# AMLODIPINE 5MG TABLETS

# PL 17907/0085

# AMLODIPINE 10MG TABLETS

# PL 17907/0086

# UKPAR

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# LAY SUMMARY

The MHRA today granted Bristol Laboratories Ltd Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg Tablets (PL 17907/0085) and Amlodipine 10mg Tablets (PL 17907/0086). These are prescription only medicines (POM) 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 17907/0085

# AMLODIPINE 10MG 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 5mg Tablets (PL 17907/0085) and Amlodipine 10mg Tablets (PL 17907/0086) on 9th March 2007. The products are prescription only medicines.

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

The products contain the active ingredient amlodipine besilate, which acts as a calcium channel blockers used for the treatment of hypertension, prophylaxis of chronic stable angina pectoris and Prinzmetal's (variant) angina when diagnosed by a cardiologist. Amlodipine works by relaxing blood vessels, so that blood passes through them more easily, and by increasing blood supply to the heart.

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 Istin 10mg (Pfizer, UK). Consequently, all sections of this Scientific Discussion refer to both products.

# PHARMACEUTICAL ASSESSMENT

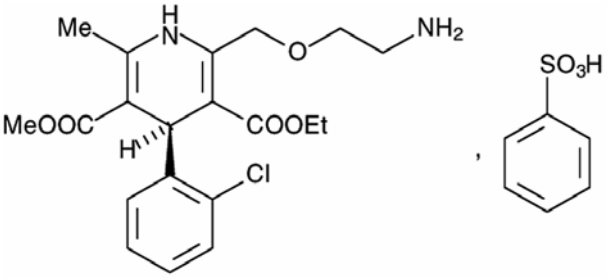
## DRUG SUBSTANCE

### Amlodipine besilate

Ph. Eur. Name Amlodipine Besilate

Chemical name 3-Ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate.

Structure




and enantiomer

Molecular formula: $C_{20}H_{25}ClN_2O_5,C_6H_6O_3S$

Molecular Mass: 567.06

Amlodipine besilate is a white or almost white powder. Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol and slightly soluble in 2-propanol.

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

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

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

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

Amlodipine besilate 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.

A working standard is used as the reference standard in the analysis of new batches. A certificate of analysis is provided demonstrating compliance with Ph Eur requirements for amlodipine besilate.

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, Silica colloidal anhydrous 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.

There were no novel excipients used and no overages.

### 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

Product is packaged in opaque blisters composed of aluminium and PVC/PVDC and in HDPE container. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food. The pack sizes are 28, 56, 84, 100, 250, and 500 tablets.

## Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. The precautions ‘Do not store above 25°C’, “Store in the original package” and “Keep the container tightly closed” have been included.

## Conclusion

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

The proposed products are considered to be a generic medicinal product to the reference product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

# PRECLINICAL ASSESSMENT

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 applications for Amlodipine Tablets for the treatment of essential hypertension and angina pectoris. The applicant under article 10.1 claims that this is a generic medicinal product of Istin Tablets(Pfizer Limited 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 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 brand leader/ reference product, Istin (PL 00057/0297-8) and are therefore acceptable.

### 1.5 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.

### 1.6 ASSESSOR'S COMMENT

The basis of the application, indication, 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. In this application, the salt is identical to the brand leader and 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, randomised study.

Study design : Single-dose, randomised, two-way crossover, two period, open label study
Subjects : Planned 26, Randomised 26, Completed 24; male & female

Reference Prod : Istin, 10 mg
Test Product : Amlodipine besilate 10mg

**Results:**

| Parameter | Test (Bristol Labs) | Ref Prod (Istin, Pfizer, Inc.,) | Point Est & 90% CI Ratio |
|---|---|---|---|
| **AUCt** (pg./ml*h) | 293964.47 ± 87892.53 | 297294.35 ± 84644.89 | **98.83** ( 94.01 to 103.90) |
| **AUC∞** (pg./ml*h) | 310447.24 ± 101012.58 | 314624.54 ± 94361.55 | **98.43** ( 93.57 to 103.55) |
| **Cmax** (pg./ml) | 5428.52 ± 1179.49 | 5483.00 ± 1275.83 | **99.58** (94.15 to 105.33) |
| **Tmax (h)** | 7.00 ±2.00 (median + IQR) | 6.00 ±1.25 | |

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 AUCt is >80% of the AUCinf 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).

Similar qualitative composition; the same active to excipient ratio; similar dissolution profiles and rates; linear drug input over therapeutic range (kinetics); and same manufacturer and site of manufacture.

These are acceptable although the expert report does not discuss these or biowaiver criteria.

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 (Istin, Pfizer Inc., UK) and the generic product (IPCA Labs, India/ Bristol Labs, UK) 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

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 SPCs are satisfactory.

## 6.2 PIL; PATIENT INFORMATION LEAFLET

The proposed PIL is satisfactory.

## 6.3 LABELS

The proposed labels are satisfactory

## 6.4 COMMENTS ON APPLICATION FORM

None medically.

# 7 CONCLUSIONS

## 7.1 PHARMACODYNAMICS & PHARMACOKINETICS

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 in acceptable bioequivalence between the test and innovator products may be concluded. This is satisfactory and acceptable.

### 7.3 EFFICACY & SAFETY

The applicant has not provided new safety or efficacy data. This is acceptable for an application based on a generic medicinal product, 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 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 Inc., UK). The clinical assessor recommends that marketing authorisations should be 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 Limited, 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

# PL 17907/0085

# AMLODIPINE 10MG TABLETS

# PL 17907/0086

## STEPS TAKEN FOR ASSESSMENT

| | |
|---|---|
| 1 | The MHRA received the marketing authorisation applications on 13th April 2004 |
| 2 | Following standard checks and communication with the applicant the MHRA considered the applications valid on 14th May 2004 |
| 3 | Following assessment of the application the MHRA requested further information relating to the clinical dossier on 15th September 2004 and quality dossiers on 24th February 2005, 16th August 2006 and 13th February 2007 |
| 4 | The applicant responded to the MHRA's requests, providing further information on clinical dossier on 15th February 2005 and on quality dossier on 11th April 2004, 13th February 2007 and 8th March 2007. |
| 5 | The applications were determined on 9th March 2007 |

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 5 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg Amlodipine as Amlodipine Besilate.

For full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Tablet

White to off white, round, biconvex, uncoated tablets with '5' embossing on one side.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Hypertension

Prophylaxis of chronic stable angina pectoris and Prinzmental's (Variant) angina when diagnosed by a cardiologist.

In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha-blocker, beta-adrenergic 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 ischaemic heart disease.

### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

**In adults**

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

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

**Use in children**

Not recommended.

**Use in the elderly**

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

**Patients with hepatic impairment**

See section 4.4" special warning and special precautions for use".

**Patients with renal impairment**

Changes in Amlodipine plasma concentrations are not correlated with degree

of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

## 4.3 CONTRAINDICATIONS

Amlodipine Tablets are contraindicated in

- Patients with known sensitivity to Dihydropyridines, Amlodipine or any of the excipients.
- Cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmental'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 tablets in hypertensive crisis has not been established.

## 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

**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 amlodpine10mg 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.

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

***Drug/Laboratory test Interactions****:* None known.

## 4.6 PREGNANCY AND LACTATION

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

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Clinical experiencewith Amlodipine indicated that therapy is unlikely to impair a patient's ability to drive or use machinery.

## 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%).

| | | |
|---|---|---|
| *Blood and the Lymphatic System Disorders* | thrombocytopenia | Very Rare |
| Immune System Disorders | allergic reaction | Very Rare |
| *Metabolism and Nutrition Disorders* | hyperglycaemia | Very Rare |
| *Psychiatric Disorders* | insomnia, mood changes | Uncommon |
| Nervous System Disorders | somnolence, dizziness, headache | Common |
| | tremor, taste perversion, syncope, hypoaesthesia, paraesthesia | Uncommon |
| | peripheral neuropathy | Very Rare |
| *Eye Disorders* | visual disturbances | Uncommon |
| *Ear and Labyrinth Disorders* | tinnitus | Uncommon |
| *Cardiac Disorders* | palpitations | Common |
| | myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation) | Very Rare |
| *Vascular Disorders* | flushing | Common |
| | hypotension | Uncommon |

| | | |
|---|---|---|
| | | |
| | vasculitis | Very Rare |
| *Respiratory, Thoracic and Mediastinal Disorders* | dyspnoea, rhinitis | Uncommon |
| | coughing | Very Rare |
| *Gastrointestinal Disorders* | abdominal pain, nausea | Common |
| | vomiting, dyspepsia, altered bowel habits, dry mouth | Uncommon |
| | pancreatitis, gastritis, gingival hyperplasia | Very Rare |
| *Hepato-biliary Disorders* | hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) | Very Rare |
| *Skin and Subcutaneous Tissue Disorders* | alopecia, purpura, skin discolouration, increased sweating, pruritus, rash | Uncommon |
| | angioedema, erythema multiforme, urticaria | Very Rare |
| *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, gynaecomastia | Uncommon |
| *General Disorders and Administration Site Conditions* | oedema, fatigue | Common |
| | chest pain, asthenia, pain, malaise | Uncommon |
| *Investigations* | weight increase, weight decrease | Uncommon |

## 4.9 OVERDOSE

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Calcium Channel Blocker

ATC Code: C08CA01

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

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

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 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.

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 enrolment) 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 adminstration 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 increase 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 studies.

## 5.3 PRECLINICAL SAFETY DATA

None.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Calcium hydrogen phosphate dihydrate

Microcrystalline cellulose

Silica colloidal anhydrous

Sodium starch glycollate

Magnesium stearate

## 6.2 INCOMPATIBILITIES

None Known

## 6.3 SHELF LIFE

3 years

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

**Blisters:** Do not store above 25ºC.

Store in the original package.

**Bulk:** Do not store above 25ºC.

Keep the container tightly closed.

## 6.5 NATURE AND CONTENTS OF CONTAINER

Aluminium/PVDC coated PVC blister strips containing 14 tablets. Blister strips packaged into outer container to give total of 28, 56, 84 tablets.

The tablets are also packed in HDPE containers containing 100, 250, 500 tablets.

Not all pack sizes may be marketed.

## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

# 7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited

Unit 3, Canalside, Northbridge Road,

Berkhamsted, Herts,

HP4 1EG

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**
PL 17907/0085

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
09/03/2007

**10 DATE OF REVISION OF THE TEXT**
09/03/2007

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 10 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg Amlodipine as Amlodipine Besilate.

For full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM
Tablet

White to off white, round, biconvex, uncoated tablets with '10' embossing on one side.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS
Hypertension

Prophylaxis of chronic stable angina pectoris and Prinzmental's (Variant) angina when diagnosed by a cardiologist.

In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha-blocker, beta-adrenergic 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 ischaemic heart disease.

### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION
**In adults**

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

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

**Use in children**

Not recommended.

**Use in the elderly**

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

**Patients with hepatic impairment**

See section 4.4" special warning and special precautions for use".

**Patients with renal impairment**

Changes in Amlodipine plasma concentrations are not correlated with degree

of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

## 4.3 CONTRAINDICATIONS

Amlodipine Tablets are contraindicated in

- Patients with known sensitivity to Dihydropyridines, Amlodipine or any of the excipients.
- Cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmental'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 tablets in hypertensive crisis has not been established.

## 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

**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 amlodpine10mg 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.

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

***Drug/Laboratory test Interactions****:* None known.

## 4.6 PREGNANCY AND LACTATION

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

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Clinical experiencewith Amlodipine indicated that therapy is unlikely to impair a patient’s ability to drive or use machinery.

