Product</th>
<th>Reference Product</th>
<th>90% CI Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCt (ng/ml*h)</td>
<td>186.38 ± 43.67</td>
<td>184.27 ± 44.65</td>
<td>101.15 (98.03 to 104.75)</td>
</tr>
<tr>
<td>AUC∞ (ng/ml*h)</td>
<td>241.17 ± 66.76</td>
<td>248.06 ± 79.27</td>
<td>97.22 (93.85 to 102.56)</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>6.06 ± 1.12</td>
<td>5.88 ± 1.10</td>
<td>103.11 ± (98.35 to 108.18)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>5.38</td>
<td>5.52</td>
<td></td>
</tr>
</tbody>
</table>

Observations:

The assay methodology appears adequate and appropriate. Only the amlodipine base is absorbed into the system and the salt has no influence on the kinetics of amlodipine. The assay sensitivity appears adequate. The sampling frequency appears satisfactory while sampling time should ideally have been slightly longer in order to provide the most appropriate point for extrapolation of AUC.

There several lacunae in the report and limitations to the biostudy; the number of subjects recruited were 34 and only 29 completed the study. Whilst n=29 may be an acceptable figure, the explanations for the 5 missing subjects does not appear entirely satisfactory, but these were not post-hoc exclusions. This may be therefore be accepted. Secondly, the residual area (AUCi – AUCt) is 22% for test, and 25.5% for reference product. This may be the result of sampling time point used for extrapolation. These lacunae however do not appear to have affected the biostudy results significantly and it is likely that the test product is bioequivalent with the reference product, as the parameters demonstrate.

**Assessor’s 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 (Pfizer UK’s Istin) and the generic product (Lek Amlodipin) may be concluded.

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

This is a non-critical report but supports the bioequivalence study on the appropriate basis. This is acceptable.

6  PRODUCT LITERATURE

6.1  SPC: SUMMARY OF PRODUCT CHARACTERISTICS

The proposed SPC is in line with that for the reference product.

6.2  PIL; PATIENT INFORMATION LEAFLET

The PIL is satisfactory.

6.3  LABELS

These are satisfactory.

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.

7.2  BIOEQUIVALENCE

As required, the applicant has provided a bioequivalence study wherein acceptable bioequivalence between the test and innovator products may be concluded. This is satisfactory and acceptable.

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 indications or posology is claimed.

7.4  RISK – BENEFIT

This is considered favourable and is, therefore, acceptable.
8 CONCLUSIONS
There are no pre-clinical issues related to this application for amlodipine as it is well established in clinical use for over 10 years. The applicant has demonstrated satisfactory bioequivalence with the innovator product (Istin, Pfizer UK). The product literature is considered satisfactory. It is recommended that marketing authorisations are granted.
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 UK). 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**  
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**AMLODIPINE 10MG TABLETS**  
PL 20765/0008  
PL 20765/0015  
PL 20765/0017  
PL 20765/0019  

**STEPS TAKEN FOR ASSESSMENT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 28th July 2003</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 1st October 2003</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 3rd February 2004 and 2nd February 2005, and further information relating to the quality dossiers on 5th July 2004.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 9th March 2004 and 1st December 2005 for the clinical sections, and again on 15th October 2004 for the quality sections.</td>
</tr>
<tr>
<td>7</td>
<td>The applications were determined on 13th January 2006</td>
</tr>
</tbody>
</table>
## AMLODIPINE 5MG TABLETS
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- PL 20765/0016
- PL 20765/0018

## AMLODIPINE 10MG TABLETS
- PL 20765/0008
- PL 20765/0015
- PL 20765/0017
- PL 20765/0019

### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>
1. NAME OF THE MEDICINAL PRODUCT
Amlodipine 5mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5mg amlodipine (as besilate).
For excipients, see 6.1.

3. PHARMACEUTICAL FORM
Tablets
The tablets are white to slightly yellow, round, debossed AML5 on one side and scored on the other.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
Hypertension.
Prophylaxis of chronic stable angina pectoris.
Prinzmetal’s angina when diagnosed by a cardiologist.

