LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Amlodipine/Valsartan/Hydroklortiazid DOC (amlodipine, hydrochlorothiazide, valsartan, amlodipine besilate)

SE/H/1750/01,05/DC

This module reflects the scientific discussion for the approval of Amlodipine/Valsartan/Hydroklortiazid DOC. The procedure was finalised on 2020-06-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Amlodipine/Valsartan/Hydroklortiazid DOC, 5 mg/160 mg/12.5 mg, 10 mg/320 mg/25 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, DOC Generici Srl, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and IT as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Exforge HCT, 5 mg/160 mg/12.5 mg, 10 mg/320 mg/25 mg, film-coated tablet authorised in the Union since 2009, with Novartis Europharm Limited as marketing authorisation holder.

The reference product used in the pivotal bioequivalence study (ACT-14088) is Exforge HCT, 10 mg/320 mg/25 mg, film-coated tablet from DE with Novartis Europharm Limited as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted three bioequivalence studies comparing Amlodipine/Valsartan/Hydrochlorothiazide with the reference product Exforge HCT.

Pivotal Fasting Study (ACT-14088)

Methods

This was a single-dose, two-treatment, three-period, three-sequence, single-dose, partially replicate crossover study conducted in 51 healthy volunteers, comparing Amlodipine/Valsartan/Hydrochlorothiazide, 10 mg/320 mg/25 mg, film-coated tablets, with Exforge HCT, 10 mg/320 mg/25 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of amlodipine, valsartan and HCT were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-72} (amlodipine), AUC_{0-t} (valsartan and HCT) and C_{max} (amlodipine, valsartan and HCT). The study was conducted between Oct 14, 2014 and Nov 22, 2014.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1, Table 2 and Table 3 below:

Table 1. Amlodipine pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range).

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (n=47)	**279.96 ± 61.73**	**7.56 ± 1.90**	**8.00 6.00-16.00**
Reference 1st adm (n=48)	**283.02 ± 63.44**	**7.56 ± 1.93**	**8.00 6.00-12.00**
Reference 2nd adm (n=43)	**281.98 ± 54.42**	**7.47 ± 1.66**	**8.00 5.00-12.00**
***Ratio (90% CI)**	**99.52 (97.56-101.52)**	**101.45 (98.60-104.39)**	**-**
AUC_{0-72} area under the plasma concentration-time curve from time 0 to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 2. Valsartan pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (n=47)	**65900 ± 24282**	**9957 ± 3215**	**3.00 1.00-5.00**
Reference 1st adm (n=48)	**61138 ± 29298**	**8820 ± 3770**	**3.50 1.00-5.00**
Reference 2nd adm (n=43)	**64716 ± 28214**	**9512 ± 3726**	**3.50 1.00-6.00**
***Ratio (90% CI)**	**109.48 (102.79-116.61)**	**114.55 (106.09-123.68)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

Table 3. Hydrochlorothiazide pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (n=47)	**986.41 ± 295.77**	**166.15 ± 48.99**	**1.50 1.00-4.00**
Reference 1st adm (n=48)	**990.76 ± 298.23**	**169.63 ± 64.97**	**1.50 1.00-3.50**
Reference 2nd adm (n=43)	**989.94 ± 303.70**	**165.22 ± 50.96**	**2.00 1.00-3.50**
***Ratio (90% CI)**	**101.59 (98.71-104.54)**	**102.67 (98.10-107.46)**	**-**
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 plasma concentration			

**calculated based on ln-transformed data*

One subject, who completed two periods of the study but did only receive the reference product, was included in the original statistical analysis. The statistical analysis was repeated and the results from the statistical analysis after excluding this subject are presented in Table 4, Table 5 and Table 6 below:

Table 4. The BE summary results of analyte amlodipine after excluding the above subject from statistical analysis for Study # ACT-14088

PK Parameter (s)	Test Geometric LSM	N	Reference Geometric LSM	N	Test/Reference Ratio (%)	90% CI (%)	
						Lower	Upper
AUC_{0-72} (ng*h/ml)	273.49	47	274.80	47	99.52	97.56	101.53
C_{max} (ng/ml)	7.33	47	7.23	47	101.46	98.59	104.40

Table 5. The BE summary results of analyte valsartan after excluding the above subject from statistical analysis for Study # ACT-14088

PK Parameter (s)	Test Geometric LSM	N	Reference Geometric LSM	N	Test/Reference Ratio (%)	90% CI (%)	
						Lower	Upper
AUC_{0-t} (ng*h/ml)	62100.47	47	56723.70	47	109.48	102.75	116.65
C_{max} (ng/ml)	9474.13	47	8271.10	47	114.54	106.04	123.73

Table 6. The BE summary results of analyte hydrochlorothiazide after excluding the above subject from statistical analysis for Study # ACT-14088

PK Parameter (s)	Test Geometric LSM	N	Reference Geometric LSM	N	Test/Reference Ratio (%)	90% CI (%)	
						Lower	Upper
AUC_{0-t} (ng*h/ml)	943.77	47	929.01	47	101.59	98.70	104.56
C_{max} (ng/ml)	159.22	47	155.07	47	102.68	98.13	107.45

For AUC and C_{max} of all three substances, the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Pilot Fasting Study (ACT-14087)
This was an open labeled, randomized, single dose, two-way crossover bioequivalence study of fixed dose combination of Amlodipine/Valsartan/Hydrochlorothiazide tablet, 10 mg/320 mg/25 mg in 24 healthy, adult, human subjects under fasting conditions. Overall the results were in accordance with the results from the pivotal study. Bioequivalence was demonstrated for amlodipine and hydrochlorothiazide C_{max} and AUC, valsartan AUC but not for valsartan C_{max}.

Pivotal Fasting Study with 10 mg/160 mg/25 mg strength (BE-1881-17)
This was an open label, randomized, single dose, full replicate crossover bioequivalence study of Amlodipine/Valsartan/Hydrochlorothiazide film-coated tablets, 10 mg/160 mg/25 mg in healthy human, adult subjects under fasting conditions. Bioequivalence was not demonstrated. Therefore, the applicant withdrew the strengths intended to be supported by this study.

Discussion and overall conclusion
The overall design of the pivotal bioequivalence study with 10 mg/320 mg/25 mg strength was in accordance with the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) and the bioanalytical methods were adequately validated.

Thus, based on the submitted bioequivalence study, Amlodipine/Valsartan/Hydrochlorothiazide, 10 mg/320 mg/25 mg, film-coated tablet is considered bioequivalent with Exforge HCT, 10 mg/320 mg/25 mg, film-coated tablet. Absence of studies with the additional strength of 5 mg/160 mg/12.5 mg is acceptable, as all conditions for biowaiver for additional strength according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) are fulfilled and since the pharmacokinetics of amlodipine, valsartan and HCT is linear within the therapeutic dose range.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 the applied product containing Amlodipin/Valsartan/Hydroklortiazid.

Summary of safety concerns	
Important identified risks	- Hypotension - Decreased renal function - Electrolyte abnormalities - Teratogenicity
Important potential risks	
Missing information	

The following RMP has been submitted for SE/H/1750/01,05/DC:
Amlodipine/Valsartan/Hydroklortiazid DOC RMP v 0.2 (2018-05-28)

The table of Summary of safety concerns in the submitted RMP is acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plans are considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet 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 language used for the purpose of user testing the PIL was English.
The results show that the package leaflet 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

The quality of the generic product, Amlodipine/Valsartan/Hydroklortiazid DOC, is found adequate. There are no objections to approval of Amlodipine/Valsartan/Hydroklortiazid DOC, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk ratio is considered positive and Amlodipine/Valsartan/Hydroklortiazid DOC, 5 mg/160 mg/12.5 mg, 10 mg/320 mg/25 mg, film-coated tablet, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

After the referral procedure EMEA/H/A-31/1471 for valsartan the Annex II D for the reference product, Exforge HCT, has been updated with “Obligation to conduct post-authorisation measures”.

For SE/H/1750/01,05/DC most comittments have been fulfilled.
There is however one outstanding condition regarding N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA) that should be fulfilled at the latest 02/04/2021 (during the transitional period after the EC decision taken 02/04/2019):
After the transitional period of 2 years, a limit for NDMA and NDEA of maximum 0.03 ppm should be implemented.

VII. APPROVAL

The decentralised procedure for Amlodipine/Valsartan/Hydroklortiazid DOC, 5 mg/160 mg/12.5 mg, 10 mg/320 mg/25 mg, film-coated tablet, was positively finalised on 2020-06-29.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/1750/01,05/IB/02	The Applicant wishes to submit Type IB B.II.d.1.g variation application for drug product Amlodipine Valsartan HCT 5/160/12.5 mg and 10/320/25 mg: - Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue A specification parameter for testing of NDMA and NDEA for Drug product is added with its corresponding test method and limits, according to EMA recommendations. This change is submitted to fulfil EMA recommendations with regard to the safe and effective use of the medicinal product (herewith enclosed).	No	2021-09-27	Approval	**The following condition to the Marketing Authorisation has been lifted as a result of this variation application:** Condition D in annex II of Commission decision (2021)1309 dated 19 Feb 2021 is lifted from the Marketing Authorisation.

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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