Public Assessment Report

Scientific discussion

Tevaltan comp.
Film-coated tablets 80 mg/12.5 mg and 160 mg/25 mg

Valsartan and hydrochlorothiazide

DK/H/1524/001-002/DC

This module reflects the scientific discussion for the approval of Tevaltan 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 Tevaltan comp. film-coated tablets 80 mg/12.5 mg and 160 mg/25 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 80 mg/12.5 mg fixed dose combination of valsartan / hydrochlorothiazide is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.
The 160 mg/25 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 80 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 80 mg/12.5 mg and 160 mg/25 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

Tevaltan comp. film-coated tablets 80 mg/12.5 mg contains as active substances 80 mg of valsartan and 12.5 mg of hydrochlorothiazide.
Tevaltan comp. film-coated tablets 160 mg/25 mg contains as active substances 160 mg of valsartan and 25 mg of hydrochlorothiazide.

The 80 mg/12.5 mg tablets are pink, film-coated round tablets, debossed with "93" on one side and with "7428" on the other side of the tablet.
The 160 mg/25 mg tablets are brown, film-coated round tablets, debossed with "93" on one side and with "7430" on the other side of the tablet.

Tevaltan comp. film-coated tablets is packed in transparent PVC/PE/PVdC – Aluminium blister packs in pack sizes of 1, 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 98, 100 and 280 tablets; and in hospital packs of 30, 50, 56 x 1, 98 x 1 and 280 x 1 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 03F24039 (80 mg/12.5 mg); Opadry 03F26816 (160 mg/25 mg); hypromellose; macrogol; talc; titanium dioxide (E171); Sunset yellow FCF (E110) (80 mg/12.5 mg);

red iron oxide (E172); black iron oxide (E172) (160 mg/25 mg) and yellow iron oxide 172) (160 mg/25 mg).

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 applicant specification is compliant with general ICH requirements for specifications and includes limits on particle size distribution.
A retest period of 4 years when stored in the proposed packaging is supported by the presented stability data.

Hydrochlorothiazide is monographed in the Ph.Eur. A Certificate of Suitability is presented in the documentation.
The applicant specification is compliant with the Ph.Eur. monograph and general ICH requirements for specifications, and includes limits on particle size distribution.
A retest period of 5 years is valid in accordance with information in the CEP.

II.3 Medicinal Product

The product composition is adequately described. The development of the product has been satisfactorily performed and explained. The excipients used are commonly employed. The packaging materials are standard and shown suitable by the presented stability studies.

Product manufacture is standard. Satisfactory validation data are provided for pilot scale manufacture showing a well controlled process.

The finished product specification is standard for the pharmaceutical form and includes relevant physicochemical, ID, assay and purity tests. Separate release and shelf-life specifications are provided where the latter has widened impurity limits. Batch analysis data of 2 pilot scale batches of each tablet strength are provided showing compliance with the release requirements.

Stability data are provided for pilot scale batches of each strength stored in the proposed market packagings. Results at long term and intermediate storage were within specification. The product degrades significantly under accelerated conditions particularly in relation to dissolution and hydrochlorothiazide degradants.

A shelf-life of 24 months stored below 30°C can be accepted on the basis of the presented data. Bulk tablet storage can be accepted for up to 6 months when stored at 25C/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 2 bioequivalence studies, one performed under fasted conditions and the second under fed conditions, in which the pharmacokinetic profile of the test product Tevaltan comp. film-coated tablets 160 mg/25 mg is compared with the pharmacokinetic profile of the reference product CoDiovan forte 160 mg/25 mg tablets, Novartis Pharma GmbH, from the German market.

Bioequivalence studies in the fasted and fed state have been performed with the 160 mg/25 mg strength. Biowaiver has been justified for the 80 mg/12.5 mg strength, since all the conditions in the guideline have been fulfilled: both strengths are manufactured by the same manufacturer and process, the qualitative composition is the same (except for colouring agents), the ratio between the active substances and excipients are the same, the pharmacokinetics is linear in the therapeutic dosage range for both active substances and the dissolution profiles of both strengths are similar. The RMS considers a biowaiver appropriate.

The first study was performed as an open-label, randomized, three-period, three-treatment, six-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/25 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. The subjects were randomly assigned one of six dosing sequences. Blood samples were collected pre-dosing and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 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. Sixteen (16) subjects completed all three periods of the study. Of the 17 subjects who were included in the data analysis, 11 were Caucasian, 5 were black and 1 was Asian; eleven (11) were males and six (6) were females.
Subject no. 8 withdrew from the study prior to period 2 check-in due to personal reasons and subject no. 1 withdrew from the study after period 2 dosing due to adverse events (rash on both arms (8 hours post-dose) and rash on the chest, back abdomen and face (16.5 hours post-dose)).
According to the protocol, subjects who completed at least 2 periods of the study, resulting in administration of at least one test product and the reference product will be included in the final data set. Therefore, subject no. 1 was included in the data analysis since this subject was administered the reference product in period 1 and the test product in period 2.

