CBG MEB

Public Assessment Report

Scientific discussion

Valsartan/HCT Jubilant 80/12.5 mg and 160/25 mg film-coated tablets

(valsartan, hydrochlorothiazide)

NL/H/3221/001-002/DC

Date: 2 August 2016

This module reflects the scientific discussion for the approval of Valsartan/HCT Jubilant 80/12.5 mg and 160/25 mg film-coated tablets. The procedure was finalised on 16 June 2015. 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
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
HCT	Hydrochlorothiazide
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 Valsartan/HCT Jubilant 80/12.5 mg and 160/25 mg film-coated tablets, from Jubilant Pharmaceuticals n.v.

The product is indicated for treatment of essential hypertension in adults. Valsartan/HCT Jubilant fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide (HCT) monotherapy. 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 products Co-Diovan 80/12.5 mg and 160/25 mg film-coated tablets (NL License RVG 22365 and 31122) which have been registered in the Netherlands by Novartis Pharma BV since 25 May 1998 and 17 January 2005, respectively, through mutual recognition procedure SE/H/0565/MR.

The concerned member states (CMS) involved in this procedure were Germany, Denmark, Sweden and the UK.

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

II. QUALITY ASPECTS

II.1 Introduction

Valsartan/HCT Jubilant are film-coated tablets, which can be distinguished based on the differences in size, engraving and colour:

- The 80/12.5 mg film-coated tablets are peach coloured, oval shaped, biconvex, film-coated tablets of approximately 11.77 mm length and of 6.16 mm width debossed with ‘364’ on one side and ‘J’ on the other side. Each tablet contains 80 mg of valsartan and 12.5 mg of HCT.
- The 160/25 mg film-coated tablets are brown coloured, oval shaped, biconvex, film-coated tablets of approximately 17.75 mm length and of 7.12 mm width debossed with ‘366’ on one side and ‘J’ on the other side. Each tablet contains 160 mg of valsartan and 25 mg of HCT.

The film-coated tablets are packed in Al/PVC/PE/PVdC or Al/OPA/Al/PVC blisters.

The excipients are:

- Tablet core
  - Cellulose, microcrystalline (E460)
  - Crospovidon (E1202)
  - Silica
  - Magnesium stearate (E470b)
  - Lactose anhydrous
- Tablet coat
  - Hypromellose (E464)
  - Titaniumdioxide (E171)
  - Macrogol
  - Iron oxide yellow (E172)
  - Iron oxide red (E172)
  - Iron oxide black (E172) – 160 mg/25 mg tablet only
  - Talc

The tablets are fully dose proportional.

II.2 Drug Substances

The active substances valsartan and hydrochlorothiazide (HCT) are established substances described in the European Pharmacopoeia (Ph.Eur.).

Valsartan is hygroscopic, practically insoluble in water and 0.1N HCl, sparingly soluble in methylene chloride and freely soluble in anhydrous ethanol. Valsartan is produced in its amorphous form and the optically pure L-isomer. The drug substance can degrade under thermal conditions and to a lesser extent under acidic conditions to an impurity (R-isomer). The R-isomer is adequately controlled in the drug substance specification.

HCT is non-hygroscopic, very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol 96%. It dissolves in dilute solutions of alkali hydroxides. HCT possesses one positional isomer. It has been adequately demonstrated that polymorphic form I is manufactured and that this form does not change into another polymorphic form during storage.

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.

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

Quality control of drug substances
The drug substances specifications are in line with the CEPs. For valsartan extra limits for impurities, residual solvents, and limits for particle size of the active substance are added. For HCT, the drug substance specification also includes particle size requirements.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches of each drug substance.

Stability of drug substances
Stability data on valsartan have been provided for 3 pilot batches and 3 industrial scaled batches stored at 25°C/60% RH (60 and 24 months respectively) and 40°C/75% RH (6 months). Except for water content no trends are observed at both conditions. The fluctuations in water content and slight increase in water content in the pilot batches are not confirmed in the larger batches. For valsartan a retest period of 48 months without any special storage conditions is considered acceptable.
For HCT, a retest period of 5 years is stated on the CEP.

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 film-coated tablets are dose-proportional. The excipients are well-known pharmacopoeial substances for oral dosage forms. The colourants are mixtures which are also well-known.

A bio-equivalence study has been performed between the 160/25 mg tablet and the reference product (Co-Diovan 160/25 mg of Novartis Pharma NV from Belgium). The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition.

A justification for the waiver for a bioequivalence study for the 80/12.5 mg tablet is given in line with the recommendations of the Guideline on the investigation of bioequivalence. Hence the MAH has provided adequate dissolution data in 0.1N HCl buffer and different pH conditions (4.5, 5.0 and 6.8). The results show that the tablet strengths have comparable dissolution characteristics throughout the pH range. The biowaiver for the 80/12.5 mg tablets is therefore granted.

Manufacturing process
The film-coated tablets are manufactured by a standard dry granulation process. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two batches of each strength in accordance with the relevant European guidelines. The description of the manufacturing process is considered adequate.

Control of excipients
The excipients (except coating mixtures) comply with Ph.Eur. For the coating mixtures the quantitative and qualitative composition is given. 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 appearance (including dimensions of the tablets), identification of active substances and colourants, water content, disintegration, uniformity of dosage units, dissolution, related substances, assay and microbial 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 from two full-scale batches of each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Two batches of both strengths are included in the stability program. The batches are packed in both types of blisters and are stored at 25°C/60% RH (12–18 months), 30°C/65% RH (6-12 months) and 40°C/75% RH (3–6 months). For one batch of the 160/25 mg tablets 18 months long-term data is available, for the other batches maximum 12 months data is available for long-term conditions. Water content increases initially at accelerated conditions in the triplex blisters, but stabilises over time. The other stability parameters remain constant and do not show any trends. Photostability studies in accordance with the ICH guidelines demonstrate that the product is not photosensitive. Based on the provided data a shelf-life of 24 months is acceptable. A storage condition of 'do not store above 25°C' is applied.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE/BSE certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

A statement regarding magnesium stearate and lactose is provided:

- Magnesium stearate: manufactured from fatty acid derived from vegetable sources. However, magnesium stearate manufactured from fatty acids derived from animal sources may also be used provided the material complies with the recommendations outlined in the current NfG on minimising the risk of transmitting animal spongiform encephalopathy agents.
- Anhydrous lactose: prepared from milk and calf rennet. Milk is sourced from healthy cows in the same conditions as milk collected for human consumption

The other excipients are not manufactured using human or animal sources.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Valsartan/HCT Jubilant 80/12.5 mg and 160/25 mg film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Valsartan/HCT Jubilant film-coated tablets are 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 Co-Diovan 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

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.

The MAH has conducted one bioequivalence study, which evaluated the Valsartan/HCT 160/25 mg tablets. For the 80/12.5 mg strength a biowaiver was requested. The bioequivalence study and the biowaiver are discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Valsartan/HCT Jubilant 160/25 mg tablets (Jubilant Pharmaceuticals n.v., Belgium) is compared with the pharmacokinetic profile of the reference product Co-Diovan 160/25 mg film-coated tablets (Novartis Pharma NV, Belgium).

The choice of the reference product
The reference product in the bioequivalence study is accepted. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The MAH has carried out the bioequivalence studies on the highest strength (160/25 mg). A biowaiver was requested for the other strength (80/12.5 mg) as Valsartan/HCT exhibits linear kinetics in the studied dose range and all the following general biowaiver criteria were fulfilled:

- The pharmaceutical products are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substances is the same for all strengths
- *In vitro* dissolution profiles of the 160/25 mg and 80/12.5 mg tablets are regarded similar in pH 4.5, 5.0 and 6.8.

Valsartan/HCT 80/12.5 mg tablets comply with the general requirements for a biowaiver. Therefore a biowaiver for this strength was granted.

Design
A single-dose, randomised, open label, four-period, two-treatment, two-sequence, fully replicate, four-way crossover bioequivalence study was carried out under fasted conditions in 46 healthy, male subjects aged 18-45 years. Each subject received a single dose (160/25 mg) of one of the 2 valsartan/HCT formulations. The tablet was orally administered after a fasting period. There were 4 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.50, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 7.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours post-dose in each study period.

The design of the study is considered acceptable, the wash-out period was long enough (half-life of valsartan is 6 hours; half-life of HCT averages 6 to 15 hours), sampling period long enough, and the sampling scheme adequate to estimate pharmacokinetic parameters. Food does not influence the therapeutic effect of valsartan and HCT. Valsartan/HCT tablets may therefore be taken without reference to food intake.

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.

This replicate-design study was analysed for scaled average bioequivalence approach. The bioequivalence acceptance criteria were based on intra-subject variability of reference product as follows:

- If the intra-subject CV for C_{max} parameter was >30% for reference product in the study, then the product was considered as highly variable and limit for bioequivalence for C_{max} was applied based on scaled average bioequivalence approach. However, in this case the point estimate (T/R) should fall between 80.00-125.00%.
- If the intra-subject CV for C_{max} parameter was <30% for reference product in the study, then conventional bioequivalence limit was considered for C_{max}. In that case, the test product was considered to be bioequivalent to the reference product if the 90% CI for the ratio of the geometric least square means of natural log transformed C_{max} of Test and Reference formulations fall within 80.00% to 125.00%.

