CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Amlodno 5 mg, tablets
Amlodno 10 mg, tablets

Krka, Slovenia

amlodipine besilate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/815/01-02/MR
Registration number in the Netherlands: RVG 31468, 31469

5 June 2008

Pharmacotherapeutic group:	Selective calcium channel blockers with mainly vascular effects, Dihydropyridine derivatives
ATC code:	C08CA01
Route of administration:	oral
Therapeutic indication:	Essential hypertension and chronic stable and vasospastic angina pectoris
Prescription status:	prescription only
Date of authorisation in NL:	19 December 2005
Concerned Member States:	Mutual recognition procedure with IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Amlodno 5 and 10 mg tablets, from Krka, Slovenia. The date of authorisation was on 19 December 2005 in the Netherlands. The product is indicated for the treatment of essential hypertension, and chronic stable and vasospastic angina pectoris.

A comprehensive description of the indications and posology is given in the SPC.

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and smooth muscle. The mechanism of the antihypertensive 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 the following two actions play a role:
1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. The mechanism of action also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilation increases the supply in oxygen to myocardiac muscle in patients with Prinzmetal anginal attack.

This application concerns a generic application claiming essential similarity with the innovator products Norvasc® 5 and 10 mg tablets (NL License RVG 13348 and 13349), containing respectively 5 and 10 mg amlodipine base, which have been registered in the Netherlands by Pfizer since 1990. In addition, reference is made to Norvasc authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Norvasc 10 mg tablet by Pfizer, registered in Italy. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new preclinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients
The active substance is amlodipine base, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ph.Eur is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU. The drug substance is a white or almost white powder that is slightly soluble in water and isopropanol, freely soluble in methanol and sparingly soluble in ethanol. Amlodipine has one chiral center and is a racemic mixture. Amlodipine exists in only one crystalline form. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, and the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

The active substance is stable for 36 months when stored in PE bags in outer black PE bags kept in fiber drums. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

Medicinal Product

Composition
Amlodno 5 mg tablets contain as active substance 6.94 mg of amlodipine besilate, corresponding to 5 mg of amlodipine base, and are white, round, slightly biconvex, bevel-edged, scored on one side, with a diameter of 8 mm.
Amlodno 10 mg tablets contain as active substance 13.88 mg of amlodipine besilate, corresponding to 10 mg of amlodipine base, and are white, round, slightly biconvex, bevel-edged, scored on one side, with a diameter of 10 mm.

The tablets are packed in OPA-Al-PVC/Al blister.

The excipients are: microcristaline cellulose (E460), pregelatinised maize starch, sodium starch glycolate, colloidal silicium dioxide (E551), magnesium stearate (E470b).

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the innovator product Norvasc 5 and 10 mg tablets.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 1 pilot batch of each strength, en 2 pilot-scale batches, although from different strengths in accordance with the relevant European guidelines. In view of the standard process and the fact that the concentration of active substance in the tablets is 2.7%, process validation on production-scale batches prior to registration is not necessary. The MAH committed to carry out process validation on the first 3 production-scale batches.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for tablets in the Ph.Eur. and includes tests for appearance, uniformity of mass, uniformity of mass of subdivided tablets, water content, hardness, disintegration, friability, identification, related substances, dissolution, content of amlodipine and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for 4 batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification. The MAH committed to submit production-scale batch analysis results for 3 batches per strength.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches for each strength in accordance with applicable European guidelines demonstrating the stability of the product over 24 months. No specific storage conditions need to be included in the SPC or on the label, except store in the original pack. The MAH committed to place the first 3 production-scale batches of each strength on stability.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Norvasc 5 and 10 mg, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of amlodipine besilate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Amlodipine base is a well-known active substance with established efficacy and tolerability.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Norvasc 5 and 10 mg tablets marketed by Pfizer.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Amlodno 10 mg is compared with the pharmacokinetic profile of the Italian reference product Norvasc 10 mg. Both products contain 14 mg amlodipine besilate, equivalent to 10 mg of amlodipine.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

A randomised, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 22 healthy male subjects, aged 19-26 years. For each subject there were 2 dosing periods of one of the 10 mg amlodipine formulations, separated by a washout period of 3 weeks. The tablet was orally administered with 200 ml water after 10 hours of fasting. All subjects completed the study periods. In total 17 blood samples were collected predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144 and 168 hours after administration of the products. After analysis of the samples of the first 10 subjects, the samples were destroyed due to fire. All the other samples were lost except for the samples of subjects 11-14. Analysis of these samples was performed at a different site. The analysis of the samples at two different analytical sites is not expected to affect bioequivalence, as the samples of the individuals were not split between analytical sites, all samples of one volunteer were analysed in the same centre and therefore each subject functions as it's own control. For the plasma samples of subject 6 no values were obtained due to an analytical problem, and reanalysis was not possible due to the fire. Therefore, 13 subjects were eligible for pharmacokinetic analysis..

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amlodipine under fasted conditions

Treatment N=13	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	248 ± 115	276 ± 137	5.1 ± 1.6	6.3 (3-10)	45 ± 14
Reference	242 ± 101	264 ± 112	5.3 ± 1.4	5.5 (2-8)	42 ± 9
***Ratio (90% CI)**	1.00 (0.94–1.07)	1.01 (0.94–1.08)	0.95 (0.89–1.02)	--	--
CV (%)	9.2%	10.1%	10.0%	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Amlodipine should be taken once daily without reference to food intake. From the literature it is known that food does not interact with the absorption of amlodipine. Therefore, no food interaction study is necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence. The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of

amlodipine besilate under fasted conditions, it can be concluded that Amlodno 10 mg tablet and the Italian reference product Norvasc 10 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. The analysis of the samples in two different analytical sites is not expected to affect bioequivalence testing and outcome, as the samples of the individuals were not splitted up between the analytical sites. Therefore, each subject functions as it own control. The inclusion of only 13 volunteers is acceptable given the argumentation of the MAH.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The Amlodno 5 and 10 mg tablets are dose proportional. The pharmacokinetics of amlodipine is linear in the range 5-10 mg. The results of the bioequivalence study performed with the 10 mg tablet therefore apply to the other tablet's strength.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan

Amlodipine was first approved in 1989, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of amlodipine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Readibility test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Amlodno 5 and 10 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Norvasc 5 and 10 mg. Norvasc is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. The member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Amlodno 5 and 10 mg tablets with the reference product, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The first PSUR will cover a 3 year period starting from 21 August 2006 till 21 August 2009. The second PSUR will cover a 2 year period to coincide with the renewal. Hereafter, the PSURs will be submitted three-yearly.

The date for the first renewal will be: 21 August 2011.

The following post-approval commitments have been made during the procedure:

Quality – Medicinal product

- The MAH committed to carry out process validation on the first 3 production-scale batches.
- The MAH committed to submit production scale batch analysis results for 3 batches per strength.
- The MAH committed to place the first 3 production-scale batches of each strength on stability.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached