# AMLODIPINE 5MG TABLETS
# PL 15764/0015

# AMLODIPINE 10MG TABLETS
# PL 15764/0016

## UKPAR

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## LAY SUMMARY

On 21st May 2007, the MHRA granted Somex Pharma Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg Tablets (PL 15764/0015) and Amlodipine 10mg Tablets (PL 15764/0016). These are prescription only medicines (POM) for the treatment of high blood pressure (hypertension) or a certain type of chest pain called angina, a rare form of which is Prinzmetal's or variant angina.

Amlodipine Tablets contain the active ingredient amlodipine besilate, which is a type of medicine known as a calcium-channel blocker. It relieves heart problems by widening blood vessels to allow more blood through. This helps reduce blood pressure and relieve the strain on heart muscles.

The test products were considered to be generic medicinal products of the original products Istin 5mg and 10mg Tablets (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
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# PL 15764/0016

## 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 15764/0015) and Amlodipine 10mg Tablets (PL 15764/0016) on 21st May 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 essential similarity to the original products Istin Tablets 5 and 10mg (Pfizer Limited, UK).

The products contain the active ingredient amlodipine besilate, a dihydropyridine calcium antagonist. 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. Amlodipine 5mg and 10mg Tablets are indicated for the treatment of essential hypertension and chronic stable and vasospastic 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 Norvasc 10mg Tablets (Pfizer Ltd, The Netherlands). Consequently, all sections of this Scientific Discussion refer to both products.

# PHARMACEUTICAL ASSESSMENT

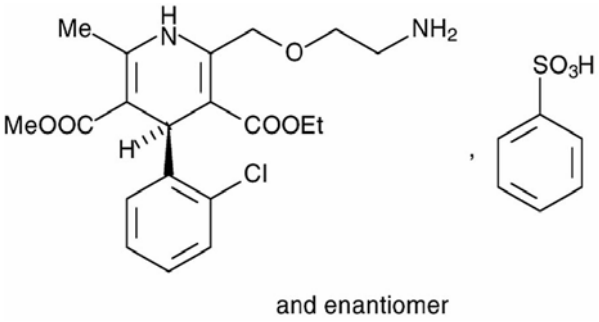
## DRUG SUBSTANCE

### Amlodipine besilate

INN: Amlodipine besilate

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

Structure:




CAS registry number: 111470-99-6

Physical form: A white or almost white powder. Slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol. No polymorphism has been encountered.

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

Molecular weight: 567.1

Amlodipine besilate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of amlodipine besilate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of amlodipine besilate for inclusion in this medicinal product.

Appropriate stability data have been generated supporting a retest period of 36 months when stored in the proposed packaging. Suitable post approval commitments have been provided to perform follow-up stability studies.

## DRUG PRODUCT

### Other ingredients

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, croscarmellose sodium, sodium starch glycollate, sodium acid citrate, crospovidone and magnesium stearate. All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of sodium acid citrate (which complies with a British Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

### Pharmaceutical development

The applicant has provided a suitable product development rationale and data.

Satisfactory impurity and dissolution data have been provided, showing that the proposed products are comparable to the comparator products (Istin 5mg and 10mg Tablets).

**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. 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**
The finished product is packaged in aluminium/polyvinylchloride/polyvinylidene chloride blisters in pack sizes of 28 tablets. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. The storage condition ‘Store in original package’ has been included.

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

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance. In addition, similar dissolution and impurity profiles have been provided for the proposed and reference products and bioequivalence has been demonstrated to a suitable reference product.

# PRECLINICAL ASSESSMENT

These applications for generic products claims essential similarity to Istin 5 and 10mg Tablets (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

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

No new data submitted. The pharmacodynamics of amlodipine are well-described. It 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 mechanism by which amlodipine relieves angina involves reduction of total peripheral resistance and dilatation of the main coronary arteries and coronary arterioles.

### Pharmacokinetics

After oral administration of therapeutic doses, amlodipine is well-absorbed, with peak blood levels between 6-12 hours post dose. Pharmacokinetics over the therapeutic range are dose proportional. 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.

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.

### Bioequivalence

A comparative, randomised, two-treatment, two-period, single-dose crossover study was performed on healthy fasted volunteers, comparing the applicant's 10mg test product versus Norvasc 10mg Tablets (Pfizer Limited, The Netherlands).

Blood samples were taken from subjects pre-dose and up to 168 hours post dose. There was a 21-day washout period between doses.

Bioequivalence results for log-transformed test/reference ratios (with 90% confidence intervals) are presented below:

| | |
|---|---|
| **$AUC_t$** | 0.992 (0.883-1.041) |
| **$AUC_{inf}$** | 0.996 (0.900-1.067) |
| **$C_{max}$** | 0.991 (0.914-1.053) |

Based on the submitted bioequivalence data, it can be considered that the applicant's Amlodipine 10mg Tablets is a generic medicinal product to Istin 10mg Tablets and Norvasc 10mg Tablets.

As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the

results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to the 5mg strength tablets.

**EFFICACY**
No new data are submitted and none are required for this type of application.

**SAFETY**
No new data are submitted and none are required for this type of application.

**EXPERT REPORTS**
A clinical expert report has been written by a suitably qualified person and is satisfactory.

**PATIENT INFORMATION LEAFLET (PIL)**
This is consistent with that for the reference products and is satisfactory.

**LABELLING**
These are satisfactory.

**APPLICATION FORMS (MAA)**
These are satisfactory.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**
These are consistent with those for the reference products and are satisfactory.

**DISCUSSION**
The applicant has satisfactorily demonstrated bioequivalence between the 10mg strengths of test and reference products. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to the 5mg strength tablets.

**MEDICAL CONCLUSION**
The bioequivalence study submitted has shown that these products can be considered as generic medicinal products to the originator products Istin 5 and 10mg Tablets (Pfizer Limited, UK).

Marketing authorisations are recommended for these applications.

# 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). As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to the 5mg strength tablets. Thus, no separate bioequivalence study is necessary for the 5mg strength.

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 15764/0016

## STEPS TAKEN FOR ASSESMENT

| | |
|---|---|
| 1 | The MHRA received the marketing authorisation applications on 30th June 2004 |
| 2 | Following standard checks and communication with the applicant the MHRA considered the applications valid on 20th July 2004 |
| 3 | Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 24th January 2005 and 27th November 2006, and further information relating to the quality dossiers on 2nd March 2005 and 28th March 2006. |
| 4 | The applicant responded to the MHRA's requests, providing further information on 16th May 2007 for the clinical sections, and again on 27th March 2006 for the quality sections. |
| 5 | The applications were determined on 21st May 2007 |

# AMLODIPINE 5MG TABLETS
# PL 15764/0015

# AMLODIPINE 10MG TABLETS
# PL 15764/0016

## STEPS TAKEN AFTER AUTHORISATION - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 5 mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: amlodipine.

One tablet contains amlodipine besilate equivalent to 5 mg amlodipine.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet.

The tablets are white, circular, biconvex and plain on both sides.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Essential hypertension
- Chronic stable and vasospastic anginal pectoris

### 4.2 Posology and method of administration

***In adults***

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

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

***Use in children and adolescents (less than 18 years of age)***

Not recommended.

***Use in the elderly***

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

***Patients with hepatic impairment***

See section 4.4 "Special warnings and special precautions for use".

***Patients with renal impairment***

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

### 4.3 Contraindications

Hypersensitivity to dihydropyridines, amlodipine or to any of the excipients.

Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

Pregnancy and lactation.

**4.4 Special warnings and precautions for use**

***Use in patients with heart failure***

In a long term, placebo controlled study, in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1 (Pharmacodynamic Properties).

***Use in patients with impaired hepatic function***

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

**4.5 Interaction with other medicinal products and other forms of interaction**

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

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

Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors and CYP3A4 inducers.

***Special Studies: Effect of other agents on amlodipine***

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

***Grapefruit juice:*** Co-administration of 240ml of grapefruit juice with single oral dose of amlodipine 10mg in in healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

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

***Special Studies: Effect of amlodipine on other agents***

***Atorvastatin:*** Co-administration of multiple 10 mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atrovastatin.

***Digoxin:*** Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

***Warfarin:*** In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

***Cyclosporin:*** Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporine.

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

**4.6 Pregnancy and lactation**

Pregnancy

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy. Accordingly, amlodipine should not be administered during pregnancy or to women of childbearing potential unless effective contraception is used (see section 4.3).

Lactation

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in lactation. Accordingly, amlodipine should not be administered during lactation (see section 4.3).

**4.7 Effects on ability to drive and use machines**

Clinical experience with amlodipine indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

**4.8 Undesirable effects**

The frequencies mentioned are subdivided on categories according to following percentages:
*Very common: more then 10%*
*Common: 10% or less, but more then 1%*
*Uncommon: 1%, or less, but more then 0,1%,*
*Rare: 0,1 % or less, but more then 0,01%*
*Very rare: 0,01% and less (this includes isolated reports).*

The most commonly reported side effects of amlodipine are headache, oedema, rash, fatigue, nausea, flushing and dizziness.

Other reported side effects are:

*Blood and the lymphatic system disorders*
Very rare: thrombocytopenia, leucocytopenia

*Immune system disorders*
Very rare: allergic reaction

*Metabolic and nutrition disorders*
Very rare: hyperglycaemia

*Psychiatric disorders*
Uncommon: mood changes, insomnia

*Nervous system disorders*
Common: somnolence
Uncommon: tremor, taste perversion, syncope, hypoaesthesia, paraesthesia
Very rare: peripheral neuropathy

*Eye disorders*
Uncommon: visual disturbances

*Ear and Labyrinth disorders*
Uncommon: tinnitus

*Cardiac disorders*
Common: Palpitations
Rare: syncope

Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation

*Vascular disorders*
Uncommon: hypotension
Very rare: vasculitis

*Respiratory, thoracic and mediastinal disorders*
Uncommon: dyspnoea, rhinitis
Very rare: coughing

*Gastrointestinal disorders*
Common: Abdominal pain
Uncommon: Vomiting, dyspepsia, altered bowel habits, dry mouth
Very rare: pancreatitis, gastritis, gingival hyperplasia

*Hepato-biliary disorders*
Very rare: abnormal liver function tests, hepatitis, jaundice,

*Skin and subcutaneous tissue disorders*
Uncommon: alopecia, pruritus, perpura, skin discolouration, increased sweating
Very rare: erythema multiforme, angioedema and urticaria

*Musculoskeletal, connective tissue and bone disorders*
Uncommon: myalgia, arthralgia, muscle cramps and back pain

*Renal and urinary disorders*
Uncommon: increased urinary frequency, micturition disorder, nocturia

*Reproductive system and breast disorders*
Uncommon: impotence, gynaecomastia

*General disorders and administration site conditions*
Uncommon: chest pain, asthenia, pain, malaise, increase or decrease in weight

**4.9 Overdose**

In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. Available data suggest that gross overdosage (> 100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. In healthy volunteers, the use of charcoal up to 2h after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

## 5 PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**

*Pharmacotherapeutic group:* calcium channel blockers – Dihydropyridine derivatives.
*ATC code:* C08CA01.

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

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has

not been fully determined but amlodipine reduces total ischaemic burden by the following two actions.

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

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

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo-controlled study (PRAISE-2) in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

## 5.2 Pharmacokinetic properties

***Absorption, distribution, plasma protein binding***

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

***Biotransformation/elimination***

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

***Use in the elderly***

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

## 5.3 Preclinical safety data

None.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose (E460)
Sodium starch glycollate
Sodium acid citrate (E331)
Magnesium stearate (E572)
Croscarmellose sodium
Crospovidone

### 6.2 Incompatibilities

None stated.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

No special precautions for storage.
Store in the original packaging.

### 6.5 Nature and contents of container

Blisters made of aluminium foil with VMCH coating (a carboxyl modified vinyl copolymer) on one side and amber coloured PVC foil. Packs of 28 tablets.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Somex Pharma
600 High Road - Seven Kings
Ilford, Essex, IG3 8BS
UK

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0015

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

21/05/2007

## 10 DATE OF REVISION OF THE TEXT

21/05/2007

## 1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: amlodipine.

One tablet contains amlodipine besilate equivalent to 10 mg amlodipine.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet.

The tablets are white, circular, biconvex and plain on both sides.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Essential hypertension
- Chronic stable and vasospastic anginal pectoris

### 4.2 Posology and method of administration

***In adults***

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

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

***Use in children and adolescents (less than 18 years of age)***

Not recommended.

***Use in the elderly***

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

***Patients with hepatic impairment***

See section 4.4 "Special warnings and special precautions for use".

***Patients with renal impairment***

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

### 4.3 Contraindications

Hypersensitivity to dihydropyridines, amlodipine or to any of the excipients.

Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

Pregnancy and lactation.

**4.4 Special warnings and precautions for use**

***Use in patients with heart failure***

In a long term, placebo controlled study, in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1 (Pharmacodynamic Properties).

***Use in patients with impaired hepatic function***

As with all calcium antagonists, amlodipine's half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

**4.5 Interaction with other medicinal products and other forms of interaction**

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

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

Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors and CYP3A4 inducers.

***Special Studies: Effect of other agents on amlodipine***

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

***Grapefruit juice:*** Co-administration of 240ml of grapefruit juice with single oral dose of amlodipine 10mg in in healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

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

***Special Studies: Effect of amlodipine on other agents***

***Atorvastatin:*** Co-administration of multiple 10 mg doses of amlodipine with 80mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atrovastatin.

***Digoxin:*** Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

***Warfarin:*** In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

***Cyclosporin:*** Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporine.

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

**4.6 Pregnancy and lactation**

Pregnancy

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy. Accordingly, amlodipine should not be administered during pregnancy or to women of childbearing potential unless effective contraception is used (see section 4.3).

Lactation

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in lactation. Accordingly, amlodipine should not be administered during lactation (see section 4.3).

**4.7 Effects on ability to drive and use machines**

Clinical experience with amlodipine indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

**4.8 Undesirable effects**

The frequencies mentioned are subdivided on categories according to following percentages:
*Very common: more then 10%*
*Common: 10% or less, but more then 1%*
*Uncommon: 1%, or less, but more then 0,1%,*
*Rare: 0,1 % or less, but more then 0,01%*
*Very rare: 0,01% and less (this includes isolated reports).*

The most commonly reported side effects of amlodipine are headache, oedema, rash, fatigue, nausea, flushing and dizziness.

Other reported side effects are:

*Blood and the lymphatic system disorders*
Very rare: thrombocytopenia, leucocytopenia

*Immune system disorders*
Very rare: allergic reaction

*Metabolic and nutrition disorders*
Very rare: hyperglycaemia

*Psychiatric disorders*
Uncommon: mood changes, insomnia

*Nervous system disorders*
Common: somnolence
Uncommon: tremor, taste perversion, syncope, hypoaesthesia, paraesthesia
Very rare: peripheral neuropathy

*Eye disorders*
Uncommon: visual disturbances

*Ear and Labyrinth disorders*
Uncommon: tinnitus

*Cardiac disorders*
Common: Palpitations
Rare: syncope

Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation

*Vascular disorders*
Uncommon: hypotension
Very rare: vasculitis

*Respiratory, thoracic and mediastinal disorders*
Uncommon: dyspnoea, rhinitis
Very rare: coughing

*Gastrointestinal disorders*
Common: Abdominal pain
Uncommon: Vomiting, dyspepsia, altered bowel habits, dry mouth
Very rare: pancreatitis, gastritis, gingival hyperplasia

*Hepato-biliary disorders*
Very rare: abnormal liver function tests, hepatitis, jaundice,

*Skin and subcutaneous tissue disorders*
Uncommon: alopecia, pruritus, perpura, skin discolouration, increased sweating
Very rare: erythema multiforme, angioedema and urticaria

*Musculoskeletal, connective tissue and bone disorders*
Uncommon: myalgia, arthralgia, muscle cramps and back pain

*Renal and urinary disorders*
Uncommon: increased urinary frequency, micturition disorder, nocturia

*Reproductive system and breast disorders*
Uncommon: impotence, gynaecomastia

*General disorders and administration site conditions*
Uncommon: chest pain, asthenia, pain, malaise, increase or decrease in weight

**4.9 Overdose**

In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. Available data suggest that gross overdosage (> 100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. In healthy volunteers, the use of charcoal up to 2h after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

## 5 PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**

*Pharmacotherapeutic group:* calcium channel blockers – Dihydropyridine derivatives.
*ATC code:* C08CA01.

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

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has

not been fully determined but amlodipine reduces total ischaemic burden by the following two actions.

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

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

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo-controlled study (PRAISE-2) in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

## 5.2 Pharmacokinetic properties

***Absorption, distribution, plasma protein binding***

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

***Biotransformation/elimination***

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

***Use in the elderly***

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

## 5.3 Preclinical safety data

None.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose (E460)
Sodium starch glycollate
Sodium acid citrate (E331)
Magnesium stearate (E572)
Croscarmellose sodium
Crospovidone

### 6.2 Incompatibilities

None stated.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

No special precautions for storage.
Store in the original packaging.

### 6.5 Nature and contents of container

Blisters made of aluminium foil with VMCH coating (a carboxyl modified vinyl copolymer) on one side and amber coloured PVC foil. Packs of 28 tablets.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Somex Pharma
600 High Road - Seven Kings
Ilford, Essex, IG3 8BS
UK

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0016

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

21/05/2007

## 10 DATE OF REVISION OF THE TEXT

21/05/2007

# PATIENT INFORMATION LEAFLET

**Read this entire leaflet carefully before you start taking this medicine.**

- *Keep this leaflet. You may need to read it again.*
- *If you have further questions, please ask your doctor or your pharmacist.*
- *This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.*

*In this leaflet*



**Amlodipine 5 mg tablets**
**Amlodipine 10 mg tablets**

- *The active substance* is amlodipine in its besilate salt form.
- *The other ingredients* are microcrystalline cellulose (E460), sodium starch glycollate, sodium acid citrate (E331), magnesium stearate (E572), croscarmellose sodium, crospovidone

*Marketing authorisation holder*
Somex Pharma, High Road, Ilford, Essex, IG3 8BS UK
*Manufacturer*
Somex Pharma, High Road , Ilford Essex , IG3 8RA, UK
*Product licence number*
PL 15764/0015-16

## 1. WHAT AMLODIPINE TABLETS ARE AND WHAT THEY ARE USED FOR?

- Your tablets are white, circular and plain on both sides. Each tablet contains 5 or 10 mg amlodipine as amlodipine besilate
- Amlodipine comes in packs of 28 tablets, in PVC/PVdC/Aluminium blisters.
- 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.
- Amlodipine is a calcium antagonist and is a derivative of dihydropyridine. It works by blocking channels in the cells who transport calcium into the cells.

In patients with high blood pressure amlodipine tablets work by relaxing blood vessels, so that blood passes through them more easily. In patients with angina amlodipine works by improving blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented. Amlodipine does not provide immediate relief of chest pain from angina.

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

## 2. BEFORE YOU TAKE AMLODIPINE TABLETS

**Do not take Amlodipine tablets**

- If you have an allergy to amlodipine, other calcium antagonists or any other ingredient of this medicine. This may have been itching, reddening of the skin or difficulty in breathing.
- If you have (had) a cardiogenic shock, aortic stenosis (narrowing of the aortic heart valve) or unstable angina.
- During pregnancy or breast feeding. If you are a woman of child-bearing potential effective contraception is advised.

**Take special care with Amlodipine tablets**

- If you just had a heart attack or are in hypertensive crisis.
- If you have liver disease.
- If you are under 18 years of age.

*Please consult your doctor, even if these statements were applicable to you at any time in the past*

**Pregnancy**

As there is no experience with amlodipine during pregnancy, it should not be used during pregnancy.

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

**Breast-feeding**

As there is no experience with amlodipine during lactation, it should not be used during lactation.

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

**Driving and using machines**

Clinical experience indicates that the use of amlodipine is unlikely to impair your ability to drive or use machines. However, certain side effects (e.g. dizziness, headache, fatigue or nausea) may affect your ability to react. Exercise caution if you are suffering from one of these side effects.

**Important information about some of the ingredients of Amlodipine.**
No special precautions.

**Taking other medicines**
No significant interactions with other medicines are known.

## 3. HOW TO TAKE AMLODIPINE TABLETS?

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

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

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

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

*If you have taken more amlodipine than you should, talk to a doctor or pharmacist immediately.*

**If you forget to take Amlodipine tablets?**

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

*Do not take a double dose to make up for individual forgotten doses.*

**Effects when treatment with Amlodipine is stopped.**

Do not stop treatment without consulting your doctor.

If you stop the treatment your symptoms might reappear.

## 4. POSSIBLE SIDE EFFECTS

*Like all medicines, amlodipine tablets can have side effects.*

The frequencies mentioned are subdivided on categories according to following percentages:

*Very common: more than 10%.*

*Common: 10% or less, but more than 1%.*

*Uncommon: 1%, or less, but more than 0.1%.*

*Rare: 0.1% or less, but more than 0.01%.*

*Very rare: 0.01% and less (this includes isolated reports).*

The most commonly reported side effects are headache, oedema (for example ankle swelling), skin rash, feeling tired, feeling sick, flushing, dizziness.

Other reported side effects are:

*Blood and the lymphatic system disorders*

*Rare*:, red blood cell damage (unusual bruising and bleeding), shortage of white blood cells.

*Immune system disorders*

*Very* rare: 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.

*Metabolic and nutrition disorders*

*Very rare:* excess sugar in blood.

*Psychiatric disorders*

*Uncommon*: mood changes, sleeplessness.

*Nervous system disorders*

*Common*: sleepiness.

*Uncommon*: trembling, pins and needles, taste perversion, diminished tactile sense, fainting

*Very rare*: loss of pain sensation.

*Eye disorders*

*Uncommon*: visual disturbances.

*Ear and labyrinth disorders*

*Uncommon*: ringing in the ears.

*Cardiac disorders*

*Common*: palpitations (a quicker or irregular heart beat).

*Rare*: fainting.

*Very rare*: heart attack (myocardial infarction), irregular heart beat (arrhythmia).

*Vascular disorders*

*Uncommon*: low blood pressure.

*Very rare*: inflammation of blood vessels.

*Respiratory, thoracic and mediastinal disorders*

*Uncommon*: shortness of breath, running nose.

*Very rare*: coughing.

*Gastrointestinal disorders*

*Common*: abdominal pain.

*Uncommon*: vomiting, altered bowel habit, dry mouth and indigestion.

*Very rare*: inflammation of the stomach or pancreas, swelling and soreness of the gums.

*Hepato-biliary disorders*

*Very rare*: abnormal liver function, inflammation of the liver, yellowing of the skin.

*Skin and subcutaneous tissue disorders*

*Uncommon*: itchy skin, hair loss, increased sweating, bruising, skin discolouration.

*Very rare*: red patches on skin, hives.

*Musculoskeletal, connective tissue and bone disorders*

*Uncommon*: muscle or joint pain, muscle cramps and back pain.

*Renal and urinary disorders*

*Uncommon*: increased need to urinate, incontinence, excessive urinating at night.

*Reproductive system and breast disorders*

*Uncommon*: inability to obtain an erection.

*Very rare*: enlargening of the male breasts.

*General disorders and administration site conditions*

*Uncommon*: increased or decreased weight, chest pain, a general feeling of discomfort.

*If you notice any side effect not mentioned in this leaflet, please inform your doctor or pharmacist.*

## 5. STORING AMLODIPINE TABLETS

*Keep all medicines out of the reach and sight of children.*

No special precautions for storage.

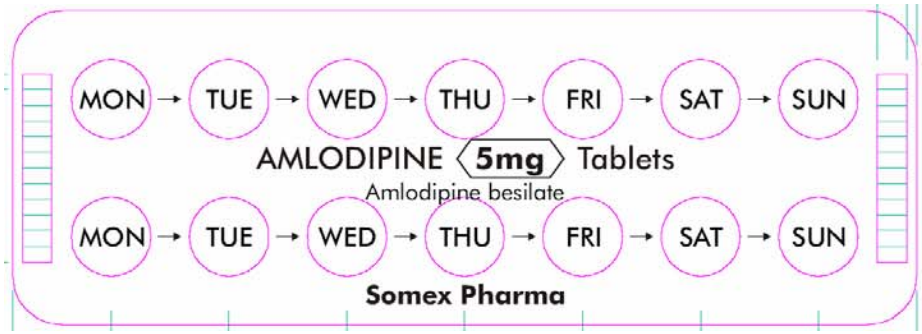
Store in the original packaging.

*Do not use amlodipine after the expiry date, which is marked on both the outer carton and on each blister strip of tablets.*

*This leaflet was approved ……*

Date of Preparation of Leaflet: January 2007.

# LABELS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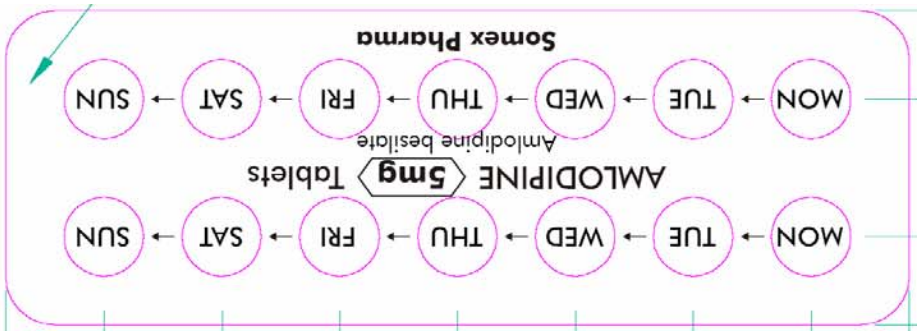
AMLODIPINE 5mg Tablets
Amlodipine besilate
MON TUE WED THU FRI SAT SUN
Somex Pharma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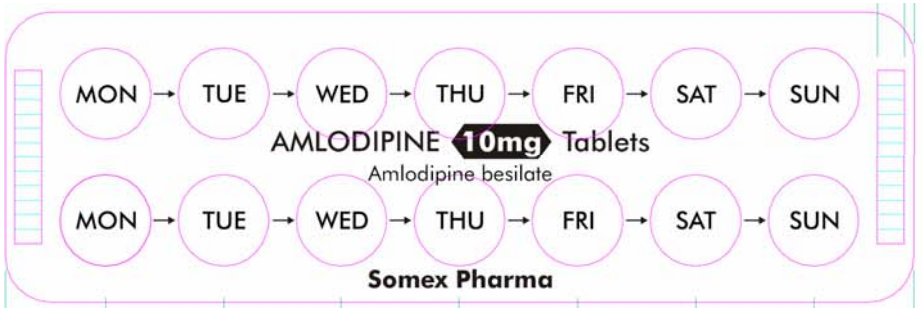
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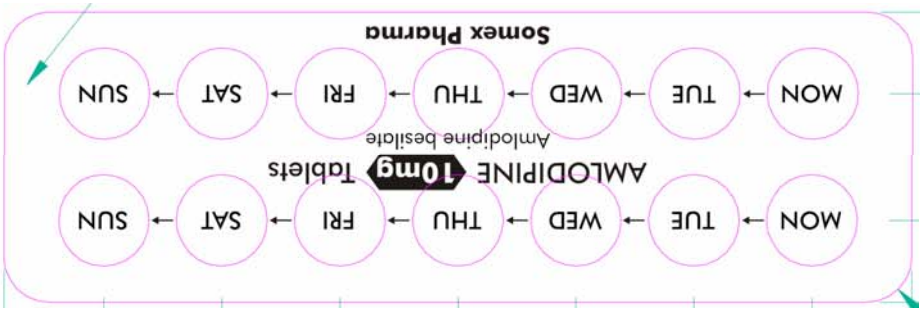
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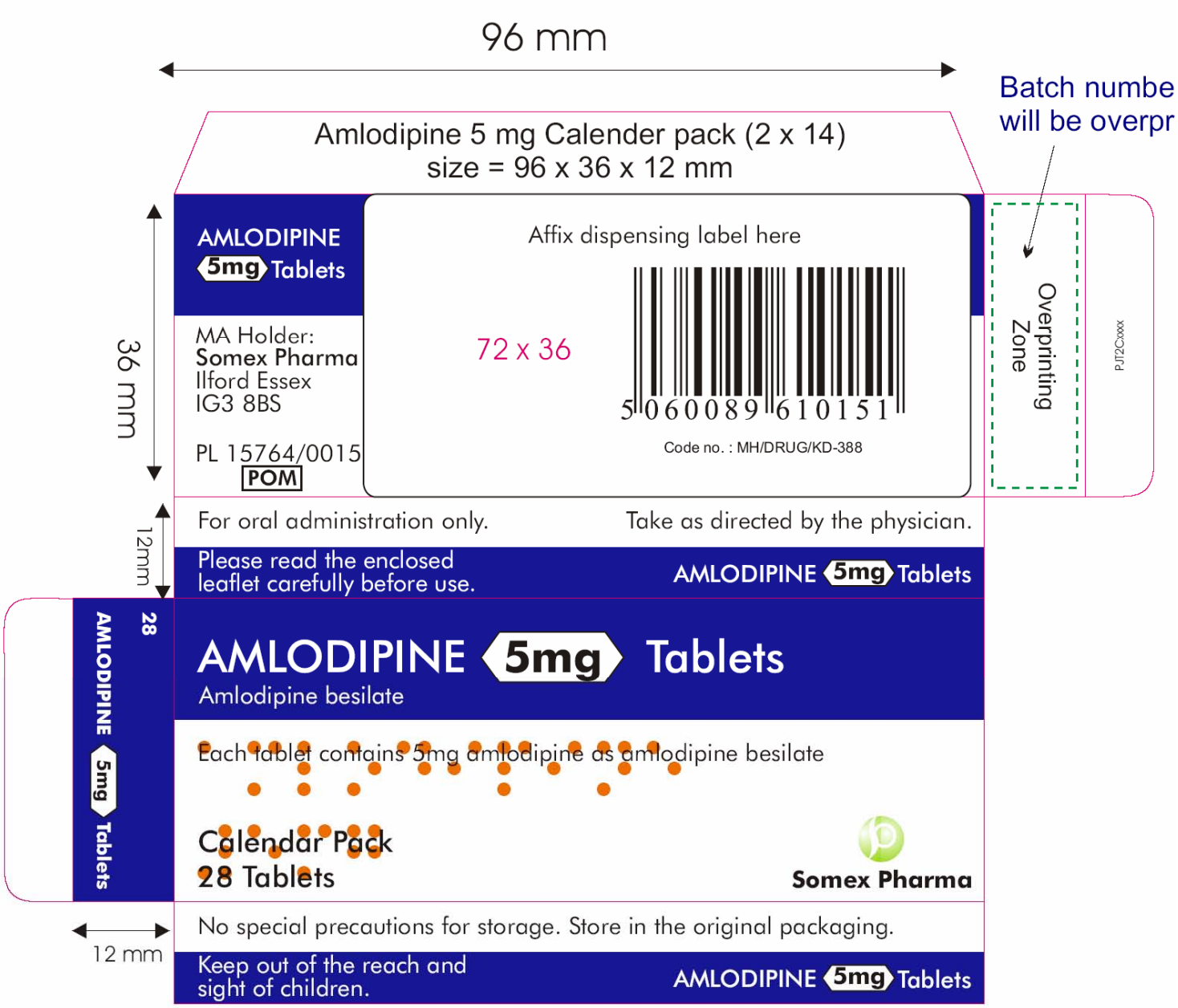
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PL 15764/0015
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For oral administration only.
Take as directed by the physician.
Please read the enclosed
leaflet carefully before use.
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Calendar Pack
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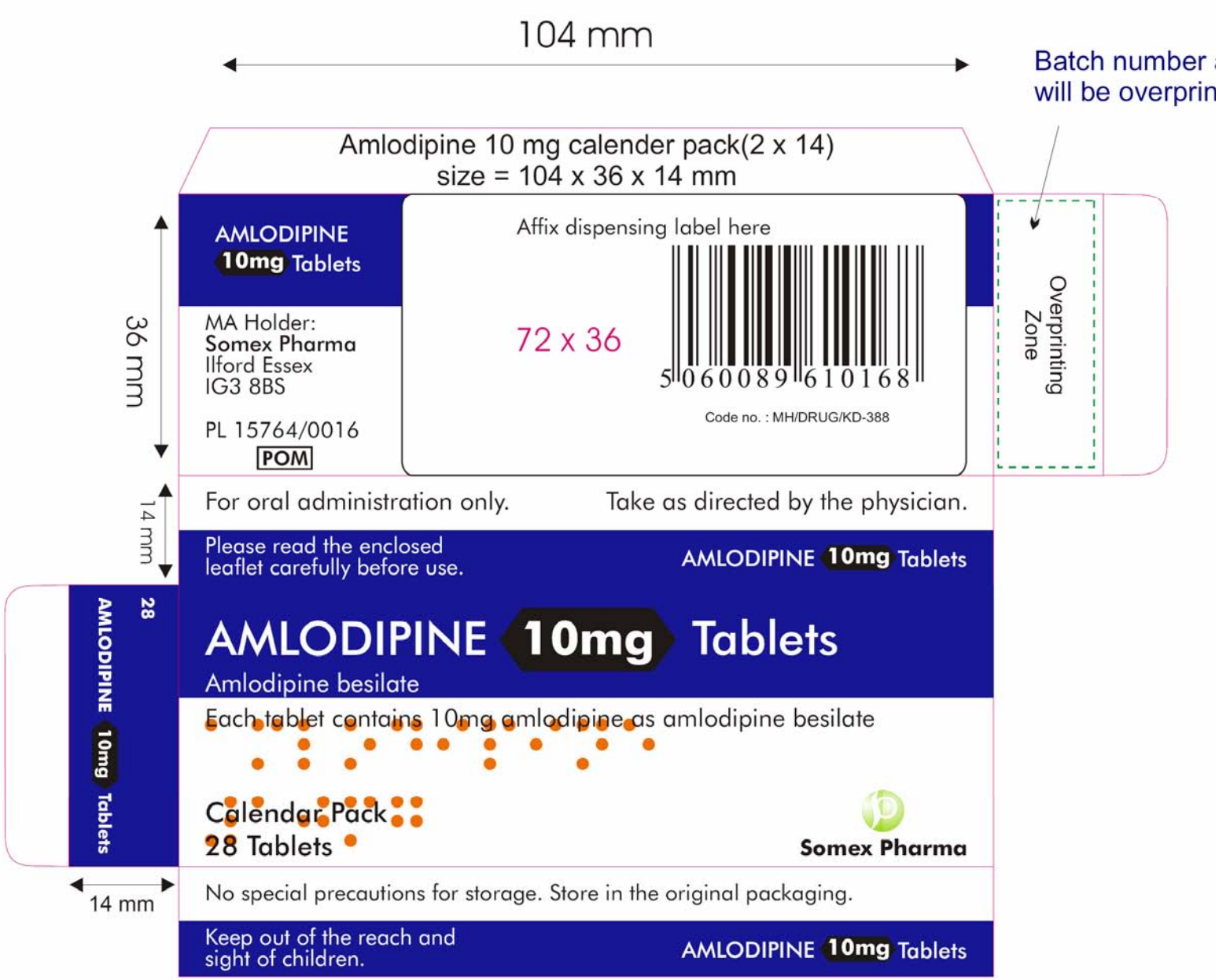
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