COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Amlodipine/Valsartan/HCT STADA 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

(amlodipine besilate/valsartan/hydrochlorothiazide)

NL/H/4220/001-005/DC

Date: 16 September 2019

This module reflects the scientific discussion for the approval of Amlodipine/Valsartan/HCT STADA 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. The procedure was finalised at 18 September 2018. 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 STADA 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 Stada Arzneimittel AG.

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 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, Germany, Spain, Finland and Ireland.

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

Scientific advice

Scientific Advice has been given by both the Dutch authority MEB on 18 September 2015 and the German authority BfArM on 14 July 2015 regarding the choice of bracketing approach for the 5 mg/160 mg/25 mg and 10 mg/160 mg/12.5 mg product strengths.

II. QUALITY ASPECTS

II.1 Introduction

- Amlodipine/Valsartan/HCT STADA 5 mg/160 mg/12.5 mg is a white, oval, biconvex film-coated tablet. 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 STADA 10 mg/160 mg/12.5 mg is a pale yellow, oval, biconvex film-coated tablet. 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 STADA 5 mg/160 mg/25 mg is a yellow, oval, biconvex film-coated tablet. Each film-coated tablet contains 5 mg of amlodipine (as amlodipine besilate), 160 mg of valsartan and 25 mg of hydrochlorothiazide.
- Amlodipine/Valsartan/HCT STADA 10 mg/160 mg/25 mg is a brown-yellow, oval, biconvex film-coated tablet. Each film-coated tablet contains 10 mg of amlodipine (as amlodipine besilate), 160 mg of valsartan and 25 mg of hydrochlorothiazide.
- Amlodipine/Valsartan/HCT STADA 10 mg/320 mg/25 mg is a brown-yellow, oval, biconvex film-coated tablet. 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/TE/PVdC/Al blisters.

The excipients are:
Tablet core - cellulose microcrystalline (E460), Povidone K30 (E1201), pregelatinised starch, crospovidone (E1202), colloidal anhydrous silica (E551), sodium starch glycolate (type A; E468), magnesium stearate (E470b)
Tablet coating:

5 mg/160 mg/12.5 mg	hypromellose 2910 (E464), macrogol 6000 (E1521) and titanium dioxide (E171)
10 mg/160 mg/12.5 mg	hypromellose 2910 (E464), macrogol 8000 (E1521), titanium dioxide (E171), talc (E553b) and iron oxide yellow (E172)
5 mg/160 mg/25 mg	hypromellose 2910 (E464), macrogol 8000 (E1521), titanium dioxide (E171), talc (E553b), iron oxide yellow (E172) and iron oxide black (E172)
10 mg/160 mg/25 mg	hypromellose 2910 (E464), macrogol 4000 (E1521), titanium dioxide (E171), iron oxide yellow (E172) and FD&C Yellow#6 Aluminium Lake (E110)
10 mg/320 mg/25 mg	hypromellose 2910 (E464), macrogol 4000 (E1521), titanium dioxide (E171), iron oxide yellow (E172) and FD&C Yellow#6 Aluminium Lake (E110)

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. 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. In addition, the MAH has included a particle size limit for the drug substance. Furthermore, a test for microbiological quality is applied for the active substance. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three 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 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. No solid-state polymorphism is known to exist.

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 CEP. In addition, a test for microbiological quality is applied for the active substance. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for six commercial scale batches stored at 25°C/60% RH (48 or 60 months) and 40°C/75% RH (6 months). The active substance is stable for 4 years, when stored under the stated conditions.

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 has 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. and the additional tests and limits as stated on the CEPs. In addition, the MAH has included an acceptable particle size limit for the drug substance. A test for microbiological quality is applied for the active substance. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three 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 choice of excipients is justified and their functions explained. The main focus of the development was to obtain a bioequivalent film-coated tablet with comparable dissolution characteristics as the reference product.
Two bioequivalence studies have been performed: one with the 10 mg/160 mg/25 mg strength and one with the 10 mg/360 mg/25 mg strength. Equivalence of the dissolution profiles of the various tablet strengths with the bio batches has been demonstrated and a biowaiver for these other strengths can be granted.

Manufacturing process
The manufacturing process is a wet granulation process. The active substances are mixed with several of the excipients and are granulated with a mixture of povidone and water.

After drying and milling the other excipients are added and mixed. This final blend is compressed into tablets, which are film-coated. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for one small commercial scale and three production scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients

Except for the film-coating mixtures, the excipients comply with the Ph. Eur. requirements. For the mixtures in-house specifications are defined. 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, identity, average mass, assay, related substances, dissolution, 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 for three commercial scaled batches 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 (up to 24 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 in which it was shown that the tablets are stable when exposed to light. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are 'store below 30°C' and '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 STADA 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 Amlodipine/Valsartan/HCT STADA 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.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Amlodipine/Valsartan/HCT STADA 10 mg/160 mg/25 mg and 10 mg/320 mg/25 mg, film-coated tablets (Stada Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product Exforge 10 mg/160 mg/25 mg and 10 mg/320 mg/25 mg, film-coated tablets (Novartis Europharm Limited, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions with the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH requests a biowaiver for the additional strengths (i.e. 5 mg/160 mg/12.5 mg, 5 mg/160 mg/25 mg and 10 mg/160 mg/12.5 mg). The 10 mg/320 mg/25 mg (biobatch) and 5 mg/160 mg/12.5 mg strengths are fully dose proportional and a waiver could therefore be acceptable. For the 5 mg/160 mg/25 mg and 10 mg/160 mg/12.5 mg strengths a bracketing approach was chosen, for which the 10 mg/320 mg/25 mg (biobatch) and 10 mg/160 mg/25 mg (biobatch) are indicated to represent the extremes, differing most in composition, so that any differences in composition in the remaining strengths are covered by the two conducted studies. This approach was endorsed by scientific advice from the MEB (18 September 2015) and BfArM (14 July 2015).

Bioequivalence studies

Bioequivalence study I - 10 mg/160 mg/25 mg under fasting conditions

Design

A monocentric, single-dose, randomised, three-period, semi-replicative, crossover bioequivalence study was carried out under fasted conditions in 70 healthy male subjects, aged 31.6 ± 9.1 years. Each subject received a single dose (10/160/25 mg) of one of the 2 amlodipine besilate/valsartan/hydrochlorothiazide formulations. The tablet was orally administered with 240 ml water after a fast of at least 10 hours. There were 3 dosing periods, separated by a washout period of 20-21 days.

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

The design of the study is acceptable. A semi-replicate design was chosen due to the expected high intra-individual variance of C_{max} of valsartan of the reference product.

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

11 subjects were screened only and 3 subjects withdrew at their own request before drug administration. A total of 4 subjects dropped out during the study, for the reasons of vomiting (2) and on own request (2). Two drop-outs were replaced whereas two drop-outs were not replaced in accordance with the protocol. Thus, the study was completed by 52 subjects, but 53 were included in the pharmacokinetic analysis as 1 drop-out had available results for both test and reference.

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

Treatment N=53 (test) N=105 (reference)	AUC_{0-t} (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)
Test	233 ± 47.7	6.43 ± 1.25	6.0 (3.0-11)
Reference	242 ± 48.8	6.60 ± 1.25	7.0 (4.0-12)
***Ratio (90% CI)**	0.96 (0.94 - 0.99)	0.97 (0.95 - 1.00)	--

$AUC_{0-\infty}$ 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=53 (test) N=105 (reference)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)
Test	27.1 ± 14.1	28.0 ± 14.6	3.85 ± 1.84	2.5 (1.0 - 5.0)
Reference	27.1 ± 13.2	28.0 ± 13.9	3.85 ± 1.66	3.0 (1.0 - 5.0)
***Ratio (90% CI)**	1.00 (0.92 - 1.08)	--	0.99 (0.90 - 1.09)	--
%CV	26.15 (R)	--	25.91 (R)	--

$AUC_{0-\infty}$ 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 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N=53 (test) N=105 (reference)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)
Test	926 ± 217	968 ± 228	127 ± 31.4	2.0 (0.5- 5.0)
Reference	927 ± 217	970 ± 230	125 ± 31.0	2.0 (1.0 - 5.0)

***Ratio (90% CI)**	1.00 (0.97 - 1.03)	--	1.02 (0.98 - 1.07)	--

$AUC_{0-\infty}$ 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*

Bioequivalence study II - 10 mg/320 mg/25 mg under fasting conditions

Design

A monocentric, single-dose, randomised, three-period, semi-replicative, crossover bioequivalence study was carried out under fasted conditions in 92 healthy male subjects, aged 31.6 ± 9.1 years. Each subject received a single dose (10/320/25 mg) of one of the 2 amlodipine besilate/valsartan/hydrochlorothiazide formulations. The tablet was orally administered with 240 ml water after a fast of at least 10 hours. There were 3 dosing periods, separated by a washout period of 20-24 days.

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

The design of the study is acceptable. A semi-replicate design was chosen due to the expected high intra-individual variance of C_{max} of valsartan of the reference product.

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

33 subjects were screened only. A total of 8 subjects dropped out during the study, for the reasons of vomiting (2), on own request (4), one subject was withdrawn for nephrolithiasis and one due not allowed concomitant medication. Five drop-outs were replaced whereas three drop-outs were not replaced in accordance with the protocol. Thus, 51 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of amlodipine under fasted conditions.

Treatment N=53 (test) N=105 (reference)	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**T_{max} (h)**
Test	229 ± 54.6	6.45 ± 1.45	7.0 (5.0-11)
Reference	225 ± 53.7	6.33 ± 1.54	7.0 (3.0-12)

***Ratio (90% CI)**	1.02 (0.99 - 1.04)	1.02 (1.00 - 1.05)	--

$AUC_{0-\infty}$ 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 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of valsartan under fasted conditions.

Treatment N=53 (test) N=105 (reference)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)
Test	48.2 ± 22.1	50.0 ± 23.0	6.10 ± 2.30	3.0 (1.0 - 7.0)
Reference	50.0 ± 22.0	48.9 ± 23.0	6.03 ± 2.57	3.0 (1.0 - 5.0)
***Ratio (90% CI)**	1.04 (0.97 - 1.11)	--	1.05 (0.97 - 1.13)	--
%CV	25.56 (R)	--	31.99 (R)	--

$AUC_{0-\infty}$ 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 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N=53 (test) N=105 (reference)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)
Test	886 ± 220	931 ± 239	115 ± 27.0	2.0 (1.0 - 4.0)
Reference	903 ± 228	954 ± 250	114 ± 25.5	2.0 (1.0 - 5.0)
***Ratio (90% CI)**	0.99 (0.95 - 1.02)	--	1.01 (0.97 - 1.05)	--

$AUC_{0-\infty}$ 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*

Conclusion on bioequivalence studies

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 Amlodipine/Valsartan/HCT STADA 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 Amlodipine/Valsartan/HCT STADA.

Table 7. 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. 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 followed by two rounds with 10 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

Amlodipine/Valsartan/HCT STADA 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 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.

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 STADA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 September 2018.

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/4220/IB/001/G	Safety, Efficacy, Pharmacovigilance Changes – other variations	Yes	20-12-2018	Approved	-
NL/H/4220/1-5/IA/002	European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.; updated certificate from an already approved manufacturer	No	09-01-2019	Approved	-
NL/H/4220/1-5/IA/003	European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.; New certificate from a new manufacturer (replacement or addition)	No	01-03-2019	Approved	-
NL/H/4220/1-5/IA/004	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan; implementation of wording agreed by the competent authority	No	13-08-2019	Approved	-