COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dipperam/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, 10 mg/320 mg/25 mg, film-coated tablets

(amlodipine besilate/valsartan/hydrochlorothiazide)

NL/H/4290/001-005/DC

Date: 4 September 2019

This module reflects the scientific discussion for the approval of Dipperam/HCT Sandoz. 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

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
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 Dipperam/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, 10 mg/320 mg/25 mg, film-coated tablets from Sandoz B.V.

The product is indicated for 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 (EMEA/H/C/001068) which has been registered in EEA by Novartis Europharm Limited since 15 October 2009. The manufacturers for the drug substances and the manufacturer of the drug product are the same using the same procedures as those for the reference product, except for the manufacturer of valsartan. Valsartan is sourced from a different manufacturer than the reference product. The drug products are manufactured at the same site by the same company using the same procedures as the reference product (Exforge HCT).

The concerned member states (CMS) involved in this procedure were Bulgaria (except 5 mg/160 mg/25 mg and 10 mg/320 mg/25 mg strength), Estonia, Croatia, Latvia, Poland, Romania (except 10 mg/320 mg/25 mg strength), Slovakia (except 10 mg/320 mg/25 mg strength).

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

II. QUALITY ASPECTS

II.1 Introduction

Dipperam/HCT Sandoz is an ovaloid, biconvex film-coated tablet with bevelled edge:
5 mg/160 mg/12.5 mg - white tablets debossed “NVR” on one side and “VCL” on the other side
10 mg/160 mg/12.5 mg - pale yellow tablets debossed “NVR” on one side and “VDL” on the other side.
5 mg/160 mg/25 mg - yellow tablets debossed “NVR” on one side and “VEL” on the other side.

10 mg/160 mg/25 mg - brown-yellow tablets debossed “NVR” on one side and “VHL” on the other side.
10 mg/320 mg/25 mg - brown-yellow tablets debossed “NVR” on one side and “VFL” on the other side.

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

The excipients are:
Tablet core - cellulose microcrystalline, crospovidone (type A), colloidal anhydrous silica, magnesium stearate
Coating - hypromellose (type 2910), titanium dioxide (E171) (except 10 mg/160 mg/25 mg, 10 mg/320 mg/25 mg), macrogol 4000, talc, iron oxide yellow (E172) (10 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg, 10 mg/160 mg/25 mg, 10 mg/320 mg/25 mg), iron oxide red (E172) (10 mg/160 mg/12.5 mg)

The 5 mg/160 mg/12.5 mg and 10 mg/320 mg/25 mg tablet strengths are weight and dose proportional. The 5 mg /160 mg/25 mg, 10 mg/160 mg/12.5 mg and 10 mg/160 mg/25 mg tablet strengths are compositionally similar, only the amounts of amlodipine and HCT are changed and microcrystalline cellulose is adjusted accordingly to keep the total tablet core weight at 400 mg.

II.2 Drug Substances

Amlodipine besilate
The active substance is amlodipine besilate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is well known and has been adequately characterised. It is a white or almost white powder. The racemic mixture of R and S isomers is used. It is slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol and slightly soluble in 2-propanol. There is no solid-state polymorphism of amlodipine besilate described in the literature.

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 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.

<u>Manufacturing process</u>
CEP’s have been submitted by two manufacturers; 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. The MAH included additional 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 three batches for each manufacturer.

Stability of drug substance

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

Valsartan

The active substance is valsartan, an established active substance described in the Ph.Eur. Valsartan is a white to practically white, fine powder. 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. The assigned (S)-configuration is defined from the synthetic origin ((L)-valine). The compound is optically active. X-ray powder analysis rated valsartan samples as poorly crystalline. No solid-state polymorphism is known to exist for valsartan. The CEP procedure is used for the active substance.

Manufacturing process

During the procedure, the MAH changed the manufacturer of valsartan. A CEP has been submitted by the current manufacturer; therefore no details on the manufacturing process have been included. The new manufacturer of the drug substance valsartan is accepted.

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. The MAH included additional tests for 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 three years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

HCT

The active substance is hydrochlorothiazide (HCT), an established active substance described in the Ph.Eur. HCT is a white to almost white powder. 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 one, optically inactive form. HCT does not absorb water at relative humidity below 97% at 23°C. Polymorphism is known to exist for HCT.

Manufacturing process

CEP's have been submitted by two manufacturers; 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. The MAH included additional tests for appearance, clarity and absorbance of the solution in dimethyl sulfoxide, particle size, consumption of NaOH and HCl, 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 three batches of each manufacturer.

Stability of drug substance

The active substance is stable for five 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 MAH adequately evaluated the compatibility of the active substances by intermixing followed by storing. The choice and concentration of each excipient is justified. The compatibility of the drug substances with the excipients has been investigated during the development of the film-coated tablets. Stability has also been sufficiently demonstrated.

The development of the drug product was based upon the formulation and manufacturing process of the already authorized Exforge HCT film-coated tablets. Based on the fact that drug products show similar dissolution profiles, it is considered that for the current application no bioequivalence study is needed.

Comparative dissolution data also confirm that the product is not changed by using valsartan sourced from the new manufacturer compared to using valsartan sourced from the initial manufacturer: for all substances the dissolution profiles are similar and more than 85% is dissolved in 15 minutes.

Manufacturing process

The manufacturing process is a standard dry granulation process including pre-blending, roller compaction, screening, final blend, compression and film coating. The manufacturing process has been demonstrated to be robust and to produce a finished product of the desired quality within the agreed finished product specification. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for sufficient batches in accordance with the relevant European guidelines.

Control of excipients

The excipients selected for the drug product are standard ingredients in tablet formulations, and meet the Ph.Eur. requirements. 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 three batches of each manufacturing site have been provided, demonstrating compliance with the specification.

Stability of drug product

Three pilot scale batches of each strength have been stored at long term conditions (25°C/60% RH), at intermediate conditions (30°C/65% RH) and at accelerated conditions (40°C/75% RH) in the proposed packaging. Supplemental batches were later included. Results of up to 36 months at long term conditions, 12 months at intermediate conditions and six months at accelerated conditions are available. At long term and intermediate conditions no significant changes were seen during storage for 36 months. At accelerated conditions no significant changes in assay values, degradation products nor in dissolution were observed within the first three months. In the packaging, however, significant water absorption was observed as the packaging offers the least resistance to moisture permeation. As the proposed tablets are known to be hygroscopic, the film-coating can crack due to tablet expansion.

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. 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 two 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 Dipperam/HCT Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

The following post-approval commitments were made:

- To submit updated parts of the valsartan dossier via an appropriate variation within two weeks after the end of the application procedure.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dipperam/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 HCT 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 HCT 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

Biowaiver

The drug product is manufactured at the same site by the same manufacturer 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 (Exforge HCT). The drug substance valsartan has the same specifications and particle size distribution as used in the reference product. There is no discernible difference between the reference product and Dipperam/HCT Sandoz. Based on the fact that drug products show similar dissolution profiles, it is considered that for the current application no bioequivalence study is needed. A waiver for the bioequivalence study is acceptable.

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 Dipperam/HCT Sandoz.

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

Important identified risks	• Decreased renal function • Hyperkalaemia • Foetotoxicity (with use during the 2nd and 3rd trimester of pregnancy)
Important potential risks	• Teratogenicity (with use during the 1st trimester of pregnancy)
Missing information	• Use during breast feeding

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 HCT. No new clinical studies were conducted. The MAH demonstrated 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

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 content of the PL of Exforge HCT and the lay-out of several other PLs (EMEA/H/C/1181-1183, DE/H/1354-1356, NL/H/1170-1172, DK/H/300/01-02/II/18, SE/357,359,361/01-04/R01 and UK/H/1374-1376/01-02/DC). 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

Dipperam/HCT Sandoz has a proven chemical-pharmaceutical quality and is a generic form of Exforge HCT. Exforge HCT is a well-known medicinal product with an established favourable efficacy and safety profile.

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.

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 Dipperam/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/4290 /IA/002/G	Addition of batch release site	--	8-7-2019	Approval	--
NL/H/4290 /IB/001/G	The manufacturing site, responsible for milling of valsartan was deleted. The MAH would like to delete the batch control testing site, responsible for QC testing of valsartan. The MAH proposes to introduce new drug substance testing sites. Two new test methods and validation results for testing of NDMA and NDEA as per EMEA-H-A-31-1471 requirement and commitment during DCP NL/H/4279-4280-4290/001-005/DC were introduced. The MAH proposes to introduce a new manufacturer for drug substance valsartan.	--	9-8-2019	Approval	--