4.2. Posology and method of administration
In hypertensive patients Amlodipine has been used in combination with a thiazide diuretic, alpha-blocker, beta-adrenoreceptor blocking agent, or an angiotensin converting enzyme inhibitor. 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.

Amlodipine is well tolerated in patients with heart failure and a history of hypertension or ischemic heart disease.

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.

No dose adjustment 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 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 dialyzable.

Method of administration: Amlodipine is taken orally with a liquid and without chewing.

4.3 Contraindications
Amlodipine is contraindicated in patients with a known hypersensitivity to dihydropyridines, amlodipine or any of the excipients of the medicinal product.

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 special 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 medicinal product should 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.

This medicinal product contains lactose. Patients with rare hereditary problems of lactose-galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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: Effects on other agents on amlodipine**

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

**Grapefruit juice:** Co-administration of 240ml of grapefruit juice with a single oral dose of amlopin 10mg in 20 healthy volunteers has no significant effect on the pharmacokinetics of amlodipin.

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

**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 and 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 patient’s ability to drive or use machinery. However, side effects such as dizziness and syncope may interfere with this ability, therefore patients should be warned accordingly.

### 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%).

<table>
<thead>
<tr>
<th>System Disorders</th>
<th>Adverse Event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the Lymphatic System</td>
<td>thrombocytopenia</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>allergic reaction</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>hyperglycaemia</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>insomnia, mood changes</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>somnolence, dizziness, headache</td>
<td>Common</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>tremor, taste perversion, syncope, hypoesthesia, paraesthesia</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>peripheral neuropathy</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Eye-disorders</td>
<td>visual disturbances</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>tinnitus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>palpitations</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>flushing</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>hypotension</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>vasculitis</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>dyspnoea, rhinitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>coughing</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>abdominal pain, nausea</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>vomiting, dyspepsia, altered bowel habit, dry mouth</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>pancreatitis, gastritis, gingival hyperplasia</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Hepato-biliary Disorders</td>
<td>hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>alopecia, purpura, skin discoulouration, increased sweating, pruritus, rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>angioedema, erythema multiforme, urticaria</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>arthralgia, myalgia, muscle cramps, back pain</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>micturition disorder, nocturia, increased urinary frequency</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>impotence, gynecomastia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>oedema, fatigue</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>chest pain, asthenia, pain, malaise</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Investigations</td>
<td>weight gain, weight decrease</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

### 4.9 Overdose

Available data suggest that gross overdose 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 upon 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**

ATC Code C08CA01

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

The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle in arterial blood vessels. 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 which lasts for 24 hours. 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 frequency of anginal attacks 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:** Hemodynamic 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 who were under treatment with 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 finding suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

5.2. Pharmacokinetic properties

Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that about 98% 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 elderly: The time needed 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 patients age group studied.

5.3. Preclinical safety data
None

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Anhydrous lactose
Microcrystalline cellulose
Maize starch
Colloidal anhydrous silica
Talc
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package.
Do not store above 25°C.
Keep out of the reach and sight of children.

6.5 Nature and contents of container
Amlodipine 5mg tablets
Aclar/Al blister in boxes of 10, 14, 20, 28, 30, 50, 56, 98, 100 and 100x1.
HDPE plastic tablet container: packs of 20, 30, 50, 100, 200 and 250 tablets.
Not all pack sizes may be marketed.

6.6. Instructions for use/handling
No special requirements

7. MARKETING AUTHORISATION HOLDER
Stichting ParkPharma, De Sitterlaan 95, 2313 Leiden, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)
PL 20765/0007
PL 20765/0014
PL 20765/0016
PL 20765/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION
13/01/2006

10 DATE OF REVISION OF THE TEXT
13/01/2006
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
   Amlodipine 10mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each tablet contains 10mg amlodipine (as besilate).
   For excipients, see 6.1.

3. PHARMACEUTICAL FORM
   Tablets
   The tablets are white to slightly yellow, round, debossed AML10 on one side and scored on the other.

4. CLINICAL PARTICULARS
   4.1 Therapeutic indications
   Hypertension.
   Prophylaxis of chronic stable angina pectoris.
   Prinzmetal’s angina when diagnosed by a cardiologist.

   4.2. Posology and method of administration
   In hypertensive patients Amlodipine has been used in combination with a thiazide diuretic, alpha-blocker, beta-adrenoreceptor blocking agent, or an angiotensin converting enzyme inhibitor. 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.

   Amlodipine is well tolerated in patients with heart failure and a history of hypertension or ischemic heart disease.

   **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.

   No dose adjustment 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 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 dialyzable.

Method of administration: Amlodipine is taken orally with a liquid and without chewing.

4.4 Contraindications

Amlodipine is contraindicated in patients with a known hypersensitivity to dihydropyridines, amlodipine or any of the excipients of the medicinal product.

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 special 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 medicinal product should 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.

This medicinal product contains lactose. Patients with rare hereditary problems of lactose-galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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: Effects on other agents on amlodipine**

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

**Grapefruit juice:** Co-administration of 240ml of grapefruit juice with a single oral dose of amlopin 10mg in 20 healthy volunteers has no significant effect on the pharmacokinetics of amlodipin.

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

**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 and 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 patient’s ability to drive or use machinery. However, side effects such as dizziness and syncope may interfere with this ability, therefore patients should be warned accordingly.
### 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%).

<table>
<thead>
<tr>
<th>Blood and the Lymphatic System Disorders</th>
<th>thrombocytopenia</th>
<th>Very Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune System Disorders</td>
<td>allergic reaction</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>hyperglycaemia</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>insomnia, mood changes</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>somnolence, dizziness, headache</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>tremor, taste perversion, syncope, hypoaesthesia, paraesthesia</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>peripheral neuropathy</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Eye-disorders</td>
<td>visual disturbances</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>tinnitus</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>palpitations</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>flushing</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>hypotension</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>vasculitis</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>dyspnoea, rhinitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>coughing</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>oesophageal pain, nausea</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>vomiting, dyspepsia, altered bowel habit, dry mouth</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>pancreatitis, gastritis, gingival hyperplasia</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Hepato-biliary Disorders</td>
<td>hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis)</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>alopecia, purpura, skin discoloration, increased sweating, pruritus, rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>angioedema, erythema multiforme, urticaria</td>
<td>Very Rare</td>
</tr>
</tbody>
</table>
### Musculoskeletal and Connective Tissue Disorders
- arthralgia, myalgia, muscle cramps, back pain | Uncommon

### Renal and Urinary Disorders
- micturition disorder, nocturia, increased urinary frequency | Uncommon

### Reproductive System and Breast Disorders
- impotence, gynecomastia | Uncommon

### General Disorders and Administration Site Conditions
- oedema, fatigue | Common
- chest pain, asthenia, pain, malaise | Uncommon

### Investigations
- weight gain, weight decrease | Uncommon

### 4.9 Overdose
Available data suggest that gross overdose 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 upon 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

**ATC Code C08CA01**

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

The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle in arterial blood vessels. 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 which lasts for 24 hours. 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 frequency of anginal attacks 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: Hemodynamic 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 who were under treatment with 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 finding suggestive or 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.

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Use in elderly: The time needed 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 patients age group studied.

5.3. Preclinical safety data
None

6. PHARMACEUTICAL PARTICULARS
6.1. List of excipients
Anhydrous lactose
Microcrystalline cellulose
Maize starch
Colloidal anhydrous silica
Talc
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package.
Do not store above 25°C.
Keep out of reach of children.

6.5 Nature and contents of container
Amlodipine 10mg tablets
Aclar/Al blister in boxes of 10, 14, 20, 28, 30, 50, 56, 98, 100 and 100x1.
HDPE plastic tablet container: packs of 20, 30, 50, 100, 200 and 250 tablets.

Not all pack sizes may be marketed.

6.7. Special precautions for disposal
No special requirements
7. MARKETING AUTHORISATION HOLDER
   Stichting ParkPharma, De Sitterlaan 95, 2313 Leiden, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)
   PL 20765/0008
   PL 20765/0015
   PL 20765/0017
   PL 20765/0019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   13/01/2006

10. DATE OF REVISION OF THE TEXT
    13/01/200
PATIENT INFORMATION LEAFLET

Amlodipine 5mg Tablets

Please read this leaflet carefully before you start to take your tablets. This leaflet gives a summary of information about your medicine. If you want to know more, or are not sure about anything, ask your doctor or pharmacist. Keep this leaflet in a safe place as you may want to read it again.

About your tablets:

Your tablets are called Amlodipine 5mg tablets. They belong to a group of medicines called calcium-antagonists.

What is in your tablets:

Each tablet contains 5mg of amlodipine in the form of amlodipine besilate (active substance). Each tablet also contains the other ingredients: lactose anhydrous, microcrystalline cellulose, maize starch, colloidal anhydrous silica, talc and magnesium stearate.

What your tablets do:

Amlodipine is used to treat high blood pressure (hypertension) or a certain type of chest pain called angina. A rare form of which is 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 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.

Amlodipine tablets can be used alone (as sole therapeutic agent) or in combination with other antianginal drugs or in combination with diuretics.

Before you take your tablets:

Do not take Amlodipine:

• if you are hypersensitive to dihydroergotamin, to amlodipine itself or any of the other ingredients of the medicinal product.
• if you have cardiogenic shock.
• if you have aortic stenosis (narrowing of the aortic heart valve).
• if you have unstable angina (excluding Prinzmetal’s angina).
• if you are pregnant or breast feeding.

Take special care with Amlodipine:

• if you have impaired hepatic function.
• if you have a heart attack.
• if you are in a hypertensive crisis.

Tell your doctor about it:

Driving and using machines:

Amlodipine may not directly affect your ability to drive or operate machinery. However, side effects such as dizziness may interfere with this ability. Take care not to drive or operate machinery if you take this medicine.

Important information about some of the ingredients of Amlodipine:

Amlodipine tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Taking other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

No interactions were observed when your tablets were taken together with ciclosporin, digoxin, omeprazole and warfarin.

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. However it can potentiate the action of other antihypertensives, tricyclic antidepressants, ACE-inhibitors and diuretics.
How to take your tablets.
You must take your tablets as your doctor has told you to. The label will tell you how many to take and how often to take them. The number of tablets you take is called the dose. If you have the impression that the dose is too strong or too weak, talk to your doctor. Do not change the dosage by yourself.

The usual dose of Amlodipine tablets is one tablet daily.
Tablets should be swallowed with half a glass of water. It is best to take your tablets at the same time each day.

Adults:
The initial daily dose is 5mg. The maximum daily dose is 10mg.

Dosage in renal insufficiency and in elderly patients:
In case of renal insufficiency or in elderly patients the normal doses are recommended.

Dosage in case of concomitant treatment with diuretics, ACE-inhibitors or Beta-Blockers:
No dose adjustment is required.

Duration of treatment:
It is important that you continue to take Amlodipine until your doctor tells you otherwise. Keep your doctor's appointment even if you feel well. Do not wait until your tablets are finished before seeing your doctor. Your doctor may wish to change dosage and give you more Amlodipine Tablets. It is important to keep taking the tablets. They may help to remain well.

What if you miss a dose:
If you miss a dose do not worry, take it as soon as you remember. Do not take two doses together. If it is almost time to take next dose, wait until then. Do not double dose to make up for the one you missed.

What if you take too many tablets:
Too many tablets at once make you feel unwell. If you have taken more amlodipine than you should, inform your doctor immediately or go to the nearest hospital casualty department. Take your medicine in the packaging with you.

After taking your tablets:
Possible side effects:
Like all medicines, Amlodipine tablets can have side effects. The most common are 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 side effects cause you any problems or if they last for more than one week.

Rare side effects:
Itchy skin, hair loss, palpitations (a quicker or irregular heart beat), shortness of breath, abdominal pain, back pain, indigestion, muscle cramps, weakness, sleeping disorders, altered bowel habit, muscle or joint pain, mood changes, increased need to urinate, dry mouth, excess sugar in the blood, 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 and visual disturbances.

Very rarely abnormal liver function, inflammation of the liver, yellowing of the skin, severe skin reactions and enlargement of the male breasts have been reported.

The following side effects have occurred in patients but the relationship to the treatment with Amlodipine tablets 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 you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Looking after your tablets:
Keep your tablets in pack they came in. Do not put them into another container. Amlodipine tablets should be protected from light and moisture. Do not store above 25°C.

