COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Diozart 5 mg/160 mg and 10 mg/160 mg film-coated tablets

(amlodipine besilate/valsartan)

NL License RVG 122444 & 122445

Date: 15 December 2020

This module reflects the scientific discussion for the approval of Diozart 5 mg/160 mg and 10 mg/160 mg film-coated tablets. The procedure was finalised at 12 May 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Diozart 5 mg/160 mg and 10 mg/160 mg film-coated tablets, from Maddox Pharma Swiss B.V.

The product is indicated for the treatment of essential hypertension in adults.

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

This national procedure concerns a generic application claiming essential similarity with the innovator products Exforge 5 mg/160 mg and 10 mg/160 mg film-coated tablets which have been registered in the EEA by Novartis Europharma since 17 January 2007 via a centralised procedure (EU/1/06/370).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Diozart 5 mg/160 mg filmcoated tablets are yellow, oval shaped, film-coated tablets, debossed with “2” on one side and “LD” on the other side. Each tablet contains 5 mg amlodipine (as amlodipine besilate) and 160 mg valsartan.
Diozart 10 mg/160 mg filmcoated tablets are white, oval shaped, film-coated tablets, debossed with “3” on one side and “LD” on the other side. Each tablet contains 10 mg amlodipine (as amlodipine besilate) and 160 mg valsartan.

The film-coated tablets are packed in PVC/PVDC blisters with aluminium foil.

The excipients are:
Tablet core – microcrystalline cellulose, povidone K30, croscarmellose sodium, magnesium stearate and talc
Tablet coating – hypromellose, titanium dioxide (E171), yellow iron oxide (E172; only the 5 mg/160 mg strength) and macrogol.

The strengths are pseudo-dose proportional with respect to the amlodipine content. The difference in amlodipine is compensated by addition of filler (cellulose, microcrystalline).

II.2 Drug Substances

The active substances are amlodipine besilate and valsartan, both established active substances described in the European Pharmacopoeia (Ph.Eur.). Both active substances have anti-hypertensive effects, and the combination of the two leads to synergistic effects.

The CEP procedure is used for both active substances. 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 suitability 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 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.

Amlodipine besilate
Amlodipine besilate is a white or almost white powder, slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and slightly soluble in 2-propanol. It is classified as a BSC Class III compound. Amlodipine besilate is not hygroscopic and no solid-state polymorphism of the compound is described in the literature.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification in line with the CEP is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Valsartan
Valsartan is a white or almost white powder, freely soluble in methanol and ethanol, soluble in acetonitrile, sparingly soluble in ethyl acetate, slightly soluble in dichloromethane, and practically insoluble in water. It is classified as a BSC Class II compound. Valsartan is slightly hygroscopic and numerous polymorphic forms are found. However, the substance used for the manufacturing of the drug product is essentially amorphous.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification in line with the CEP is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three full-scale batches.

Stability of drug substance

The active substance is stable for 4 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. A bioequivalence study has been performed using the 10 mg/160 mg strength. The dissolution profiles of the test and reference product were found to be similar at all three pH levels tested (0.1M HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8), except for amlodipine at pH 4.5. However, due to the similarity demonstrated in the bioequivalence study, this is not raised as an issue. A biowaiver has been requested for the lowest 5 mg/160 mg strength on the basis of the successful ”fasting” bioequivalence study conducted on the 10 mg/160 mg strength, the common composition and manufacturing process, and the comparable in vitro dissolution of both test product strengths in three different release media.

Manufacturing process

The manufacturing process is a simple wet granulation followed by compression and film-coating of the tablet cores; it is considered as standard process for the 10/160 mg strength. The amlodipine content in the 5/160 mg strength is below 2% and the process is considered as non-standard. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two to three batches of each strength at both manufacturing facilities in accordance with the relevant European guidelines.

Control of excipients

All excipients are commonly used in medicinal products and comply with their respective monographs in the Ph.Eur., except for Opadry White (03B28796) and Opadry yellow (03B220017). The specifications for Opadry white and yellow coating are included and all components comply with the Ph.Eur., except for Iron oxide yellow (E172) in Opadry yellow, which complies with United States Pharmacopeia/National Formulary. No further validation is required and the specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average tablet mass, dissolution, related substances, assay, uniformity of dosage units and microbiological quality. 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 six batches of each proposed strength (three from each production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 11 batches (three to four of each strength) batches stored at 30°C/70% RH (up to 24 months) and 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. A photostability study was conducted according to ICHQ1B and the drug product did not show signs of degradation after exposure to light. On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are: 'Store below 30' and 'Store in the original package to protect from moisture'.

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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Diozart has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Diozart is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Exforge which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which

is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agrees that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amlodipine besilate and valsartan are well-known active substances with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Diozart 5 mg/160 mg and 10 mg/160 mg film-coated tablets (Maddox Pharma Swiss B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Exforge 5 mg/80 mg and 10 mg/160 mg film-coated tablets (Novartis Europharm Ltd., the United Kingdom).

The choice of the reference product in the bioequivalence studies is accepted, as Exforge has been registered trough a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

For the other strength of the drug product (5 mg/160 mg) a biowaiver has been requested, based on the requirements as set in the guideline on bioequivalence. The lower strength) is manufactured by the same manufacturing process and has the same qualitative composition. The 5/160 mg strength is not exactly quantitatively proportional/identical compared to the 10/160 mg strength, as the amount of amlodipine differs. the amount of amlodipine is less than 5% of the tablets core weight and the amount of a filler is changed to account for the change in amount of amlodipine. Comparative dissolution was presented between the requested strength using three different buffers. The results showed comparable dissolution. All requirements have been fulfilled and the biowaiver has been granted.

Bioequivalence study

Design

An open-label, single-dose, randomised, three-period crossover, three-sequence, two-treatment, single dose bioequivalence study was carried out under fasted conditions in 78 healthy male subjects, aged 18-44 years. Each subject received a single dose (10 mg amlodipine and 160 mg valsartan) of one of the 2 formulations. The tablet was orally administered with 240 ml water after an overnight fast for at least 10 hours. There were 3 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9 9.5, 10, 11, 12, 16, 24, 36, 48 and 72 hours post dosing after administration of the products.

The design of the study is acceptable. The sampling frequency, as well as duration seems to be adequate to characterise the concentration time profiles of both amlodipine and valsartan. The washout is of sufficient duration

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Due to 6 drop-outs (serious adverse event (1), adverse event (2), not reporting for the second period (3), 72 subjects were dosed in the second period. There were 7 drop-outs before the third period (adverse event (3), positive alcohol test (1), not reporting for the third period (3)). Thus, 65 subjects were dosed in the third period, completed the study and 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=65	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} h**
Test	299 ± 65	7.41 ± 1.4	8.00 (4.50, 12.00)
Reference 1	300 ± 67	7.33 ± 1.4	8.50 (3.50, 12.00)
Reference 2	297 ± 68	7.35 ± 1.3	7.50 (4.50, 12.00)
***Ratio (90% CI)**	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.04)	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of valsartan under fasted conditions.

Treatment N=65	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	34.3 ± 13.3	34.8 ± 13.3	5.69 ± 2.4	3.50 (1.50, 6.50)
Reference 1	33.6 ± 14.6	34.1 ± 14.7	5.52 ± 2.2	3.25 (1.50, 4.50)
Reference 2	35.2 ± 14.7	35.8 ± 14.8	5.61 ± 2.0)	3.75 (1.50, 5.00)
***Ratio (90% CI)**	1.02 (0.97 to 1.08)	--	1.03 (0.97 to 1.10)	--

$AUC_{0-\infty}$	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
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Diozart is considered bioequivalent with Exforge.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Diozart.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	- Hyperkalaemia - Hypotension - Fetotoxicity (with use in 2nd or 3rd trimester of pregnancy) - Decreased renal function
Important potential risks	- Teratogenicity (with use during 1st trimester of pregnancy)

Missing information	- Use during breast feeding

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Exforge. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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: a pilot test with three participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Diozart 5 mg/160 mg and 10 mg/160 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Exforge 5 mg/80 mg and 10 mg/160 mg film-coated tablets. Exforge 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.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Diozart with the reference product, and has therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 12 May 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse