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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Amlodipine Heumann 5 mg, tablets
Amlodipine Heumann 10 mg, tablets

Heumann Pharma GmbH & Co. Generica KG, Germany

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/776/01-02/MR
Registration number in the Netherlands: RVG 31487, 31488

3 July 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:	21 June 2005
Concerned Member States:	Mutual recognition procedure with DE and 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 Amlodipine Heumann 5 mg and 10 mg tablets, from Heumann Pharma GmbH & Co. Generica KG. The date of authorisation was on 21 June 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 cells. The mechanism of the antihypertensive action is due to the direct spasmolytic effect on vascular smooth muscle cells. The precise mechanism by which amlodipine relieves angina pectoris has not been fully determined.

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.). 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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph

in the Ph.Eur with in-house specifications for particle size and residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

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, 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 is stable for 36 months without special storage conditions. 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
Amlodipine Heumann 5 mg tablets contain as active substance 7 mg of amlodipine besilate, corresponding to 5 mg of amlodipine base, and are white round tablets.
Amlodipine Heumann 10 mg tablets contain as active substance 14 mg of amlodipine besilate, corresponding to 10 mg of amlodipine base, and are white round tablets with a break score on both sides.
The composition of the tablets is based on drug substance granules (10 mg), and drug substance granules + placebo granules (5 mg), rendering the same tablet weight.

The tablets are packed in PVC/PVDC-alu blisters or in HDPE containers.

The well known excipients are: povidone K 30, microcrystalline cellulose (E460), calcium hydrogen phosphate, anhydrous (E341), crospovidone, and 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 3 pilot-scale batches in accordance with the relevant European guidelines. The MAH committed to submit post-approval validation data on production-scale batches for both strengths when results are available.

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, identity of drug substance, water content, average mass, uniformity of mass, hardness, dissolution, related substances, microbiological quality and assay. 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 from 3 pilot-scale batches of 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 as soon as the batches are available.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches of each strength in accordance with applicable European guidelines demonstrating the stability of the product over 24 months in PVC/PVDC-aluminium blister or HDPE bottles. In view of the sensitivity for humidity and the guideline on declaration of storage conditions of the tablets the labelled storage conditions are for the PVC/PVDC-aluminium blister: “Do not store above 25C°C. Store in the original package in order to protect from moisture.”, and for the HDPE bottles “Do not store above 25°C. Keep the bottle tightly closed in order to protect from moisture.
The MAH committed that stability studies on the first commercial batches will be undertaken post granting of marketing authorisation and that results will be submitted when available.

In-use stability data on the product have been provided for 3 batches of the 5 mg strength demonstrating the stability of the product over 3 months when stored in a HDPE bottle. In general not more than 3 months supply of medicines is supplied by health-system pharmacists; in view of this the 3 months in-use stability data is adequate.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

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 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.

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 Amlodipine Heumann 10 mg tablet 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.

A single-dose, randomised, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 24 healthy male subjects (including 2 spare subjects), aged 18-35 years with a wash-out period of 20 days. Each subject received daily a single dose (10 mg) of one of the 2 amlodipine besilate formulations. The tablet was orally administered with 240 ml water after an overnight fast. Blood samples were collected at pre-dose and at 1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 24, 30, 36, 48, 72, 96, 120, 168, 216, and 240 hours after administration. Two subjects were withdrawn from the study, because of not showing up. Twenty-four subjects were eligible for pharmacokinetic analysis. The bioavailability of the test, Amlodipine Heumann 10 mg tablet was compared to the British reference product Istin 10 mg tablet, Pfizer.

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} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng.ml	t_{max} h	$t_{1/2}$ h
Test	246 ± 98	270 ± 102	4.3 ± 1.0	9.0 (5-10)	47 ± 16
Reference	237 ± 84	263 ± 87	4.3 ± 0.82	8.5 (5-13)	45 ± 10
***Ratio (90% CI)**	1.03 (0.98-1.08)	1.02 (0.97-1.06)	1.00 (0.95-1.04)	--	--
CV (%)	9.7 %	9.3 %	9.1 %	--	--

$AUC_{0-\infty}$ 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. Therefore, 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 $AUC_{0-\infty}$, AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. The other pharmacokinetic variables were comparable between both products. Based on the pharmacokinetic parameters of amlodipine besilate under fasted conditions, it can be concluded that test Amlodipine Heumann 10 mg tablet and the reference product Istin 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 formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The 5 and 10 mg tablets have the same qualitative composition, a similar ratio between the amounts of excipients, and similar in vitro dissolution profiles. The 5 mg tablet contains less than 5% active ingredient of the tablet weight. 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 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.

Readability test

The package leaflet has been evaluated via an 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 Heumann® 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 Amlodipine Heumann 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 concerned member states was reached during a written procedure.

The first PSUR will cover a 3 year period starting from 8 September 2006 till 8 September 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: 8 September 2011.

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

Quality

- The MAH committed to submit post-approval validation data on production scale batches for both strengths when results are available.
- The MAH committed to submit production scale batch analysis results for 3 batches per strength as soon as the batches are available.
- The MAH committed that stability studies on the first commercial batches will be undertaken post granting of marketing authorisation and that results will be submitted when available.

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