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	TRT	Means		Contrast	Contrast Ratio (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
		Arithmetic (CV%)	Geometric				
AUCt (ng·h/mL)	A	30418.5 (48)	27080.9	A vs. C	95.63	82.76 - 110.51	25
	B	31615.2 (50)	28438.7	B vs. C	100.43	86.64 - 116.42	
	C	28778.2 (26)	28317.5				
AUCinf (ng·h/mL)	A	31304.0 (47)	27994.4	A vs. C	96.36	83.87 - 110.70	24
	B	33142.9 (49)	29842.9	B vs. C	102.72	89.14 - 118.37	
	C	29631.5 (27)	29052.8				
Cmax (ng/mL)	A	5054.1 (48)	4517.9	A vs. C	99.49	86.29 - 114.70	25
	B	5086.9 (35)	4792.2	B vs. C	105.53	91.24 - 122.04	
	C	4707.1 (34)	4541.2				
Tmax (h)	A	2.54 (44)	-	-	-		
	B	2.42 (46)	-				
	C	2.97 (45)	-				
Kel (1/h)	A	0.0641 (33)	-	- -	-		
	B	0.0601 (36)	-				
	C	0.0649 (31)	-				
Thalf (h)	A	12.03 (36)	-	-	-		
	B	14.69 (80)	-				
	C	11.61 (30)	-				

Hydrochlorothiazide

Analyte: Hydrochlorothiazide (N = 17)							
Parameter	TRT	Means		Contrast	Contrast Ratio (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
		Arithmetic (CV%)	Geometric				
AUCt (ng·h/mL)	A	1088.921 (22)	1063.468	A vs. C	93.04	86.32 - 100.28	13
	B	1127.841 (27)	1071.067	B vs. C	93.70	86.80 - 101.16	
	C	1166.648 (22)	1143.028				
AUCinf (ng·h/mL)	A	1129.857 (21)	1106.434	A vs. C	93.86	87.03 - 101.21	13
	B	1163.214 (27)	1108.228	B vs. C	94.01	87.03 - 101.55	
	C	1202.810 (21)	1178.852				
Cmax (ng/mL)	A	157.071 (32)	148.658	A vs. C	95.93	87.50 - 105.18	16
	B	170.906 (29)	160.108	B vs. C	103.32	94.05 - 113.51	
	C	161.994 (28)	154.961				
Tmax (h)	A	2.08 (40)	-	-	-		
	B	1.87 (47)	-				
	C	1.93 (32)	-				
Kel (1/h)	A	0.0644 (16)	-	-	-		
	B	0.0654 (15)	-				
	C	0.0648 (15)	-				
Thalf (h)	A	10.99 (14)	-	-	-		
	B	10.79 (13)	-				
	C	10.89 (12)	-				

The second study was performed under fed (high fat) conditions with the 160 mg/25 mg tablets. The study was an open-label, randomized, two-period, two-treatment, two-sequence, crossover, single-dose bioavailability study with a wash out period of 7 days between the administrations. 160 mg/25

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 being given a high fat, high calorie breakfast. The high fat, high calorie breakfast was served 30 minutes prior to drug administration.
Blood samples were collected pre-dosing and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.50, 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 and in period 2. Subject no. 8 withdrew from the study after 24 hours in period 2 due to personal reasons.
17 subjects completed the study. Of the 17 subjects who completed the study, 12 were Caucasian, 3 were black and 2 were Asian; seven (7) were males and ten (10) 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, Subject 08 Excluded)					
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	15847.9 17672.3 (47)	14656.8 15692.3 (38)	108.13	95.59 - 122.31	21
AUCinf (ng*h/mL)	16398.2 18226.6 (46)	15469.3 16507.9 (37)	106.00	94.08 - 119.45	20
Cmax (ng/mL)	2199.5 2322.9 (31)	2306.0 2418.8 (31)	95.38	85.29 - 106.67	19
Tmax[a] (h)	4.07 (58)	3.36 (33)	-	-	-
Kel[a] (1/h)	0.0711 (37)	0.0596 (36)	-	-	-
Thalf[a] (h)	11.67 (52)	14.15 (60)	-	-	-
[a]Presented as arithmetic mean (CV%) only.					

Hydrochlorothiazide

Analyte: Hydrochlorothiazide (HCTZ) (N = 17, Subject 08 Excluded)					
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	1160.8 1186.4 (22)	1165.5 1189.7 (23)	99.60	95.85 - 103.49	6
AUCinf (ng*h/mL)	1192.4 1219.4 (23)	1197.3 1222.3 (23)	99.60	96.02 - 103.30	6
Cmax (ng/mL)	155.4 158.9 (23)	160.9 165.0 (26)	96.59	87.37 - 106.78	17
Tmax[a] (h)	2.67 (40)	2.58 (43)	-	-	-
Kel[a] (1/h)	0.0708 (14)	0.0706 (10)	-	-	-
Thalf[a] (h)	9.97 (14)	9.92 (10)	-	-	-
[a]Presented as arithmetic mean (CV%) only.					

In both studies, 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

and fed condition, it can be concluded that Tevaltan comp. film-coated tablets 160 mg/25 mg and CoDiovan forte 160 mg/25 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 80 mg/12.5 mg and 160 mg/25 mg 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

Tevaltan comp. film-coated tablets 80 mg/12.5 mg and 160 mg/25 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.