AMLODIPINE 5MG TABLETS

PL 20692/0014
PL 20692/0016
PL 20692/0018
PL 20692/0020
PL 20692/0022
PL 20692/0024

AMLODIPINE 10MG TABLETS

PL 20692/0015
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PL 20692/0021
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PL 20692/0025

UKPAR

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AMLODIPINE 5MG TABLETS

AMLODIPINE 10MG TABLETS

LAY SUMMARY

The MHRA granted Vale Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Amlodipine 5mg Tablets (PL 20692/0014, 6, 8, 20, 22, and 24) and Amlodipine 10mg Tablets (PL 20692/0015, 7, 9, 21, 23, and 25). These are prescription only medicines (POM) for the treatment of high blood pressure and angina.

The products were considered generic equivalents of the reference products Istin Tablets 5 and 10mg (Pfizer Limited, UK), based on the supporting data provided .

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.

The licences for PL 20692/0016-0025 were cancelled on 07/01/2008.

AMLODIPINE 5MG TABLETS

AMLODIPINE 10MG TABLETS

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 20692/0014, 6, 8, 20, 22, and 24) and Amlodipine 10mg Tablets (PL 20692/0015, 7, 9, 21, 23, and 25) on 15th May 2007. The products are prescription only medicines.

These are two strengths of amlodipine tablets 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. 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.

The licences for PL 20692/0016-0025 were cancelled on 07/01/2008.

PHARMACEUTICAL ASSESSMENT

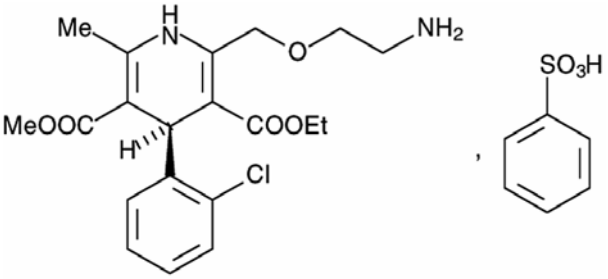
DRUG SUBSTANCE

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, H^1NMR 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.

Appropriate stability data have been generated supporting a retest period of 3 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 anhydrous, sodium starch glycollate (Type A), and magnesium stearate. All excipients used comply with their respective Ph Eur monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin. The manufacturer of magnesium stearate has confirmed that this is a vegetable origin.

There were no novel excipients used and no overages.

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce products containing 5mg and 10mg Amlodipine that could be considered as generic products to the originator products Istin 5mg and 10mg Tablets.

The rationale and function of each excipient added is discussed. Levels of each ingredient are typical for a product of this nature and have been optimised on the basis of results from development studies.

Dissolution and Impurity profiles
Dissolution and impurity profiles for both strengths of drug product were found to be similar to the originator products. 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, white blisters composed of aluminium and PVC. 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 20, 28, 30, 50, and 100 tablets.

Stability
Finished product stability studies have been conducted in accordance with current guidelines.
Based on the results, a shelf-life of 3 years when stored in the original packaging has been set, which is satisfactory.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Bioequivalence between the test and reference product has been demonstrated.

SPC, PIL, Labels
The SPC, PIL and labels are acceptable.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Conclusion
The proposed product has been shown to be a generic medicinal product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.. It is recommended that Marketing Authorisations should be granted for these applications.

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

These are abridged national, non-committee applications for two strengths of amlodipine besilate, based on the criteria of generic medicinal products under EC article 10.1, of EC directive 2001/83/EC as amended. In accordance with the article, the applicant has provided a bioequivalence study comparing the generic and the innovator product, (Istin 10 mg, Pfizer UK].

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

1.4 Regulatory Status

The current product has not been authorised either within or outside the EU thus far.

1.5 Indications, Dosage and dosage regimen.

Hypertension
Prophylaxis of chronic stable or effort angina including Prinzmetal's angina

As proposed in SPC, the indications are similar to the innovator product.

In adults
It can be administered alone or in combination with other antihypertensive agents, such as ACE-inhibitors, thiazide-diuretics or beta-blockers.
Amlodipine is also indicated for the prophylaxis of stable or effort angina (coronary stenosis), and in Prinzmetal's angina (vasospastic angina), alone or in combination with other antianginal drugs, even in non-responders to nitrates and/or beta-blockers.

The usual initial dose both in hypertension and angina is 5 mg once daily, with a maximum dose of 10 mg once daily.

Dosage generally should be adjusted to each patient’s need. In general, titration should proceed over 7 to 14 days, so that the physician can fully assess the patients’ response to each dose level.
Use in children
Amlodipine is not recommended for use in children. Safety and effectiveness of Amlodipine in children have not been established.

Use in the elderly
Amlodipine, used at similar doses in elderly or younger patients, was 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.

The dose and regimen as proposed in the SPC are identical to the reference product, Istin (PL 00057/0297-8) and are therefore 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. Moreover, in this application, the salt is identical to the brand leader. The applicant has provided a bioequivalence study comparing the two products, which is discussed below.

2.2.2 Bioequivalence study.

This is a single-dose, two-way crossover, block- randomised study.

Study Code : 02323
Study design : Single-dose, randomised, two-way crossover, open-label
Reference Prod : Istin, 10 mg
Test Product : Amlodipine Besilate 10mg

Results:

Parameter	Test	Reference Prod	Point Est & 90% CI Ratio
$AUC_{t\ (pg./ml*h)}$	352507.23 ± 109654.08	352528.86 ± 113498.89	100.71 (95.80 to 105.87)
$AUC_{\infty\ (pg./ml*h)}$	372017.48 ± 128326.48	370814.70 ± 128753.22	100.89 (95.93 to 106.11)
$C_{max\ (pg./ml)}$	6935.57 ± 1709.66	6866.67 ± 1648.57	101.13 (95.14 to 107.49)
T_{max} (h)	7.54 ± 1.13	7.00 ± 2.00	

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 AUC_{inf} 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). The expert report (clinical overview, module 2.5) provides the biowaiver criteria for the lower strengths and justification for using the higher strength:
Same 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.

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 and the generic product 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.

5.1 SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The proposed SPC is inline with the reference product SPC.

5.2 PIL; Patient Information Leaflet

This is satisfactory

5.3 Labels

Medically satisfactory.

6 CONCLUSIONS

6.1 Pharmacodynamics & Pharmacokinetics

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

6.2 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. Furthermore, biowaiver criteria for lower strengths are fulfilled.

6.3 Efficacy & Safety

The applicant has not provided new safety or efficacy data. This is acceptable for an application based on a generic medicinal product of the innovator product, as no new indication or posology is claimed.

6.4 Risk – benefit

This is considered favourable and is therefore acceptable.

7 CLINICAL AND PRE-CLINICAL ASSESSORS' CONCLUSIONS

There are no pre-clinical issues related to these applications 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).

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 tablets 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.

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AMLODIPINE 10MG TABLETS

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STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications on 12th February 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 10th March 2004
3	Following assessment of the application the MHRA requested further information relating to the clinical dossier on 13th September 2004 and quality dossiers on 2nd November 2004, , and 29th March 2006
4	The applicant responded to the MHRA's requests, providing further information on 30th March 2005, and 29th March 2006,
5	The applications were determined on 15th May 2007

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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
07/01/2008	National	To cancelled applications PL 20692/0016-0025	Approved 07/01/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
AMLODIPINE 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 5 mg amlodipine as amlodipine besilate form.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet for oral administration

White or almost white oblong tablets with engraved “5” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension

Prophylaxis of chronic stable or effort angina including Prinzmetal's angina

4.2 Posology and method of administration
In adults

It can be administered alone or in combination with other antihypertensive agents, as ACE-inhibitors, thiazide-diuretics or beta-blockers.

Amlodipine is also indicated for the prophylaxis of stable or effort angina (coronary stenosis), and in Prinzmetal's angina (vasospastic angina), alone or in combination with other antianginal drugs, even in non-responders to nitrates and/or beta-blockers.

The usual initial dose both in hypertension and angina is 5 mg once daily, with a maximum dose of 10 mg once daily.

Dosage generally should be adjusted to each patient’s need. In general, titration should proceed over 7 to 14 days, so that the physician can fully assess the patients’ response to each dose level.

Use in children

Amlodipine is not recommended for use in children. Safety and effectiveness of Amlodipine in children have not been established.

Use in the elderly

Amlodipine, used at similar doses in elderly or younger patients, was 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 the active substance or other dihydropyridines or to any of the excipients.

Amlodipine should not be used in:

cardiogenic shock

clinically significant aortic stenosis

unstable angina

pregnancy and lactation (see section 4.6., Pregnancy and lactation)

4.4 Special warnings and precautions for use

Use in patients with heart failure

In general calcium channel blockers should be used with caution in patients with heart failure. In a long-term placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA grade III and IV heart failure of nonischaemic aetiology Amlodipine was assotiated 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 hepatic impairment

Amlodipine is metabolized by the liver. As with all calcium antagonists, the plasma elimination half-life is prolonged in patients with impaired hepatic function, and dosage recommendations have not been established. Thus caution should be exercised when administering Amlodipine to such patients.

Hypertensive crisis

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

Myocardial infarction

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Special Studies: Effect of other agents on Amlodipine

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

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

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

Special Studies: Effect of Amlodipine on other agents

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

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

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

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

Drug/Laboratory test Interactions*:* None known.

4.6 Pregnancy and lactation

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

Use during lactation

It is unknown whether Amlodipine is excreted in human breast milk. In the absence of this information, it is recommended that nursing be discontinued while Amlodipine is administered.

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. However, dizziness, vertigo and rarely syncope may occur as adverse events which may affect ability to drive or operate machinery.

4.8 Undesirable effects

Most adverse reactions reported during therapy with Amlodipine were of mild or moderate severity.

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%).

System Organ Class	Common (≥l/100, <l/10)	Uncommon (≥1/1000, <l/100)	Rare (≥l/10000, <l/1000)	Very rare (<1/10000)
Blood and the lymphatic system disorders				thrombocytopenia
Immune system disorders				hypersensitivity
Metabolism and Nutrition Disorders				hyperglycaemia
Psychiatric Disorders		insomnia, mood altered		
Nervous System Disorders	dizziness, headache, somnolence	tremor, taste perversion, syncope, hypoaesthesia, paraesthesia		peripheral neuropathy
Eye Disorders		visual disturbances		
Ear and Labyrinth Disorders		tinnitus		
Cardiac Disorders	palpitations			myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation
Vascular Disorders	flushing	hypotension		vasculitis
Respiratory, Thoracic and Mediastinal Disorders		dyspnoea, rhinitis		cough
Gastrointestinal	abdominal	vomiting,		pancreatitis, gastritis,

Disorders	pain nausea	dyspepsia, altered bowel habits, dry mouth		gingival hyperplasia
Hepatobiliary disorders				hepatitis, jaundice, cholestasis
Skin and Subcutaneous Tissue Disorders		alopecia, purpura, skin discolouration, increased sweating, pruritus, rash		angioedema, erythema multiforme, urticaria
Musculoskeletal and Connective Tissue Disorders		arthralgia, myalgia, muscle cramps, back pain		
Renal and Urinary Disorders		micturition disorder, nocturia, increased urinary frequency		
Reproductive System and Breast Disorders		impotence, gynaecomastia		
General Disorders and Administration Site Conditions	oedema, fatigue	chest pain, asthenia, pain, malaise		
Investigations		weight increase, weight decrease		hepatic enzyme increased

4.9 Overdose

In humans, experience with intentional overdose is limited. Overdosage might be expected to cause subsequent excessive peripheral vasodilatation with marked and probably prolonged systemic hypotension, and possibly a reflex tachycardia. After oral administration the absorption of Amlodipine is slow, gastric lavage can be useful. In case of massive overdose active cardiac and respiratory monitoring is required. If severe hypotension occurs, cardiovascular support, including elevation of the extremities, judicious administration of fluids should be initiated. In case of insufficient response to these conservative measures administration of peripheral vasopressors should be considered (attention to fluid volume and urinary output). Intravenous calcium gluconate may be useful to help to reverse the effects of calcium entry blockade. Hemodialysis is not likely to be effective since Amlodipine is highly protein bound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Selective calcium channel blockers with mainly vascular effects, ATC Code: C08C A01

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 enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

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

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

The long-term effects of Amlodipine on growth, puberty and general development have not been studied.

The long-term efficacy of Amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2 Pharmacokinetic properties

Absorption:

After oral administration of therapeutic doses of Amlodipine, absorption produces peak plasma concentrations between 6-12 hours. Absolute bioavailability has been estimated between 64-80%. The bioavailability of Amlodipine is not altered by the presence of food.

Distribution:

Distribution volume is about 21 l/kg. Approximately 97 % of the circulating drug is bound to plasma proteins.

Metabolism and Elimination:

Amlodipine is extensively (approx. 90%) converted to inactive metabolites via hepatic metabolism, and 10% of the parent compound and 60% of the metabolites excreted in the urine. Elimination from the plasma is biphasic with a terminal elimination half-life about 30-50 hours. Steady-state plasma levels of Amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Effects of Age and Disease States on Pharmacokinetics

Age, cardiac and hepatic impairment:

Elderly patients and those with moderate to severe heart failure tend to show a decreased clearance of Amlodipine, with a resulting increase in AUC of approximately 40-60%, and a lower initial dose might be required. A similar increase in AUC was observed in patients with hepatic impairment.

Renal Impairment:

The pharmacokinetics of Amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In animal studies with respect to the reproduction in rats at high doses delayed parturition, difficult labour and impaired foetal and pup survival were seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline

Calcium hydrogen phosphate, anhydrous

Sodium starch glycolate (type A)

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage.

Store in original packaging.

6.5 Nature and contents of container
Aluminium/PVC blister in boxes of 20, 28, 30, 50 and 100. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Vale Pharmaceuticals Ltd.

Oasis House, Mary Street, Clonmel

Co. Tipperary

Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 20692/0014
PL 20692/0016
PL 20692/0018
PL 20692/0020
PL 20692/0022
PL 20692/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/2007

10 DATE OF REVISION OF THE TEXT

15/05/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
AMLODIPINE 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 10 mg amlodipine as amlodipine besilate form.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Tablet for oral administration

White or almost white oblong tablets with engraved “10” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hypertension

Prophylaxis of chronic stable or effort angina including Prinzmetal's angina

4.2 Posology and method of administration
In adults

It can be administered alone or in combination with other antihypertensive agents, as ACE-inhibitors, thiazide-diuretics or beta-blockers.

Amlodipine is also indicated for the prophylaxis of stable or effort angina (coronary stenosis), and in Prinzmetal's angina (vasospastic angina), alone or in combination with other antianginal drugs, even in non-responders to nitrates and/or beta-blockers.

The usual initial dose both in hypertension and angina is 5 mg once daily, with a maximum dose of 10 mg once daily.

Dosage generally should be adjusted to each patient’s need. In general, titration should proceed over 7 to 14 days, so that the physician can fully assess the patients’ response to each dose level.

Use in children

Amlodipine is not recommended for use in children. Safety and effectiveness of Amlodipine in children have not been established.

Use in the elderly

Amlodipine, used at similar doses in elderly or younger patients, was 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 the active substance or other dihydropyridines or to any of the excipients.

Amlodipine should not be used in:

cardiogenic shock

clinically significant aortic stenosis

unstable angina

pregnancy and lactation (see section 4.6., Pregnancy and lactation)

4.4 Special warnings and precautions for use

Use in patients with heart failure

In general calcium channel blockers should be used with caution in patients with heart failure. In a long-term placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA grade 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 hepatic impairment

Amlodipine is metabolized by the liver. As with all calcium antagonists, the plasma elimination half-life is prolonged in patients with impaired hepatic function, and dosage recommendations have not been established. Thus caution should be exercised when administering Amlodipine to such patients.

Hypertensive crisis

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

Myocardial infarction

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Special Studies: Effect of other agents on Amlodipine

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

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

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

Special Studies: Effect of Amlodipine on other agents

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

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

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

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

Drug/Laboratory test Interactions*:* None known.

4.6 Pregnancy and lactation

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

Use during lactation

It is unknown whether Amlodipine is excreted in human breast milk. In the absence of this information, it is recommended that nursing be discontinued while Amlodipine is administered.

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. However, dizziness, vertigo and rarely syncope may occur as adverse events which may affect ability to drive or operate machinery.

4.8 Undesirable effects

Most adverse reactions reported during therapy with Amlodipine were of mild or moderate severity.

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%).

System Organ Class	Common (≥l/100, <l/10)	Uncommon (≥1/1000, <l/100)	Rare (≥l/10000, <l/1000)	Very rare (<1/10000)
Blood and the lymphatic system disorders				thrombocytopenia
Immune system disorders				hypersensitivity
Metabolism and Nutrition Disorders				hyperglycaemia
Psychiatric Disorders		insomnia, mood altered		
Nervous System Disorders	dizziness, headache, somnolence	tremor, taste perversion, syncope, hypoaesthesia, paraesthesia		peripheral neuropathy
Eye Disorders		visual disturbances		
Ear and Labyrinth Disorders		tinnitus		
Cardiac Disorders	palpitations			myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation
Vascular Disorders	flushing	hypotension		vasculitis
Respiratory, Thoracic		dyspnoea,		cough

and Mediastinal Disorders		rhinitis		
Gastrointestinal Disorders	abdominal pain nausea	vomiting, dyspepsia, altered bowel habits, dry mouth		pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders				hepatitis, jaundice, cholestasis
Skin and Subcutaneous Tissue Disorders		alopecia, purpura, skin discolouration, increased sweating, pruritus, rash		angioedema, erythema multiforme, urticaria
Musculoskeletal and Connective Tissue Disorders		arthralgia, myalgia, muscle cramps, back pain		
Renal and Urinary Disorders		micturition disorder, nocturia, increased urinary frequency		
Reproductive System and Breast Disorders		impotence, gynaecomastia		
General Disorders and Administration Site Conditions	oedema, fatigue	chest pain, asthenia, pain, malaise		
Investigations		weight increase, weight decrease		hepatic enzyme increased

4.9 Overdose

In humans, experience with intentional overdose is limited. Overdosage might be expected to cause subsequent excessive peripheral vasodilatation with marked and probably prolonged systemic hypotension, and possibly a reflex tachycardia. After oral administration the absorption of Amlodipine is slow, gastric lavage can be useful. In case of massive overdose active cardiac and respiratory monitoring is required. If severe hypotension occurs, cardiovascular support, including elevation of the extremities, judicious administration of fluids should be initiated. In case of insufficient response to these conservative measures administration of peripheral vasopressors should be considered (attention to fluid volume and urinary output). Intravenous calcium gluconate may be useful to help to reverse the effects of calcium entry blockade. Hemodialysis is not likely to be effective since Amlodipine is highly protein bound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Selective calcium channel blockers with mainly vascular effects, ATC Code: C08C A01

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 enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

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

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

The long-term effects of Amlodipine on growth, puberty and general development have not been studied.

The long-term efficacy of Amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2 Pharmacokinetic properties

Absorption:

After oral administration of therapeutic doses of Amlodipine, absorption produces peak plasma concentrations between 6-12 hours. Absolute bioavailability has been estimated between 64-80%. The bioavailability of Amlodipine is not altered by the presence of food.

Distribution:

Distribution volume is about 21 l/kg. Approximately 97 % of the circulating drug is bound to plasma proteins.

Metabolism and Elimination:

Amlodipine is extensively (approx. 90%) converted to inactive metabolites via hepatic metabolism, and 10% of the parent compound and 60% of the metabolites excreted in the urine. Elimination from the plasma is biphasic with a terminal elimination half-life about 30-50 hours. Steady-state plasma levels of Amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Effects of Age and Disease States on Pharmacokinetics

Age, cardiac and hepatic impairment:

Elderly patients and those with moderate to severe heart failure tend to show a decreased clearance of Amlodipine, with a resulting increase in AUC of approximately 40-60%, and a lower initial dose might be required. A similar increase in AUC was observed in patients with hepatic impairment.

Renal Impairment:

The pharmacokinetics of Amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In animal studies with respect to the reproduction in rats at high doses delayed parturition, difficult labour and impaired foetal and pup survival were seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline

Calcium hydrogen phosphate, anhydrous

Sodium starch glycollate (Type A)

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage
No special precautions for storage.

Store in original packaging.

6.5 Nature and contents of container
Aluminium/PVC blister in boxes of 14, 20, 28, 30, 50 and 100. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Vale Pharmaceuticals Ltd.

Oasis House, Mary Street, Clonmel

Co. Tipperary

Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 20692/0015
PL 20692/0017
PL 20692/0019
PL 20692/0021
PL 20692/0023
PL 20692/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/05/2007

10 DATE OF REVISION OF THE TEXT
15/05/2007

PATIENT INFORMATION LEAFLET

AMLODIPINE 5mg , 10 mg

PATIENT INFORMATION LEAFLET

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

In this leaflet:

Amlodipine tablets. 5 mg and 10 mg tablets.
- The active substance is amlodipine besilate.
- The other ingredients are cellulose microcrystalline, calcium hydrogen phosphate, anhydrous, sodium starch glycolate, magnesium stearate.

Amlodipine comes in packs containing 28 tablets of 5 mg or 10 mg.

Marketing Authorisation Holder:
Vale Pharmaceuticals Limited, Oasis House, Mary Street, Clonmel, Co Tiperrary, Ireland

Manufacturer:
Gedeon Richter Ltd., Budapest, Hungary.

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

AMLODIPINE is one of a group of medicines called calcium antagonists.
Your doctor has prescribed AMLODIPINE for you as a result of one of the following reasons:
- Your blood pressure is too high.
- You have a certain type of chest pain called angina, a rare form of which is Prinzmetal's or variant angina.

In patients with high blood pressure AMLODIPINE works by relaxing blood vessels, so that blood passes through them more easily. AMLODIPINE is also used to treat a certain chest pain called angina. AMLODIPINE does not provide immediate relief of chest pain from angina, but is useful in preventing anginal attacks.

2. BEFORE YOU TAKE AMLODIPINE

Do not take AMLODIPINE:
- if you are hypersensitive (allergic) to AMLODIPINE or other calcium antagonists or any of the other ingredients of AMLODIPINE tablet. (This may have been -itching, reddening of the skin or difficulty in breathing.)
- if you have very low blood pressure
- if you have cardiogenic shock (not enough blood supply to your tissues)
- if you have aortic stenosis (narrowing of the aortic heart valve)
- if you have unstable angina (except Prinzmetal's angina)
- if you have suffered a heart attack within the last 30 days
- if you are pregnant or think you may be pregnant
- if you are breastfeeding

Take special care with AMLODIPINE:
- if you have heart failure
- if you have liver disease
- if you are under 18 years of age

Using AMLODIPINE with food and drink
Grapefruit juice may interact with AMLODIPINE to increase the plasma concentration. However this increase is too small to significantly alter blood pressure or heart rate.

Pregnancy
Do not take AMLODIPINE tablets during pregnancy. If you are a woman of child-bearing potential effective contraception is advised.

Breast-feeding
Do not take AMLODIPINE tablets during breast feeding or stop breast feeding when taking AMLODIPINE tablets.

Driving and using machines
The tablets may cause dizziness, headache, the feeling

that you are about to be sick or the feeling of mental and physical tiredness. If this applies to you take care, as the ability to drive or operate machinery may be impaired.

Taking other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, especially any of the following:

- medicines used to treat high blood pressure such as:
  - beta-blockers (e.g. atenolol, carvedilol)
  - ACE inhibitors (e.g. captopril, enalapril)
  - alpha-1-blockers (e.g. doxazosin, terazosin)
  - water tablets (e.g. metolazone, indapamide)
- diltiazem, a medicine to treat high blood pressure and angina (chest pain)

3. HOW TO TAKE AMLODIPINE TABLETS

Take AMLODIPINE tablets exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.
The usual dose of AMLODIPINE is one tablet daily. It is best to take AMLODIPINE tablets at the same time each day with a drink of water.
If you have the impression that the effect of AMLODIPINE is too strong or too weak, talk to your doctor or pharmacist.
Continue to take your tablet each day. It is important to keep taking the tablets.
Do not wait until your tablets are finished before seeing your doctor. Your doctor may wish to give you more AMLODIPINE tablets.

If you take more AMLODIPINE than you should

If several tablets are taken it may be dangerous. Contact your doctor immediately.

If you forget to take AMLODIPINE

If you accidentally miss a dose of AMLODIPINE, do not worry. Leave out that dose completely just take the next dose as normal. Do not take an extra dose to make up for the missed one.

Effects when treatment with AMLODIPINE is stopped

if you get any swelling of the face, lips, tongue or throat
if you get any rash, itching, inflamed or reddened skin especially affecting the whole body)
if you have any problems of breathing

4. POSSIBLE SIDE EFFECTS

Like all medicines, AMLODIPINE can have side effects.
The most common are:
Headache, oedema (for example ankle swelling), skin rash, feeling tired, feeling sick, dizziness and nausea, flushing.
Tell your doctor if these effects cause you any problems or if they last for more than one week.
Rare undesirable effects:
itchy skin, palpitations (a quicker or irregular heart beat), shortness of breath, abdominal pain, indigestion, muscle cramps, weakness, sleepiness, altered bowel habit, muscle or joint pain, mood changes, increased need to urinate, dry mouth, thirst, swelling or soreness of the gums, loss of pain sensation, increased sweating, fainting, red patches on skin, inability to obtain an erection.
Very rarely abnormal liver function test, inflammation of the liver, yellowing of the skin, severe skin reactions and enlargement 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), chest pain, malaise, back pain and visual disturbances.
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) red blood cell damage (unusual bruising and bleeding) should be reported to a doctor immediately.
If you experience any other unwanted effects not listed in this leaflet, please inform your doctor.

5. STORING AMLODIPINE

There is no other special requirement for the storage of tablets.
Do not take the tablets beyond the expiry date shown on the pack.
Keep AMLODIPINE tablets out of the reach and sight of children.

6. FURTHER INFORMATION

This leaflet was written in January, 2006.

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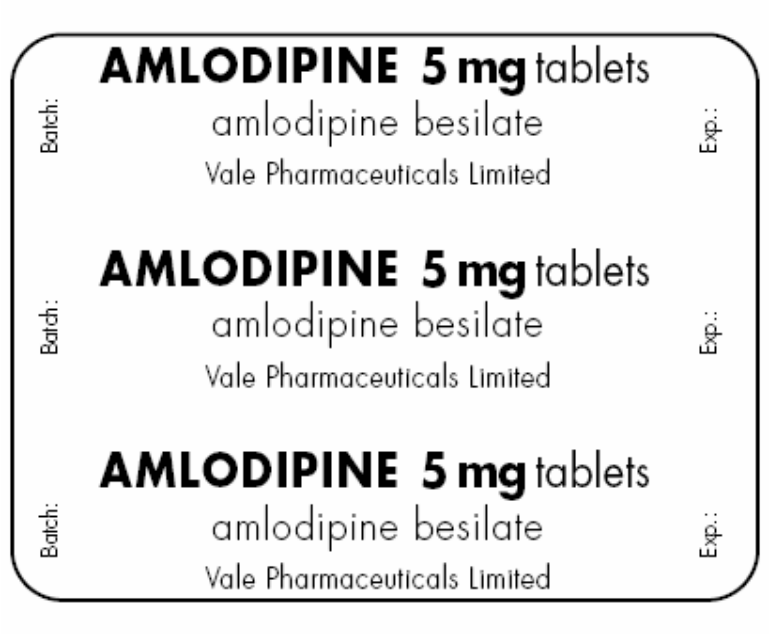
LABELLING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28 tablets
AMLODIPINE 5mg tablets
amlodipine besilate
Batch No:
Expiry Date:
Each tablet contains 5 mg Amlodipine
(as amlodipine besilate).
For oral use.
Please read the enclosed leaflet before use.
Keep out of the reach and sight of children.
Store in the original packaging.
Use as directed by medical practitioner.
PL 20692/0014
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Vale Pharmaceuticals Limited
Oasis House, Mary Street, Clonmel, Co. Tipperary
Ireland
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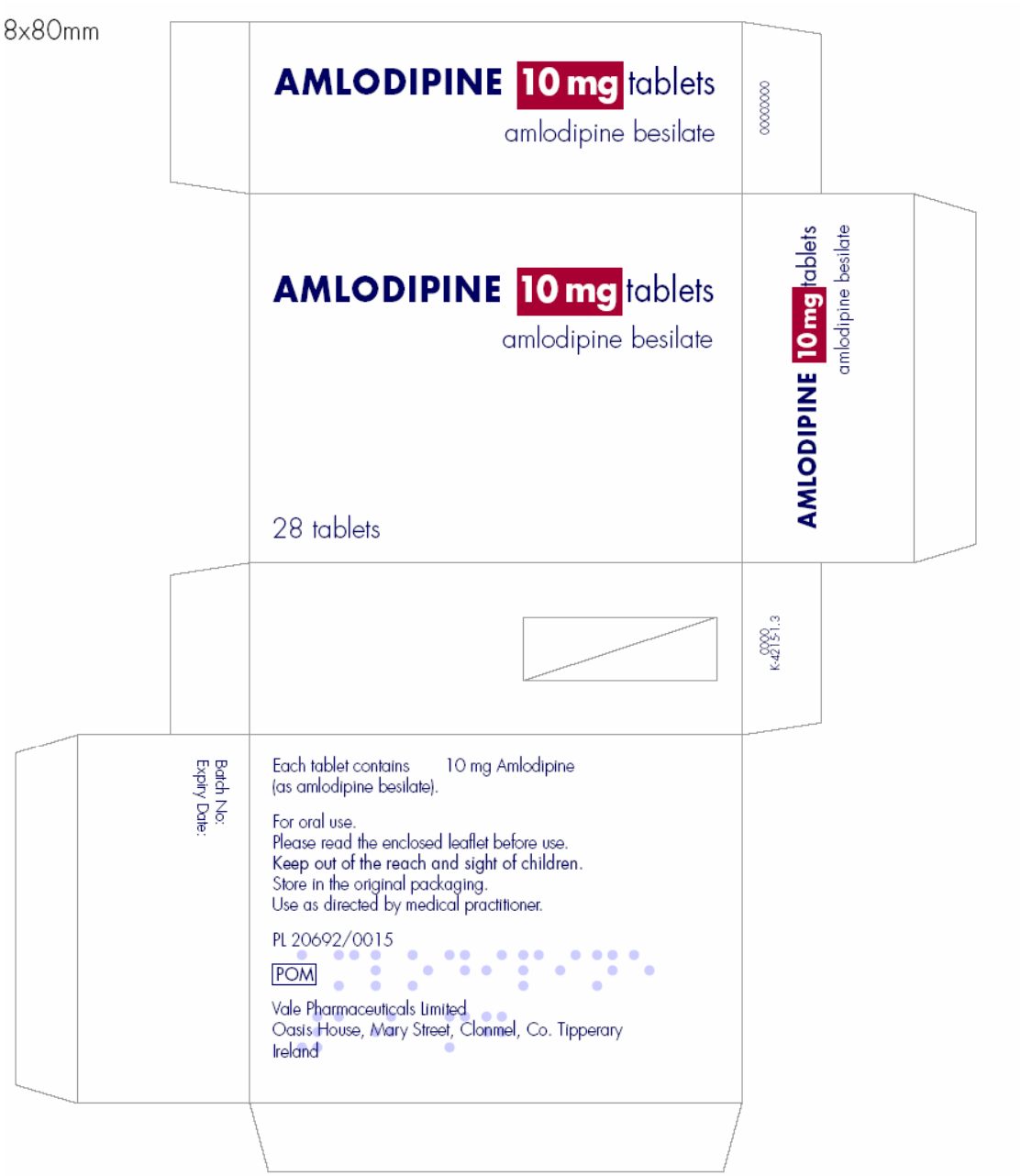
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Batch No:
Expiry Date:
Each tablet contains 10 mg Amlodipine
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AMLODIPINE 5 mg tablets
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28 tablets
AMLODIPINE 5 mg tablets
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Batch No:
Expiry Date:
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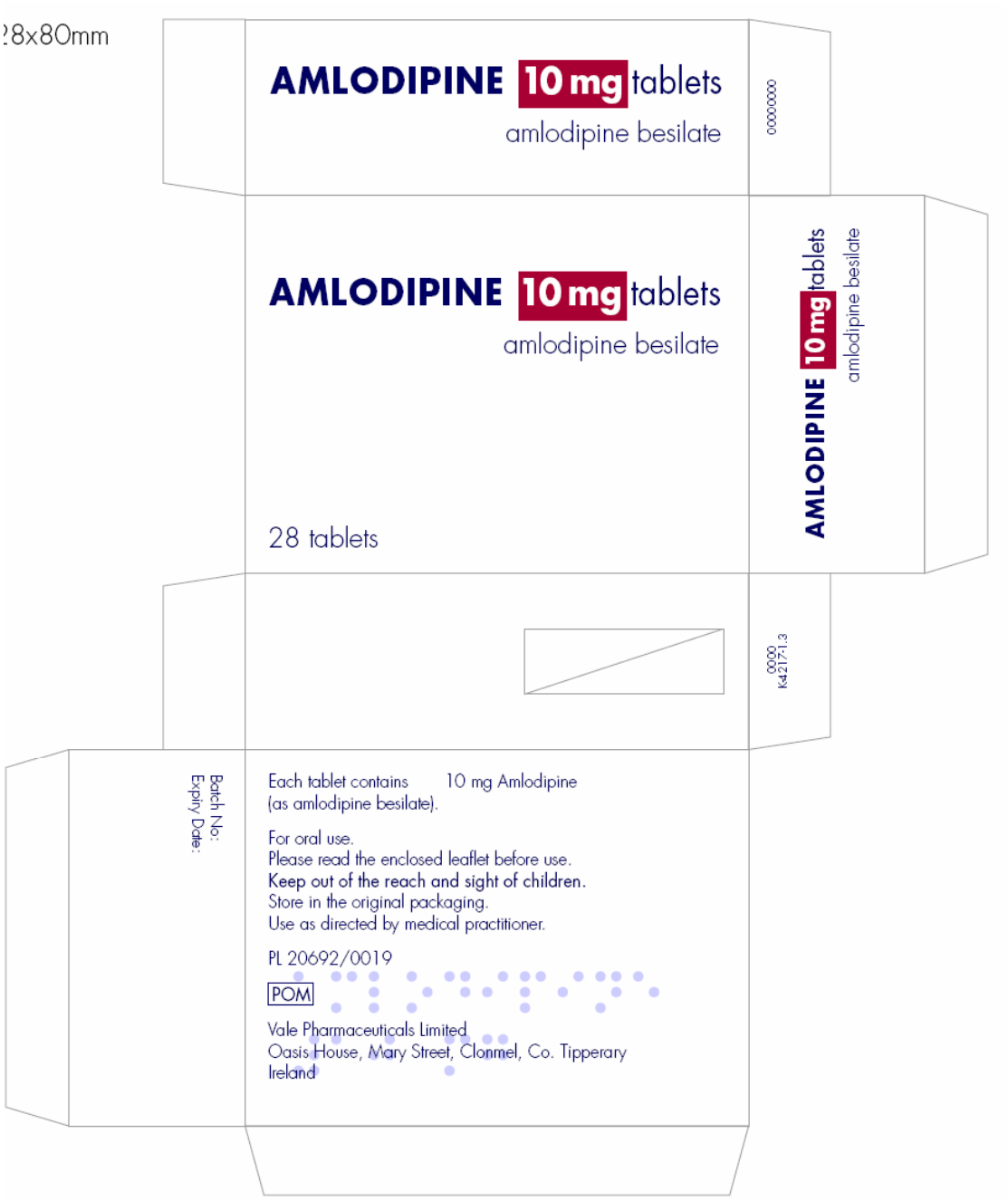
28x80mm
AMLODIPINE 10 mg tablets
amlodipine besilate
0000000
AMLODIPINE 10 mg tablets
amlodipine besilate
28 tablets
AMLODIPINE 10 mg tablets
amlodipine besilate
0000
K4217-1.3
Batch No:
Expiry Date:
Each tablet contains 10 mg Amlodipine
(as amlodipine besilate).
For oral use.
Please read the enclosed leaflet before use.
Keep out of the reach and sight of children.
Store in the original packaging.
Use as directed by medical practitioner.
PL 20692/0019
POM
Vale Pharmaceuticals Limited
Oasis House, Mary Street, Clonmel, Co. Tipperary
Ireland
P 280
P 200
vakírás
A M L O D I P I N E
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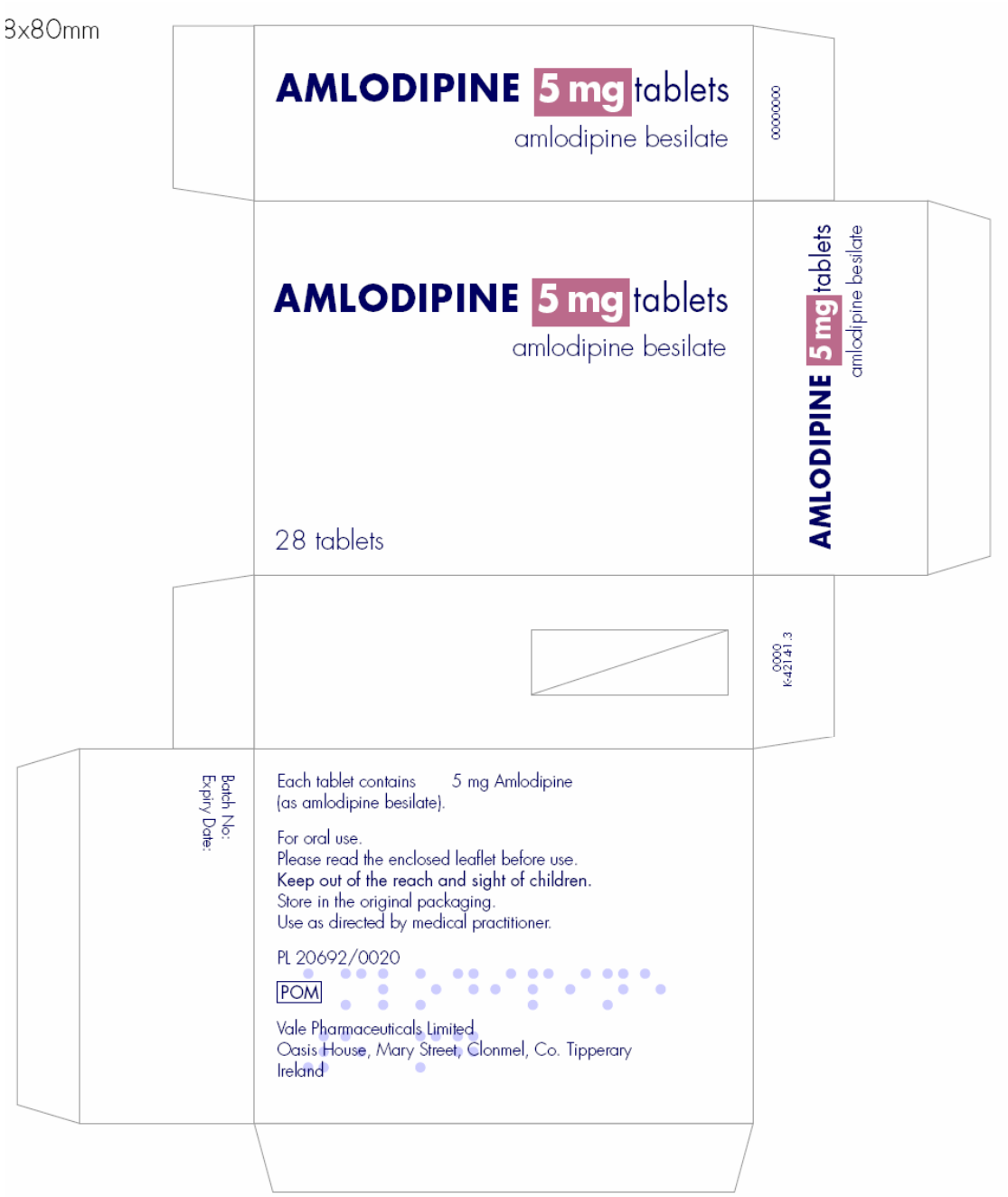
3x80mm
AMLODIPINE 5 mg tablets
amlodipine besilate
AMLODIPINE 5 mg tablets
amlodipine besilate
28 tablets
AMLODIPINE 5 mg tablets
amlodipine besilate
Batch No:
Expiry Date:
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Ireland
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vakírás
A M L O D I P I N E
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28x80mm
AMLODIPINE 10 mg tablets
amlodipine besilate
00000000
AMLODIPINE 10 mg tablets
amlodipine besilate
28 tablets
AMLODIPINE 10 mg tablets
amlodipine besilate
0000
K-42181.3
Batch No:
Expiry Date:
Each tablet contains 10 mg Amlodipine
(as amlodipine besilate).
For oral use.
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POM
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Ireland
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A M L O D I P I N E
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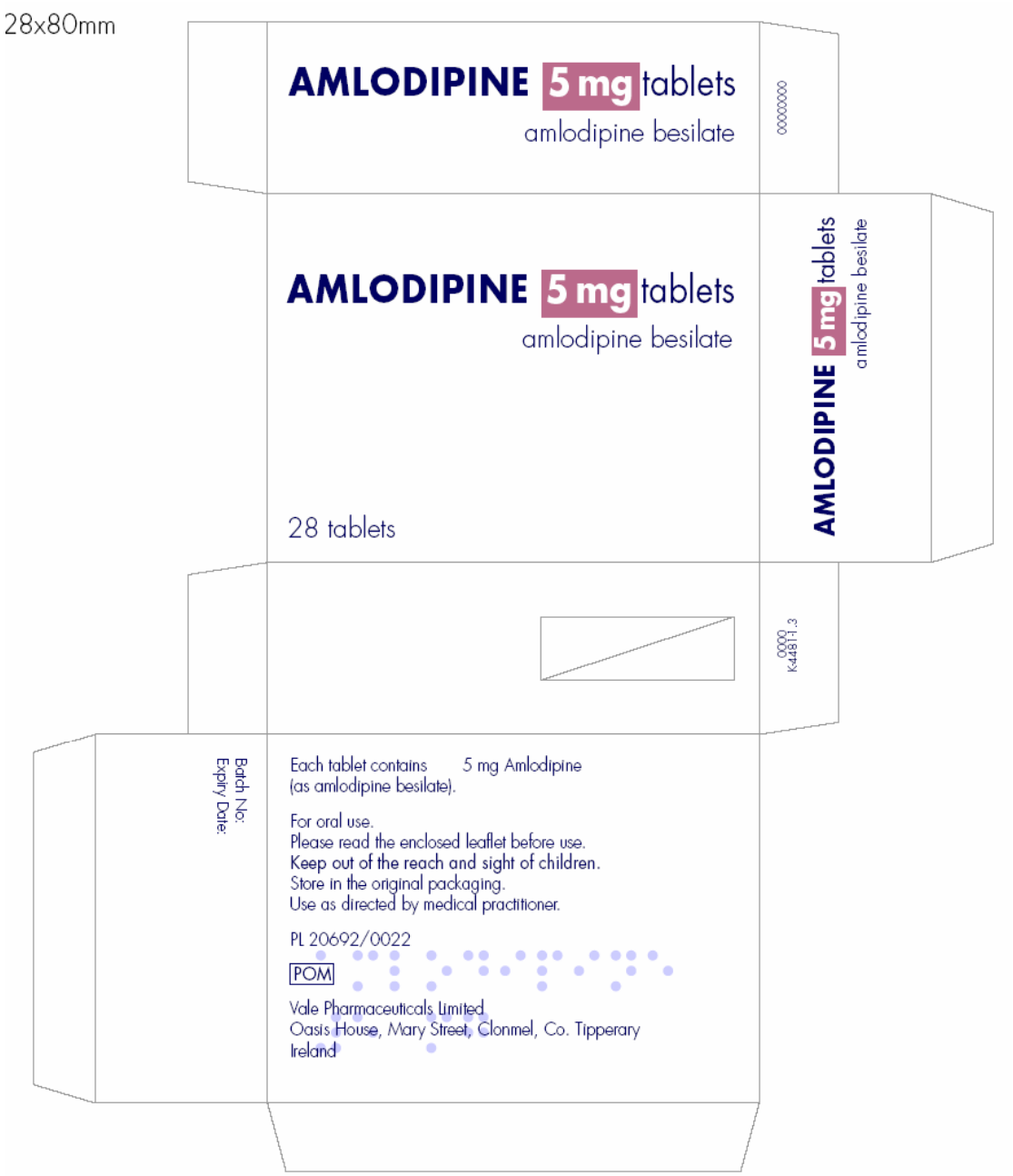
28x80mm
AMLODIPINE 5 mg tablets
amlodipine besilate
AMLODIPINE 5 mg tablets
amlodipine besilate
28 tablets
AMLODIPINE 5 mg tablets
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Batch No:
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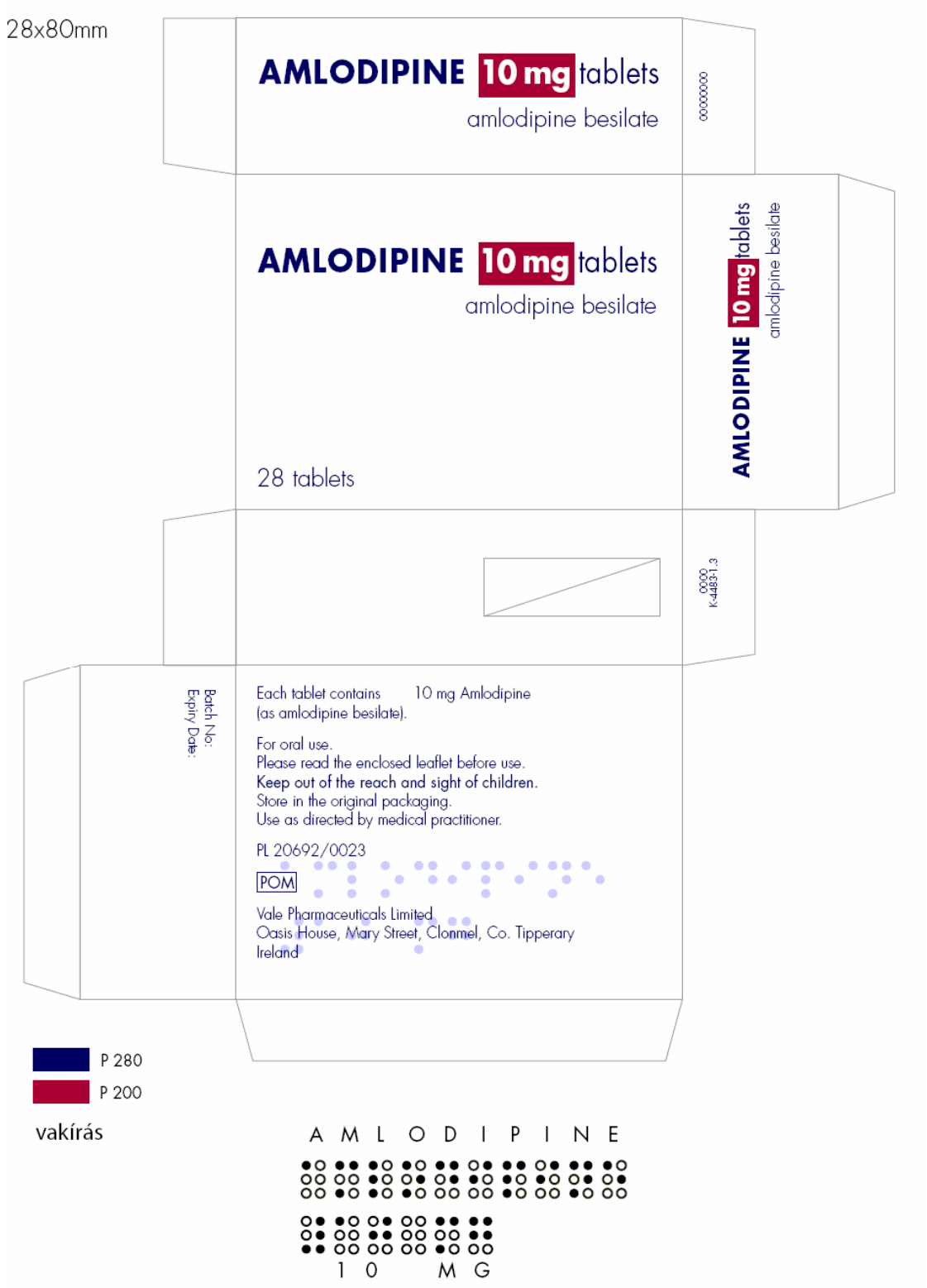
5 M G


28x80mm
AMLODIPINE 10 mg tablets
amlodipine besilate
AMLODIPINE 10 mg tablets
amlodipine besilate
28 tablets
AMLODIPINE 10 mg tablets
amlodipine besilate
Batch No:
Expiry Date:
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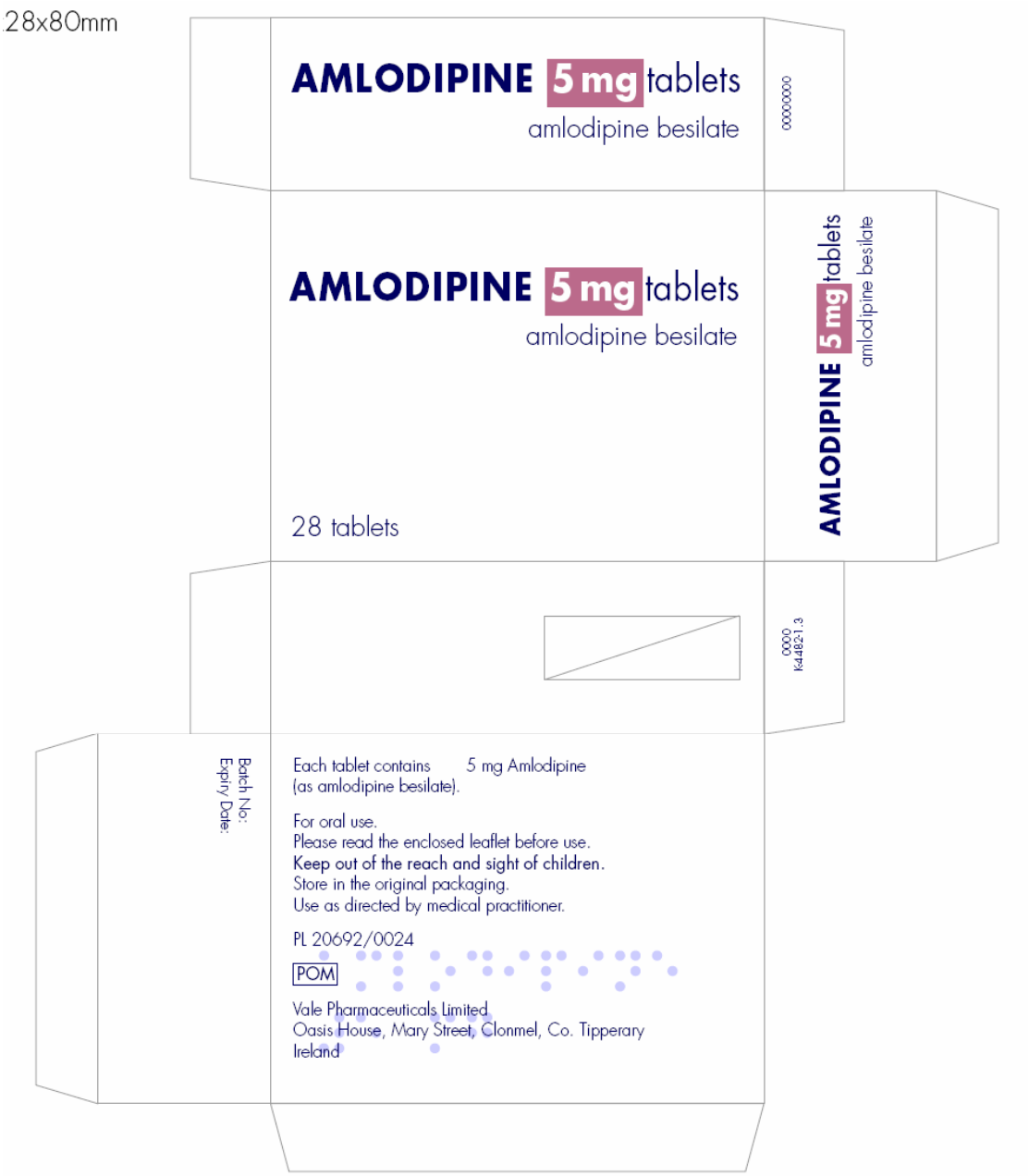

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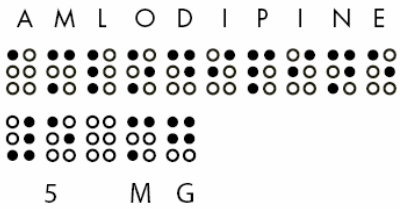


‹28x80mm
AMLODIPINE 10 mg tablets
amlodipine besilate
AMLODIPINE 10 mg tablets
amlodipine besilate
28 tablets
AMLODIPINE 10 mg tablets
amlodipine besilate
K-44841.2
Batch No:
Expiry Date:
Each tablet contains 10 mg Amlodipine
(as amlodipine besilate).
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