CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Amlopidine 5 mg ratiopharm, tablets
Amlopidine 10 mg ratiopharm, tablets
Ratiopharm GmbH, Germany

amlodipine (as 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/881/01-02/MR
Registration number in the Netherlands: RVG 31807, 31808

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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:	9 December 2005
Concerned Member States:	Mutual recognition procedure with DE
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 Amlodipine 5 mg ratiopharm and Amlodipine 10 mg ratiopharm tablets, from Ratiopharm GmbH. The date of authorisation was on 9 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 Istin 10 mg tablets by Pfizer, registered in the United Kingdom. Istin® is the trade name for the innovator product in the United Kingdom, which is identical with the innovator product on the Dutch market. 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.). The drug substance is a white or almost white powder that is slightly soluble in water and in 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 CEP procedure is used for two manufactures of 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, or 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 Master File (ASMF) procedure is used for the third manufacturer of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional requirements for residual solvents, relevant impurities and particle size. There are three manufacturers of the active substance: for two of these the CEP procedure is used, and for the third manufacturer the EDMF procedure. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches for the third manufacturer.

Stability of drug substance
For one manufacturer the retest period of 3 years is stated in the CEP. For the other two manufacturers stability data of the active substance for 12 months have been provided. Based on the data submitted an adequate retest period of 2 years was granted for these ASMs. The MAH committed to monitor one batch per year.

* *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.*

Medicinal Product

Composition
Amlodipine 5 mg ratiopharm tablets contain as active substance 7 mg of amlodipine besilate, corresponding to 5 mg of amlodipine base, and are white to off-white, round uncoated tablets with "*A*" and "*5*" engraved on scored side and "*mp*" engraved on convex side.
Amlodipine 10 mg ratiopharm tablets contain as active substance 14 mg of amlodipine besilate, corresponding to 10 mg of amlodipine base, and are white, round uncoated tablets with "*A*" and "*10*" engraved on scored side and "*mp*" engraved on convex side.
Update: "*mp*" is no longer engraved into the tablets, see variation NL/H/881/001-002/IA/006 in table '*steps taken after finalisation of the initial procedure*'. In addition, the tablet dimensions were changed by a post approval variation (NL/H/881/001-002/IB/007).

The tablets are packed in PVC/PVDC/Aluminium blisters.

The excipients are: microcrystalline cellulose (E460), calcium hydrogen phosphate (E341), sodium starch glycolate (Type A), 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.

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

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 3 pilot-scale batches for each strength in accordance with the relevant European guidelines.

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, diameter, identity, average mass, uniformity of mass, uniformity of mass of tablet halves, hardness, dissolution, related substances, assay and microbiological purity. Limits in the specification have been tightened and justified during the procedure and are considered appropriate for adequate quality control of the product. The MAH committed to re-evaluate the specification for total impurities at the end of shelf life, and to tighten this if possible. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches (10% of full scale) for each strength in accordance with applicable European guidelines demonstrating the stability of the product for 3 years. No specific storage conditions need to be included in the SPC or on the label. The MAH committed to perform a photostability study and to re-evaluate the storage labeling based upon the results (see also page 10 Steps taken after the finalisation of the initial procedure).

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

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Amlodipine 10 mg ratiopharm is compared with the pharmacokinetic profile of the British reference product Istin 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.

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

From the literature it is known that concomitant food intake has no influence on the absorption of both active substances and a food interaction study was not deemed necessary.

Bioequivalence study
A randomised, single-dose, 3-way cross-over, bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 19-44 years. For each subject there were 3 dosing periods of one of the 10 mg amlodipine formulations, separated by a washout period of 14 days. The tablet was orally administered with 250 ml water after 11 hours of fasting. One subject was withdrawn for personal reasons and was replaced by another volunteer during the first treatment period. In total 25 blood samples were collected predose and at 1, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144 and 192 hours after administration of the products. All subjects were eligible for pharmacokinetic analysis. The bioavailability of the test product Amlodipine Ratiopharm 10 mg tablets was compared to the British reference product Istin 10 mg tablet, Pfizer and to the Swiss reference product Norvasc 10 mg tablet, Pfizer.

Results

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

Treatment N=24	**AUC_{0-t}** pg/ml.h	**$AUC_{0-\infty}$** pg/ml.h	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	214.1 ± 70.6	229.3 ± 76.1	5.38 ± 1.26	6.08 ± 2.26	48.4 ± 15.3
Reference 1 (Istin)	202.2 ± 68.5	218.9 ± 75.2	5.31 ± 1.36	5.77 ± 1.31	52.4 ± 16.0
***Ratio (90% CI)**	1.06 (0.98–1.14)	1.04 (0.97–1.13)	1.02 (0.95–1.09)	--	--

CV (%)*	16	15	14	--	--

$AUC_{0-\infty}$ 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*

The AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of the test tablet and reference 1 (Istin, United Kingdom) were tested for bioequivalence. Reference 2 (Norvasc, Pfizer, Switzerland) is not registered in the EU, and was therefore not assessed. 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 Amlodipine 10 mg ratiopharm tablet and the British reference product Istin 10 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation of results
The composition of Amlodipine 5 mg ratiopharm and Amlodipine 10 mg ratiopharm 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.

Product information

SPC
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.

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

Amlodipine 5 mg ratiopharm and Amlodipine 10 mg ratiopharm 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 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 SPC was adapted (to agreed CSP) by means of a post approval variation (NL/H/881/001-002/II/013).

The Board followed the advice of the assessors. Amlodipine 5 mg ratiopharm and Amlodipine 10 mg ratiopharm tablets are authorised in the Netherlands on 9 December 2005. The member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Amlodipine 5 mg ratiopharm and Amlodipine 10 mg ratiopharm 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 22 December 2006 till 22 December 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: 22 December 2011.

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

<u>Quality – Active substance</u>
- The MAH committed to monitor one batch per year.
- The MAH committed to continue the stability study up to 5 years.

<u>Quality – Medicinal product</u>
- The MAH committed to re-evaluate the specification for total impurities at the end of shelf life, and to tighten this if possible.
- The MAH committed to perform a photostability study and to re-evaluate the storage labeling based upon the results.

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
The MAH committed to perform a photostability study and to re-evaluate the storage labelling based upon these results. The storage conditions are changed to "*Store in the original package in order to protect from light*".	NL/H/881/ 01-02/MR	Post-approval commitment	NA	NA	Approval	N
Change in the qualitative and/or quantitative composition of the immediate packaging material. All other pharmaceutical forms.	NL/H/881/ 001-002/ IB/001	IB	11-2-2008	12-3-2008	Approval	N
Change to in-process tests or limits applied during the manufacture of the product. Addition of new tests and limits.	NL/H/881/ 001-002/ IB/003	IB	2-7-2008	1-8-2008	Approval	N
Change in batch size of the finished product. Other situations.	NL/H/881/ 001/IB/004	IB	2-7-2008	16-7-2008	Approval	N
Change in batch size of the finished product. Up to 10-fold compared to the original batch size appoved at the grant of the marketing authorisation.	NL/H/881/ 002/IA/005	IA	2-7-2008	16-7-2008	Approval	N
Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marketing. The imprint "*mp*" is erased from each tablet.	NL/H/881/ 001-002/ IA/006	IA	2-7-2008	16-7-2008	Approval	N
Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass. Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets.	NL/H/881/ 001-002/ IB/007	IB	2-7-2008	1-8-2008	Approval	N
Change in test procedure of the finished product. Minor change to an approved test procedure.	NL/H/881/ 001-002/ IA/008	IA	2-7-2008	16-7-2008	Approval	N
Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).	NL/H/881/ 001-002/ IA/009	IA	2-7-2008	16-7-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/881/ 001-002/ IA/010	IA	2-7-2008	16-7-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/881/ 001-002/ IA/011	IA	3-7-2008	16-7-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. All other manufacturing operations except batch release.	NL/H/881/ 001-002/ IB/012	IB	27-10-2008	26-11-2008	Approval	N
Adaptation of SmPC/PIL to agreed CSP.	NL/H/881/ 001-002/ II/013	II	31-8-2009	20-1-2010	Approval	N

Update of finished product specifications, reference standards and stability data. Addition of storage advise.	NL/H/881/ 001-002/ II/014	II	31-8-2009	23-12-2009	Approval	N