## 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%).

| | | |
|---|---|---|
| Blood and the Lymphatic System Disorders | thrombocytopenia | Very Rare |
| Immune System Disorders | allergic reaction | Very Rare |
| Metabolism and Nutrition Disorders | hyperglycaemia | Very Rare |
| Psychiatric Disorders | insomnia, mood changes | Uncommon |
| Nervous System Disorders | somnolence, dizziness, headache | Common |
| | tremor, taste perversion, syncope, hypoaesthesia, paraesthesia | Uncommon |
| | peripheral neuropathy | Very Rare |
| Eye Disorders | visual disturbances | Uncommon |
| Ear and Labyrinth Disorders | tinnitus | Uncommon |
| Cardiac Disorders | palpitations | Common |
| | myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation) | Very Rare |
| Vascular Disorders | flushing | Common |
| | hypotension | Uncommon |
| | vasculitis | Very Rare |
| Respiratory, Thoracic and Mediastinal Disorders | dyspnoea, rhinitis | Uncommon |
| | coughing | Very Rare |
| Gastrointestinal Disorders | abdominal pain, nausea | Common |
| | vomiting, dyspepsia, altered | Uncommon |

| | | |
|---|---|---|
| | bowel habits, dry mouth | |
| | pancreatitis, gastritis, gingival hyperplasia | Very Rare |
| Hepato-biliary Disorders | hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) | Very Rare |
| Skin and Subcutaneous Tissue Disorders | alopecia, purpura, skin discolouration, increased sweating, pruritus, rash | Uncommon |
| | angioedema, erythema multiforme, urticaria | Very Rare |
| 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, gynaecomastia | Uncommon |
| General Disorders and Administration Site Conditions | oedema, fatigue | Common |
| | chest pain, asthenia, pain, malaise | Uncommon |
| Investigations | weight increase, weight decrease | Uncommon |

## 4.9 OVERDOSE

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Calcium Channel Blocker

ATC Code: C08CA01

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

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

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 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.

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 enrolment) 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 adminstration 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 increase 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 studies.

## 5.3 PRECLINICAL SAFETY DATA

None.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Calcium hydrogen phosphate dihydrate

Microcrystalline cellulose

Silica colloidal anhydrous

Sodium starch glycollate

Magnesium stearate

**6.2 INCOMPATIBILITIES**
None Known

**6.3 SHELF LIFE**
3 years

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**
**Blisters:** Do not store above 25ºC.

Store in the original package.

**Bulk:** Do not store above 25ºC.

Keep the container tightly closed.

**6.5 NATURE AND CONTENTS OF CONTAINER**
Aluminium/PVDC coated PVC blister strips containing 14 tablets. Blister strips packaged into outer container to give total of 28, 56, 84 tablets.

The tablets are also packed in HDPE containers containing 100, 250, 500 tablets.

Not all pack sizes may be marketed.

**6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**
No special requirements.

**7 MARKETING AUTHORISATION HOLDER**
Bristol Laboratories Limited

Unit 3, Canalside, Northbridge Road,

Berkhamsted, Herts,

HP4 1EG

United Kingdom

**8 MARKETING AUTHORISATION NUMBER(S)**
PL 17907/0086

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
09/03/2007

**10 DATE OF REVISION OF THE TEXT**
09/03/2007

# PATIENT INFORMATION LEAFLET

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**AMLODIPINE 5MG TABLETS**
**AMLODIPINE 10MG TABLETS**

**Active Substance: Amlodipine Besilate**

**Read all of this leaflet carefully before you start taking this medicine**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- The 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 These Tablets Are And What They Are Used For

- Amlodipine belongs to a group of medicines called calcium-channel blockers. 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.
- If you have high blood pressure Amlodipine works by relaxing blood vessels, so that blood passes through them more easily.
- If you have angina, you may get chest pains when your heart cannot get enough blood. Amlodipine helps prevent this by increasing blood supply to the heart. Amlodipine Tablets do not work immediately to stop chest pain from angina.
- Amlodipine tablets are well tolerated in patients with heart failure and a history of high blood pressure or angina.

## 2. Before You Take Amlodipine Tablets

**Do not take Amlodipine Tablets if you:**

- are allergic to Amlodipine or any other calcium channel blockers or any other ingredients of Amlodipine Tablets (these are listed in section 6, Further Information). This may have been itching, reddening of the skin or difficulty in breathing.
- have any of the following conditions:
  - cardiogenic shock
  - aortic stenosis (narrowing of the aortic heart valve)
  - unstable angina.
- are pregnant or breast feeding.
- are a woman of child-bearing potential effective contraception is advised.

**Before you take Amlodipine Tablets take special care if you:**

- have suffered a heart attack within the last 28 days or if your doctor has advised that you are in hypertensive crisis.
- have liver disease.
- are under 18 year of age.

If any of the above apply to you, talk to your doctor.

**Taking other medicines with Amlodipine Tablets:**

Please inform your doctor or pharmacist if you are taking or have taken any of the following medicines as they may interact with your Amlodipine Tablets:

- Other medicines for the treatment of high blood pressure
- Other medicines used to treat chest pain such as angina
- Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

**Pregnancy and Breast-feeding**

- The use of Amlodipine during pregnancy and breastfeeding is not recommended.
- Ask your doctor or pharmacist before taking any medicine.

**Driving and using machines**

- Amlodipine Tablets may cause dizziness, tiredness or make you feel that you are about to be sick. If this happens to you do not drive or use machinery.

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## 3. How To Take The Tablets

- Always take Amlodipine tablets exactly as prescribed by your doctor. You should check with your doctor or pharmacist if you are unsure.
- Amlodipine tablets should be swallowed whole with a glass of water. Take a tablet(s) at the same time each day.

**Adults and Elderly**:

- The usual initial dose is 5mg Amlodipine Tablets once daily which may be increased to a maximum dose of 10mg depending on the individual patient's response.

**Amlodipine Tablets are not recommended for children.**

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

- If you accidentally take more tablets than you should, immediately seek medical attention. Take your medicine in its original packaging with you in order to enable the doctor to identify your medication easily.

**If you forget to take Amlodipine Tablets**:

- Do not worry and take the next dose at the right time. Do not take a double dose to make up for the forgotten individual dose.
- Do not stop taking the tablets without speaking to your doctor first. 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 Tablets can cause side effects, although not everybody gets them.

- Tell your doctor if you notice any of the following after taking Amlodipine Tablets: Headache, oedema, skin rash, feeling tired, feeling sick, indigestion, dizziness, swelling or soreness of the gums, muscle cramps, dry mouth, mood changes, abdominal pain, back pain. These are all mild side effects of Amlodipine tablets.

Rare undesirable effects:

- itchy skin, red blood cell damage (unusual bruising and bleeding), red patches on skin, increased sensitivity particularly of the skin, pins and needles, trembling, bruising more easily or purplish marks on the 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, inability to obtain an erection, visual disturbances, weight increase or decrease, coughing, taste abnormalities, ringing in the ears, sneezing/running nose and hives.
- Very rarely abnormal liver function, inflammation of the liver, yellowing of the skin, severe skin reactions and enlargening of the male breasts have been reported.
- 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 Your Medicine

Keep out of the reach and sight of children. All medicines that are no longer being taken or used should be returned to your pharmacist for disposal.

**Do not use Amlodipine Tablets after expiry date stated on the pack.**

Keep your medicine in a dry place and protect from sunlight and moisture.

Blister Packs: Do not store above 25ºC. Store in the original package.

Containers: Do not store above 25ºC. Keep the container tightly closed.

## 6. Further Information

**What Amlodipine Tablets contain:**

Active Ingredient is Amlodipine (as besilate). Each tablet contains 5mg or 10mg of Amlodipine.

The other ingredients are calcium hydrogen phosphate dihydrate, microcrystalline cellulose, sodium starch glycollate, silica colloidal anhydrous and magnesium stearate.

**What Amlodipine Tablets look like and contents of pack:**

Amlodipine 5 mg Tablets are white to off white, round, with '5' embossing on one side.

Amlodipine 10 mg Tablets are white to off white, round, with '10' embossing on one side.

Amlodipine Tablets come in packs containing 28, 56, 84, 100, 250 & 500 tablets (Not all pack sizes may be marketed).

**Marketing Authorisation Holder and Manufacturer:**

Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, HP4 1EG, UK

Leaflet last modified: September 2006

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# LABELLING


Amlodipine
Tablets
amlodipine besilate
5 mg
28 Tablets
Amlodipine 5 mg
Each tablet contains Amlodipine 5 mg
(as Amlodipine Besilate)
as the active ingredient.
For oral administration only.
Take as directed by the physician.
For further information please read
the enclosed patient information leaflet.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Do not store above 25°C.
Store in the original package.
PLACE DISPENSARY LABEL HERE
BN :
EXP.:
BRISTOL
PL 17907/0085
Code: BL 501
POM
PL Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK.
2728 C
186 C
BLACK
123 C
424 C
Artwork Same Size
Size: 116 x 16 x 50 mm
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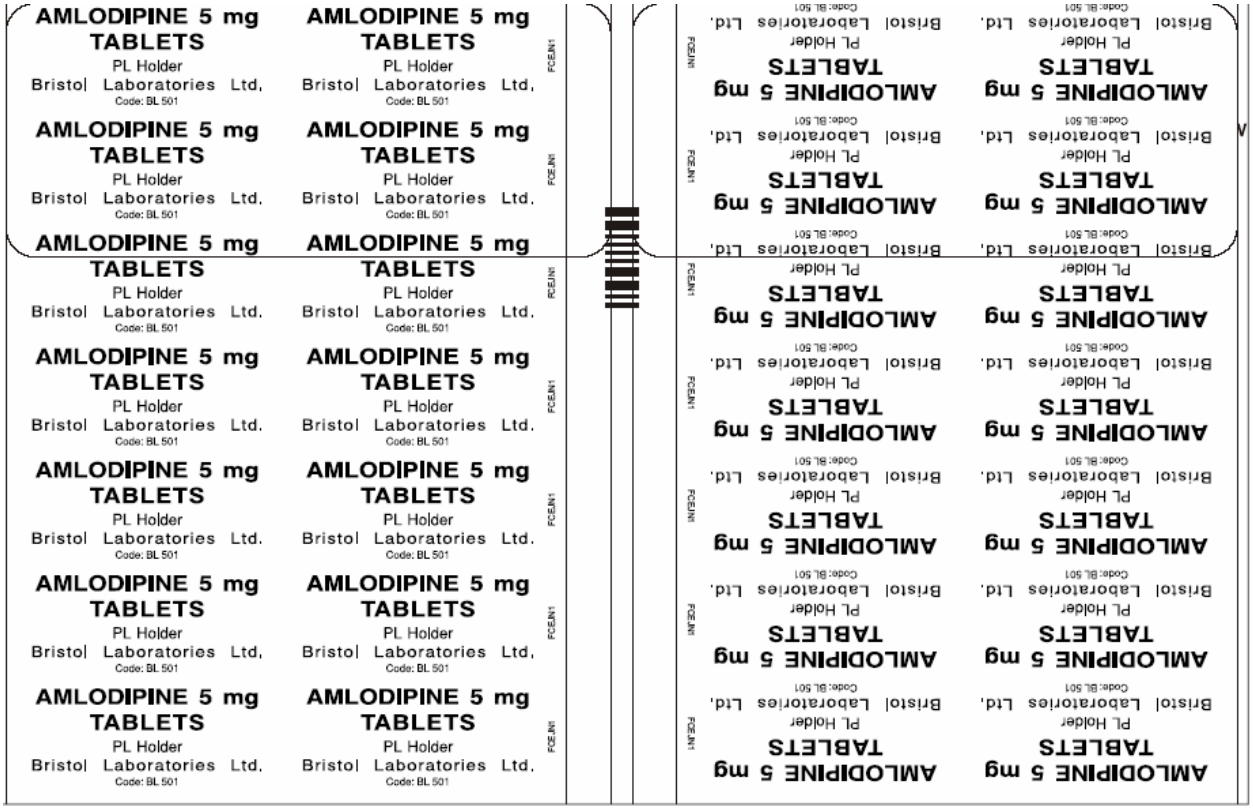
AMLODIPINE 5 mg
TABLETS
PL Holder
Bristol Laboratories Ltd,
Code: BL 501
FCE.IN1


Amlodipine
Tablets
amlodipine besilate
10 mg
28 Tablets
Amlodipine
Tablets
amlodipine besilate
10 mg
28 Tablets
BRISTOL
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For further information please read
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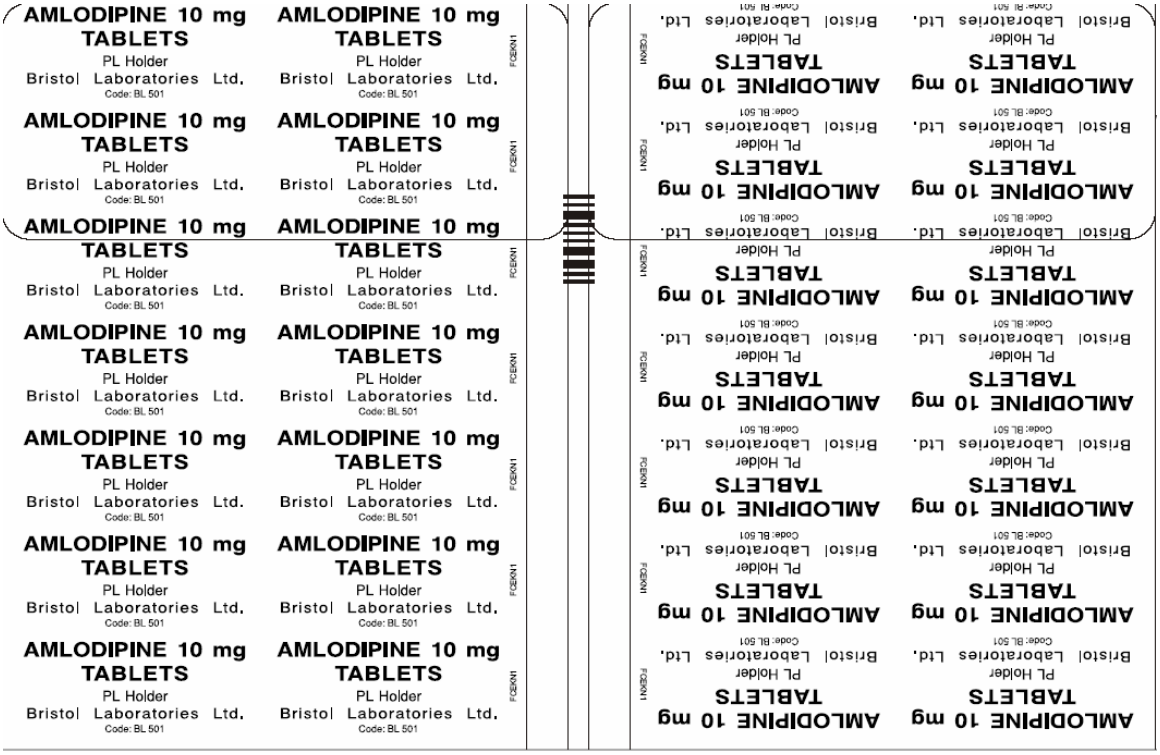
Do not store above 25°C.
Store in the original package.
PLACE DISPENSARY
LABEL HERE
BN :
EXP:


AMLODIPINE 10 mg
TABLETS
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Code: BL 501
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