Do not use your tablets after the expiry date stated on the carton.

Keep out of the reach and sight of children.

These tablets are only for you. Only a doctor can prescribe them for you. Never give them to anyone else.

This leaflet was written in February 2005
PATIENT INFORMATION LEAFLET

Amlodipine 10mg Tablets

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Your tablets come in:

Blister packs of 10, 14, 20, 20, 50, 50, 90, 100 and 100 x 1 tablets.

Plastic containers of 20, 30, 50, 100, 200 and 250 tablets.

Marketing Authorisation Holder:

Stichting ParkPharma, De Sitterlaan 95, 2313 Leiden, The Netherlands

Manufacturer responsible for batch release:

Lek Pharmaceuticals d.d., Verovnikova 57, Ljubljana, Slovenia

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• if you have aortic stenosis (narrowing of the aortic heart valve)
• if you have unstable angina (excluding Prinzmetal’s angina).
• if you are pregnant or breast-feeding

Take special care with Amlodipine:

• if you have impaired hepatic function
• if you had a heart attack
• if you are in hypertensive crisis
Tell your doctor about it.

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Duration of treatment
It is important that you continue to take Amlodipine until your doctor tells you otherwise. Keep your doctor's appointment even if you feel well. Do not visit until your tablets are finished before seeing your doctor. Your doctor may wish to change dosage and give you more Amlodipine Tablets. It is important to keep taking the tablets. They may help to remain well.

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Too many tablets at once may make you feel unwell. If you have taken more Amlodipine than you should, inform your doctor immediately or go to the nearest hospital casualty department. Take your medicine in the packaging with you.

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Rare side effects:
itchy skin, hair loss, palpitations (a quicker or irregular heart beat), shortness of breath, abdominal pain, back pain, indigestion, muscle cramps, weakness, sleeping disorders, altered bowel habit, muscle or joint pain, mood changes, increased need to urinate, dry mouth, excess sugar in the blood, loss of pain sensation, inflammation of the gut, increased sweating, feeling, red blood cell damage (unusual bruising and bleeding), red patches on skin, inability to obtain an erection and visual disturbances.
Very rarely abnormal liver function, inflammation of the liver, yellowing of the skin, severe skin reactions and enlargement of the male breasts have been reported.

The following side effects have occurred in patients but the relationship to the treatment with Amlodipine tablets or the disease state is uncertain: heart attack (myocardial infarction), irregular heartbeat (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 you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Looking after your tablets.
Keep your tablets in pack they came in. Do not put them into another container.
Amlodipine tablets should be protected from light and moisture. Do not store above 25°C.

Do not use your tablets after the expiry date stated on the carton.

Keep out of the reach and sight of children.

These tablets are only for you. Only a doctor can prescribe them for you. Never give them to anyone else.

This leaflet was written in February 2005
Amlodipine 5mg Tablets

For oral use.
Swallow the tablets with half a glass of water at the same time each day.
Contains lactose anhydrous
PL 20765/0007

Marketing authorisation holder:
Stichting QurkPharma
UKPAR Amlodipine 5 and 10mg Tablets

Amlodipine BESILATE

Please read the enclosed leaflet carefully before using this medicine.

Amlodipine is in the form of tablets.

Store below 25°C.

Gloss in the original package.

Dosage:

Take one tablet daily as directed by the doctor.

Keep out of the reach and sight of children.

PL 20765/0007-8, 0014-19
For oral use. Swallow the tablets with half a glass of water at the same time each day. Contains lactose anhydrous.

Marketing authorisation holder: Janssen Pharmaceutica

Lot No.: 3915

Exp. date:
UKPAR Amlodipine 5 and 10mg Tablets

PL 20765/0007-8, 0014-19

Amlodipine Besilate Tablets

Please read the enclosed leaflet carefully before using this medicine.

Each tablet contains 10mg amlodipine in the form of amlodipine besilate.

Do not store above 25°C.

Not for use in children.

One tablet once daily or as directed by the doctor.

Swallow the tablets with half a glass of water at the same time each day.

Keep out of the reach and sight of children.

EL 2065/0000

10 tablets