COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amlodipine/Valsartan/HCT Sandoz 5 mg/160 mg/12.5 mg, film-coated tablets
Amlodipine/Valsartan/HCT Sandoz 10 mg/160 mg/12.5 mg, film-coated tablets
Amlodipine/Valsartan/HCT Sandoz 5 mg/160 mg/25 mg, film-coated tablets
Amlodipine/Valsartan/HCT Sandoz 10 mg/160 mg/25 mg, film-coated tablets
Amlodipine/Valsartan/HCT Sandoz 10 mg/320 mg/25 mg, film-coated tablets

(amlodipine besilate/valsartan/hydrochlorothiazide)

NL/H/4280/001-005/DC

Date: 15 August 2019

This module reflects the scientific discussion for the approval of Amlodipine/Valsartan/HCT Sandoz, film-coated tablets. The procedure was finalised at 1 May 2019. 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
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 Member States have granted a marketing authorisation for Amlodipine/Valsartan/HCT Sandoz 5 mg/160 mg/12.5 mg, 10 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/25 mg and 10 mg/320 mg/25 mg, film-coated tablets, from Sandoz B.V.

The product is indicated for the treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Exforge HCT 5 mg/160 mg/12.5 mg, 10 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/25 mg and 10 mg/320 mg/25 mg film-coated tablets which has been registered in the EEA by Novartis Europharm Limited since 16 October 2009 through a centralised procedure (EU/1/09/569).

The concerned member states (CMS) involved in this procedure were Austria and Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

- Amlodipine/Valsartan/HCT Sandoz 5 mg/160 mg/12.5 mg is a white, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with “NVR” on one side and “VCL” on the other side. Each film-coated tablet contains 5 mg of amlodipine (as amlodipine besilate), 160 mg of valsartan and 12.5 mg of hydrochlorothiazide.
- Amlodipine/Valsartan/HCT Sandoz 10 mg/160 mg/12.5 mg is a pale yellow, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with “NVR” on one side and “VDL” on the other side. Each film-coated tablet contains 10 mg of amlodipine (as amlodipine besilate), 160 mg of valsartan and 12.5 mg of hydrochlorothiazide.
- Amlodipine/Valsartan/HCT Sandoz 5 mg/160 mg/25 mg is a yellow, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with “NVR” on one side and “VEL” on the other side. Each film-coated tablet contains 5 mg of amlodipine (as amlodipine besilate), 160 mg of valsartan and 25 mg of hydrochlorothiazide.

- Amlodipine/Valsartan/HCT Sandoz 10 mg/160 mg/25 mg is a brown-yellow, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with "NVR" on one side and "VHL" on the other side. Each film-coated tablet contains 10 mg of amlodipine (as amlodipine besilate), 160 mg of valsartan and 25 mg of hydrochlorothiazide.
- Amlodipine/Valsartan/HCT Sandoz 10 mg/320 mg/25 mg is a brown-yellow, ovaloid, biconvex film-coated tablet with bevelled edge, debossed with "NVR" on one side and "VFL" on the other side. Each film-coated tablet contains 10 mg of amlodipine (as amlodipine besilate), 320 mg of valsartan and 25 mg of hydrochlorothiazide.

The film-coated tablets are packed in PVC/PVDC-Alu blisters or PVC/PVDC-Alu perforated unit dose blisters.

The excipients are:
Tablet core - cellulose microcrystalline, crospovidone (type A), colloidal anhydrous silica and magnesium stearate
Tablet coating – hypromellose (type 2910), macrogol 4000, talc, titanium dioxide (E171) [only the 5 mg/160 mg/12.5 mg, 10 mg/160 mg/12.5 mg and 5 mg/160 mg/25 mg strengths], iron oxide yellow (E172) [only the 10 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/25 mg and 10 mg/320 mg/25 mg strengths] and iron oxide red (E172) [only the 10 mg/160 mg/12.5 mg strength]

II.2 Drug Substances

The active substances are amlodipine besilate, valsartan and hydrochlorothiazide. These three active substances are established active substances and all described in the European Pharmacopoeia (Ph.Eur.).

The CEP procedure is used for the 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 fine powder. It is slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol and slightly soluble in 2-propanol. The racemic mixture of R and S isomers is used. There is no solid-state polymorphism of amlodipine besilate described in the literature.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

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 as stated on the CEPs. The satisfactory quality is generally ensured through the CEP. However, in addition to these tests the MAH included additional tests in his drug substance specifications. These tests include tests for particle size, clarity and colour of solution, identification, alkyl benzene sulphonates, residual solvents, heavy metals and microbial limit test. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance

Assessment of the re-test period was part of granting the CEPs and has been granted by the EDQM.

Valsartan

Valsartan is a white to practically white, fine powder. It is melting at 105-110 °C with decomposition. Its solubility in water is 0.18 mg/ml and in 0.1N HCl 0.084 mg/ml. There is one chiral centre in the valine moiety of the molecule but essentially the pure (S)-enantiomer is used. Valsartan is poorly crystalline. No solid-state polymorphism is known to exist.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included, except for the last step, micronization. Description of micronization procedure is included in the dossier.

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 as stated on the CEP. In addition, the MAH included additional tests in the specification, for example absorbance, particle size distribution, identity and clarity of solution in methanol. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Hydrochlorothiazide

Hydrochlorothiazide is a white to almost white powder, melting at 263-275°C. It is very slightly soluble in water and in 0.1N HCl. It does not possess an asymmetric centre and is therefore non-chiral. It exists in only one, optically inactive form. Hydrochlorothiazide does not absorb water at relative humidity below 97% at 23°C. Polymorphism is known to exist for hydrochlorothiazide.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

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. However, in addition to these tests the MAH applies in-house specifications. These include tests for appearance, clarity and absorbance, particle size, consumption, identity, assay and related substances, residual solvents, organic volatile impurities, loss on drying, sulphated ash, heavy metals and microbial limit test. Batch analytical data demonstrating compliance with this specification have been provided for two 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.

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 aim of formulation development was to develop an immediate release tablet combination product that would be bioequivalent to the marketed medicinal products containing each drug substance individually.
During the development phase, the MAH evaluated adequately the compatibility of the three active substances by intermixing followed by storing. The excipients selected for the drug product are standard ingredients in tablet formulations, and meet the Ph. Eur. requirements. The concentration of each excipient is within the usual range of application. The compatibility of the drug substances with the excipients has been investigated during the development of the film-coated tablets; stability has been demonstrated.
The tablet cores are coated with a non-functional coating to provide a distinctive tablet colour to aid in the identification of assorted tablet strengths and to mask the slightly bitter taste of the valsartan drug substance.
No bioequivalence study has been performed. Amlodipine/Valsartan/HCT Sandoz is manufactured at the same site by the same company using the same procedures as the reference product Exforge HCT. Amlodipine and hydrochlorothiazide are also sourced from the same sites and are manufactured in the same way as for the reference product. The drug substance valsartan has the same specifications and the particle size (distribution) as used in the reference product. Based on the fact that drug product manufactured with either drug substance manufacturer of valsartan show similar dissolution profiles, no bioequivalence study is needed.
Overall, the pharmaceutical development is considered acceptable.

Manufacturing process

The manufacturing process is a standard dry granulation process including pre-blending, roller compaction, screening, final blend, compression and film coating. The process has been validated according to relevant European guidelines and demonstrated to be robust and to produce a finished product of the desired quality within the agreed finished product specification. A holding time of 12 months has been established for the bulk film coated tablets, before packaging. Adequate stability studies justify this holding time and the expiry date will be calculated in line with the applicable regulations. Process validation data on the product have been presented for a sufficient amount of batches in accordance with the relevant European guidelines.

Control of excipients

Except for the iron oxides, the excipients and individual components of the film-coating materials are of Ph. Eur. quality. The red and yellow iron oxides are in compliance with the United States Pharmacopeia and National Formulary and EU regulation 95/94/EC. These 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 appearance, identification, identification of colourants, dissolution, water, degradation products, assay, uniformity of dosage units and microbial limit tests. 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 the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three pilot scale batches of each strength stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Supplemental batches were later included. The batches were stored in accordance with applicable European guidelines. In addition, a photostability study has been carried out with each tablet strength, in which it was shown that the tablets are sensitive to light. However, it has been demonstrated that the proposed blister packaging adequately protects the finished product from light. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are ‘Do not store above 30°C. Store in the original package in order 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 member states consider that Amlodipine/Valsartan/HCT Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitments were made:

- The MAH shall complete, within the stated timeframe, the agreed measures as result of the Article 31 Referral for Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (EMEA/H//A-31/1471)

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Amlodipine/Valsartan/HCT Sandoz 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amlodipine besilate, valsartan and hydrochlorothiazide 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 member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

No bioequivalence study has been performed. Amlodipine/Valsartan/HCT Sandoz is manufactured at the same site by the same company using the same procedures as the

reference product Exforge HCT. Amlodipine and hydrochlorothiazide are also sourced from the same sites and are manufactured in the same way as for the reference product. The drug substance valsartan has the same specifications and the particle size (distribution) as used in the reference product. Based on the fact that drug product manufactured with either drug substance manufacturer of valsartan show similar dissolution profiles, no bioequivalence study is needed.

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 Amlodipine/Valsartan/HCT Sandoz.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Hypokalaemia - Foetotoxicity (with use in second and third trimester of pregnancy
Important potential risks	- Teratogenicity (with use during first trimester of pregnancy)
Missing information	- Use during breastfeeding

The member states agreed 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. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the innovator product Exforge for content and to multiple Sandoz products to assure readability. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Amlodipine/Valsartan/HCT Sandoz 5 mg/160 mg/12.5 mg, 10 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/25 mg and 10 mg/320 mg/25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Exforge HCT 5 mg/160 mg/12.5 mg, 10 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/25 mg and 10 mg/320 mg/25 mg film-coated tablets. Exforge is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are manufactured at the same site by the same company using the same procedure, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Amlodipine/Valsartan/HCT Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 May 2019.

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
NL/H/4280 /IA/002/G	Replacement or addition of a manufacturer responsible for importation and/or batch release; not including batch control /testing	-	03-08-2019	Approved	-
NL/H/4280 /IB/001/G	- Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier) - Changes to quality control testing arrangements for the active substance- replacement or addition of a site where batch control/testing takes place - Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance; other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate - New certificate from a new manufacturer (replacement or addition)	-	09-08-2019	Approved	-