Public Assessment Report

Scientific discussion

Valtension comp.
Film-coated tablets 160 mg/12.5 mg

Valsartan and hydrochlorothiazide

DK/H/1507/001/DC

This module reflects the scientific discussion for the approval of Valtension comp. The procedure was finalised on 2 March 2009. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Valtension comp. film-coated tablets 160 mg/12.5 mg, from Teva Danmark A/S. The date of authorisation was on 23 March 2009 in Denmark. The product is indicated for treatment of essential hypertension.
The 160 mg/12.5 mg fixed dose-combination of valsartan/hydrochlorothiazide is indicated in patients whose blood pressure is not adequately controlled on valsartan monotherapy.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product CoDiovan 160 mg/12.5 mg film-coated tablets, which has been registered in Germany by Novartis Pharma GmbH since 21 October 1997. The reference product in Denmark is Diovan Comp 160 mg/12.5 mg film-coated tablets, Novartis Healthcare A/S.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC. This decentralised procedure concerns a so-called fixed dose application for a combination of 2 active substances, valsartan and hydrochlorothiazide.

Valsartan is an orally active and specific angiotensin II antagonist acting on the AT_1 receptor subtype. It blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues.
Hydrochlorothiazide is a thiazide diuretic. Thiazides directly increase the excretion of sodium and chloride by affecting the renal tubular mechanism of electrolyte re-absorption. The co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.
The fixed combination product is indicated for the treatment of essential hypertension when valsartan or hydrochlorothiazide monotherapy fail provide sufficient control.

II. QUALITY ASPECTS

II.1 Introduction

Valtension comp. film-coated tablets 160 mg/12.5 mg contains as active substances 160 mg of valsartan and 12.5 mg of hydrochlorothiazide.

The 160 mg/12.5 mg tablets are red, film-coated, standard convex round tablets, debossed with "VH" on one side.

Valtension comp. film-coated tablets is packed in transparent PVC/PE/PVdC – Aluminium blister packs in pack sizes of 1, 14, 15, 28, 30, 56, 60, 84, 90, 98 and 100 film-coated tablets, and in hospital packs of 50 (50 x 1) film-coated tablets. However, not all pack sizes may be marketed.

The excipients in the tablet core are: Colloidal anhydrous silica; sodium starch glycolate (Type A); crospovidone; microcrystalline cellulose; maize starch and magnesium stearate.

The film-coating consists of: Opadry 03F25380 red; hypromellose; macrogol; talc; titanium dioxide (E171); red iron oxide (E172) and yellow iron oxide (E 172).

Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substances are valsartan and hydrochlorothiazide.

The documentation on valsartan is presented as a European Drug Master File (DMF) in CTD-format. Both Applicant's and Restricted Parts have been presented together with a suitable letter of access. The information provided is satisfactory.
The drug substance specification is in line with general ICH requirements and closely allied to that of valsartan monographed in the USP. Stability data has been obtained on batches stored at 25ºC/60% RH and 40 ºC/75% RH in the proposed packaging. The data show the substance to be very stable with negligible degradation in the solid state. A re-test period of 4 years is acceptable.

Hydrochlorothiazide is monographed in the Ph.Eur. A Certificate of Suitability is presented in the documentation.
The applicant drug substance specification is Ph.Eur. compliant and includes additional testing for particle size. A retest period of 5 years applies as this is approved on the CEP.

II.3 Medicinal Product

The product composition is adequately described. The excipients used are common for manufacture of a film coated tablet product. The packaging materials are standard and shown suitable by the presented stability studies.

The development of the product has been described, the choice of excipients is justified and their functions explained. Product manufacture consists of aqueous granulation and is satisfactorily described including IPCs. Validation data are presented for pilot scale batches showing that product manufacture is consistent and can produce a product conforming to the proposed specifications.

The finished product specification is standard for the pharmaceutical form and includes relevant physicochemical, ID, assay and purity tests in line with ICH requirements and Ph.Eur. general monograph for film-coated tablets. Release and shelf-life specifications are provided where the latter has widened assay and impurity limits. The limits are justified on the basis of the presented batch analysis and stability data. Batch analysis data of 2 pilot scale batches have been provided showing compliance with the release requirements.

Stability data are provided for 2 pilot scale batches stored at 25ºC/60%RH, 30°C/65%RH and 40ºC/75%RH stored in the proposed market pack. No out of specification results were obtained on storage at 25°C or 30°C for 12 months. The product was unstable at 40°C with out of specification results observed for dissolution and hydrochlorothiazide degradants. No significant degradation was observed on exposure to light. A shelf-life of 24 months stored below 30°C has been accepted. Bulk tablet storage can be accepted for up to 6 months when stored at 25°C/60%RH stored in double PE bags.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of valsartan and hydrochlorothiazide are well known. This product is a generic formulation of CoDiovan film-coated tablets, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. An overview based on a literature review is therefore appropriate and acceptable. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

The pharmacokinetics of valsartan and hydrochlorothiazide are well established. For this generic application, the MAH has submitted 1 bioequivalence study performed under fasted conditions, in which the pharmacokinetic profile of the test product Valtension comp. film-coated tablets 160 mg/12.5 mg is compared with the pharmacokinetic profile of the reference product CoDiovan 160 mg/12.5 mg tablets, Novartis Pharma GmbH, from the German market.

The study was performed as an open-label, randomized, two-period, two-treatment, two-sequence, crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between each of the three administrations. 160 mg/12.5 mg was administered in each period. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours prior to drug administration. Blood samples were collected pre-dosing and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 12.0, 16.0, 24.0, 36.0 and 48.0 hours post administration. Eighteen (18) healthy non-smoking male and female subjects were dosed in period 1. Subject no. 18 was dismissed from the study prior to period 2 check-in due to a positive pregnancy test. Seventeen (17) subjects completed the study. Of the 17 subjects who were included in the data analysis, 15 were Caucasian, 1 was black and 1 was Asian; six (6) were males and eleven (11) were females.

Bioequivalence was determined based on AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} as primary variables for both valsartan and hydrochlorothiazide.

Valsartan

Analyte: Valsartan (N = 17)					
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	24864.8 27919.8 (49)	26107.1 27802.0 (36)	95.24	82.31 - 110.21	25
AUCinf (ng*h/mL)	25757.1 28751.9 (47)	26858.7 28543.3 (35)	95.90	83.51 - 110.12	23
Cmax (ng/mL)	4226.3 4691.8 (49)	4449.7 4665.3 (30)	94.98	80.94 - 111.45	27
Tmax[a] (h)	2.35 (47)	2.87 (37)	-	-	-
Kel[a] (1/h)	0.0654 (34)	0.0670 (33)	-	-	-
Thalf[a] (h)	12.27 (47)	11.68 (40)	-	-	-

Hydrochlorothiazide

Analyte: Hydrochlorothiazide (N = 17)					
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	520.938 540.242 (24)	538.926 563.292 (25)	96.66	89.79 - 104.06	12
AUCinf (ng*h/mL)	533.876 552.814 (24)	551.520 575.857 (25)	96.80	89.86 - 104.28	12
Cmax (ng/mL)	84.645 89.212 (30)	87.176 92.500 (31)	97.10	89.24 - 105.64	14
Tmax[a] (h)	1.43 (29)	1.61 (27)	-	-	-
Kel[a] (1/h)	0.0737 (13)	0.0741 (13)	-	-	-
Thalf[a] (h)	9.55 (12)	9.51 (13)	-	-	-
[a]Presented as arithmetic mean (CV%) only.					

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of valsartan/hydrochlorothiazide under single dose fasting condition, it can be concluded that Valtension comp. film-coated tablets 160 mg/12.5 mg and CoDiovan 160 mg/12.5 mg tablets, Novartis Pharma GmbH are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The RMS 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.2 Risk management plan & Pharmacovigilance system

Valsartan/hydrochlorothiazide was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substances. The safety profile of valsartan/hydrochlorothiazide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any a potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the decentralised procedure is in accordance with that accepted for the reference product Diovan Comp film-coated tablets marketed by Novartis Healthcare A/S.

The MAH has agreed to update the content of the SmPC and package leaflet in accordance with the SmPC and package leaflet harmonised via art 30 of the Directive 2001/83/EC for Diovan Comp and to

align the SmPC and package leaflet to the PhVWP´s wording for recommendation regarding use of hydrochlorothiazide/ACE inhibitors and AT2 antagonist during lactation once it has been agreed.

Readability test
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 test consisted of a pilot test, followed by two rounds with 10 participants each. The readability test has been sufficiently performed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Valtension comp. film-coated tablets 160 mg/12.5 mg has a proven chemical-pharmaceutical quality and is a generic form of CoDiovan film-coated tablets. CoDiovan 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other valsartan/hydrochlorothiazide containing products.

A European harmonised birth date has been allocated (1997-09-25) and subsequently the first data lock point for valsartan/hydrochlorothiazide is September 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 2 March 2014.

The following post-approval commitments have been made during the procedure:

SPC and PIL:
1. To update the SPC and PIL in line with the results of the referral for the brand-leader Diovan comp.
2. To align the SPC and PIL to the PhVWP´s wording for recommendation regarding use of hydrochlorothiazide/ACE inhibitors and AT2 antagonist during lactation once it has been agreed.

Quality:
1. The finished product manufacturer commits to check the granulate stability on the first three commercial scale validation batches.
2. The first three consecutive commercial scale batches of each tablet strength will be added to the stability program.

Administrative:
1. The renewed Israeli GMP for the additional packaging site Teva Pharmaceutical Industries Ltd, Jerusalem, will be submitted as soon as available.