In any case, the conventional average bioequivalence criteria using 90% CI was to be considered as 80.00% to 125.00% for AUC_{0-t}.
The above bioequivalence criteria were applicable for valsartan and HCT.

Results
40 subjects completed all periods of the study. One subject was withdrawn from the study due to an adverse event and five subjects dropped out of the study. Four out of the five refused to continue further for personal reasons. One out of the five dropped out of the study as the subject failed to follow up.

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

Treatment N=40	**AUC_{0-t}** ng/ml/h	**C_{max}** ng/ml	**$AUC_{0-\infty}$** ng/ml/h	**t_{max}** h
Test	1082 ± 293	158 ± 40	1152 ± 287	1.92 (1.17 – 3.33)
Reference	1051 ± 338	144 ± 32	1123 ± 339	2.00 (1.00 – 5.17)
***Ratio** **(90% CI)**	1.04 (0.99-1.08)	1.09 (1.03–1.14)	--	--

Intra subject CV (%)				
Test	17.51	22.83	--	--
Reference	14.55	17.59	--	--

AUC_{0-t} area under the plasma concentration curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
CV coefficient of variation
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

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

Treatment N=40	**AUC_{0-t}** µg/ml/h	**C_{max}** µg/ml	**$AUC_{0-\infty}$** µg/ml/h	**t_{max}** h
Test	36.4 ± 13.5	5.7 ± 2.0	37.3 ± 13.6	3.17 (1.67 – 4.84)
Reference	33.8 ± 15.8	5.4± 2.1	34.5 ± 15.9	3.17 (1.17 – 5.09)
***Ratio (90% CI)**	1.12 (1.03-1.22)	1.08 (0.98-1.19)	--	--
Intra subject CV (%)				
Test	33.72	41.39	--	--
Reference	34.59	35.90	--	--

AUC_{0-t} area under the plasma concentration curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
CV coefficient of variation
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study

The ratios of geometric least square means of Test and Reference formulations (point estimates) of parameters C_{max} and AUC_{0-t} for valsartan as well as HCT were within the range within the range defined as per the respective bioequivalence criteria set forth in the protocol. For valsartan the intra-subject CV of Reference product for C_{max} parameter was >30%, therefore widened confidence interval range was calculated. The confidence limits for the C_{max} parameter was within the widened range of 76.75 - 130.29 and within the conventional average bioequivalence range of 80.00% – 125.00% for the AUC_{0-t} parameter.

For HCT the intra-subject CV of Reference product for C_{max} parameter was <30%, therefore conventional average bioequivalence criteria were considered. The C_{max} and AUC_{0-t} parameters were within the conventional average bioequivalence range of 80.00% – 125.00%.

For valsartan the mean extrapolated AUC for the Test Product was 2.679 ± 1.8536 % as compared to 2.672 ± 1.2049% for the Reference Product and not higher than 20% in any subject.

For HCT the mean extrapolated AUC for the Test Product was 6.603 ± 2.9663% as compared to 6.917 ± 3.2105%, for the Reference Product and not higher than 20% in any subject. No pre-dose levels were detected for valsartan and HCT and for both analytes the t_{max} was not observed in the first sample time in any of the subjects.

Based on the submitted bioequivalence study Valsartan/HCT Jubilant 160/25 mg film-coated tablets are considered bioequivalent with Co-Diovan 160/25 mg film-coated tablets.

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 Valsartan/HCT Jubilant film-coated tablets.

Summary table of safety concerns as approved:

Important identified risks	• Hyperkalaemia • Hypotension • Foetotoxicity • Elevation of liver function values • Renal impairment • Hypersensitivity reactions incl. angioedema and serum sickness
Important potential risks	• Medication error including overdose
Important missing information	• Clinical management and use of pharmacotherapy in paediatric heart failure • Clinical management and use of pharmacotherapy in paediatric recent myocardial infarction • Clinical management and use of pharmacotherapy in paediatric hypertension with renal impairment • Clinical management and use of pharmacotherapy in paediatric hypertension with mild to moderate hepatic impairment • Benefit-risk ratio of pharmacotherapy in hypertensive children <5 years of age

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 Co-Diovan film-coated tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the products are 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 Valsartan/HCT film-coated tablets (PT/H/0607/DC). The content of the PL of the test products is nearly the same as the content of the PL approved in the procedure PT/H/0607. The PL of the test products has been updated taking into account the current QRD-template and the latest version of the PL of the innovator. The mock up is the same as the mock up of the PL in the procedure PT/H/0607/DC. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Valsartan/HCT 80/12.5 and 160/25 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Co-Diovan 80/12.5 mg and 160/25 mg film-coated tablets. Co-Diovan 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 Valsartan/HCT 80/12.5 and 160/25 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 June 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached