CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Valsacell 40 mg, 80 mg and 160 mg, film-coated tablets
Medcell Pharma B.V., the Netherlands

valsartan

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 112914-112916

8 April 2014

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA03
Route of administration:	oral
Therapeutic indication:	hypertension; recent myocardial infarction; symptomatic heart failure
Prescription status:	prescription only
Date of authorisation in NL:	28 August 2013
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Valsacell 40 mg, 80 mg and 160 mg, film-coated tablets from Medcell Pharma B.V. The date of authorisation was on 28 August 2013 in the Netherlands.

The product is indicated for:

- treatment of hypertension. The 40 mg is indicated in children and adolescents 6 to 18 years of age. The 80 mg and 160 mg strengths are used for essential hypertension in adults and hypertension in children and adolescents 6 to 18 years of age.
- treatment of clinically stable adult patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction.
- treatment of symptomatic heart failure in adult patients when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to ACE inhibitors when beta blockers cannot be used.

A comprehensive description of the indications and posology is given in the SmPC.

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing.

This national procedure concerns a generic application claiming essential similarity with the innovator product Diovan 40 mg, 80 mg and 160 mg tablets (NL License RVG 32137, 26939-26940), which have been registered in the Netherlands by Novartis Pharma B.V. since 7 November 2011 (80 mg, 160 mg) and 25 July 2005 (40 mg) through mutual recognition procedure SE/H/0406/004-006.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the 80 mg and 160 mg products is compared with the pharmacokinetic profile of the reference product Diovan 80 mg and 160 mg tablets, registered in Germany. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB 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.

Active substance
The active substance is valsartan, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white powder, which is practically insoluble in water and soluble in methanol. Valsartan shows stereoisomerism and is manufactured as pure L-enantiomer.

The CEP procedure is used for the active substance. 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 European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
Except for assay, the specification is in accordance with the Ph.Eur. monograph, with additional tests for absorbance, residual solvents and particle size distribution. Residual solvents is tested in accordance with the additional requirements on the CEP. 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 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbooks (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Valsacell 40 mg is a yellow, oval, biconvex, film-coated tablet, with a score on one face, and a V logo on the other face.
Valsacell 80 mg is a pink, round, biconvex, film-coated tablet, with a score on one face, and a V logo on the other face.
Valsacell 160 mg is a yellow, oval, biconvex, film-coated tablet, with a score on one face, and a V logo on the other face.

The film-coated tablets are packed in PVC/PE/PVdC-Al blisters or in HDPE bottles with a PE snap-on cap or a PP screw cap.

The excipients are: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone K29-K32, talc, silica colloidal anhydrous and magnesium stearate.

The coating contains polyvinyl alcohol, talc, titanium dioxide, macrogol 3350, iron oxides, lecithin, yellow iron oxide and red iron oxide (80 mg only).

The different tablet strengths are fully dose proportional to each other with regard to their tablet cores.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of the development was to develop a generic product essentially similar to the originator product Diovan 40 mg, 80 mg and 160 mg. The main development studies comprised of optimizing the formulation and performing comparative dissolution studies. The suitability of the score lines for division of the tablets into equal halves was adequately confirmed.
Bioequivalence studies were performed with the 80 mg and 160 mg products. The test batches used in the bioequivalence studies were manufactured according to the finalized composition and manufacturing process. A biowaiver for the 40 mg additional strength is supported by the results of comparative dissolution studies. The 80 mg and 160 mg reference products from Germany used in the bioequivalence study are representative for the Dutch reference products as they were authorised through the same procedure (SE/H/0406/004-006). The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are wet granulation, drying, final blending, compression and film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for at least three production-scale batches per strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph.Eur. or in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, resistance to crushing, dissolution, loss on drying, average tablet mass, uniformity of dosage units, subdivision of tablets, related substances, enantiomeric purity, assay and microbiological quality. The release and shelf-life requirements are identical. The drug product specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on at least three full-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on at least two full-scale batches and several pilot-scale batches stored at 25°C/60% RH (36-60 months), 30°C/65% RH (12 months) or 30°C/75% RH (6-12 months) and 40°C/75% RH (3-6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PE/PVdC-Al blisters or HDPE containers. A significant drop in dissolution is seen for the batches that were packed in PVC/PE/PVdC-Al blisters already after 3 months storage at 40°C/75% RH as well as an increase in loss on drying. No changes or trends were observed for any other of the test parameters at the other storage conditions and for the batches stored in HDPE containers. The proposed shelf-life of 36 months for both packaging materials and storage condition ‘Store below 30°C’ for the blister pack and ‘This medicinal product does not require any special storage conditions’ for the HDPE pack are justified. Results of a photostability study demonstrated that the product is not sensitive to light exposure.
The results of an in-use stability study justify the absence of a separate in-use shelf-life for the bottle pack.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Only lactose monohydrate is of animal origin. This is produced from milk sourced from healthy cows in the same conditions as milk collected for human consumption in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products.

II.2 Non-clinical aspects

This product is a generic formulation of Diovan, which is available on the European market. 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 Board agreed

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of valsartan released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Valsartan is a well-known active substance 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 Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Valsacell 80 mg and 160 mg (Medcell Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference products Diovan 80 mg and 160 mg film-coated tablets (Novartis Pharma GmbH, Germany).

The choice of the reference products
The choice of the reference products in the bioequivalence studies is justified, as it is the same product as the Dutch innovator product, registered through procedure SE/H/0406/004-006.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – 80 mg tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 74 healthy subjects (53 males, 21 females), aged 18-55 years. Each subject received a single dose (80 mg) of one of the 2 valsartan formulations under fasted conditions. There were 2 dosing periods, separated by a washout period of 14 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, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design is acceptable, the wash-out period was long enough, sampling period was long enough.

Results
The final analysis was done using the results from 70 participants (51 males and 19 females). The reasons for excluding 4 participants can be accepted and do not influence the final results. Once subject withdrew because of adverse effects, another did not return, a third had low blood pressure and for one subject there were problems with obtaining blood samples.

Safety
A total of 5 subjects experienced adverse events associated with the test formulation and 4 subjects associated with the reference formulation. No serious adverse events were reported and none were supposed to impact the safety of the subjects or the integrity of the study results.

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

Treatment N=70	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	12.8 ± 5.7	13.1 ± 5.8	2.3 ± 1.1	2.5 (1.0-4.5)	--
Reference	13.0 ± 5.7	13.3 ± 5.8	2.3 ± 1.1	2.5 (1.0-4.5)	--
***Ratio (90% CI)**	0.98 (0.91-1.05)	0.97 (0.90-1.05)	0.99 (0.90-1.08)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life

**ln-transformed values*

Bioequivalence study II – 160 mg tablet
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 70 healthy subjects, both male and female, aged 20-54 years. Each subject received a single dose (160 mg) of one of the 2 valsartan formulations under fasted conditions. There were 2 dosing periods, separated by a washout period of 14 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, 8, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design is acceptable, the wash-out period was long enough, sampling period was long enough.

Results
A total of 62 subjects (31 males, 31 females) were included in the statistical analysis as there were 6 drop-outs due to personal reasons and 2 drop-outs due to adverse events.

Safety
A total of 24 adverse events were reported involving 14 subjects, of which 14 were associated with the test formulation and 10 were associated with the reference formulation. No serious adverse events were reported and none were supposed to impact the safety of the subjects or the integrity of the study results.

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

Treatment N=62	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	25.4 ± 9.6	26.5 ± 9.7	4.2 ± 1.5	2.5 (1.5-6.0)	--
Reference	22.5 ± 11.2	23.2 ± 11.4	3.7 ± 1.6	3.5	--

				(1.0-6.0)	
***Ratio (90% CI)**	1.08 (1.01-1.16)	1.08 (1.01-1.16)	1.09 (1.01-1.18)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on study I and II
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 under fasted conditions, it can be concluded that Valsacell 80 mg and 160 mg are bioequivalent to Diovan 80 mg and 160 mg tablets with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Food decreases exposure (as measured by AUC) to valsartan by about 40% and C_{max} by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Biowaiver
A biowaiver was granted for the 40 mg strengths, as:
- The pharmaceutical products are manufactured by the same manufacturer and process;
- The pharmacokinetics has been shown to be linear over the therapeutic dose range;
- The qualitative composition of the different strengths is the same;
- The ratio between amounts of active substance and excipients is similar
- The dissolution profile is similar under identical conditions for the additional strength and the strengths of the batch used in the bioequivalence studies.

The MEB has been assured that the bioequivalence studies have 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).

Risk management plan
There is now more than 10 years post-authorisation experience with the active substance valsartan. The safety profile of the active substance can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SmPC. 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.
In accordance with the current legislation, the MAH provided a Risk Management Plan (RMP).
A summary of the RMP is provided below:

Important identified risks	– Hyperkalaemia – Hypotension – Foetotoxicity
Important potential risks	– Decrease in haemoglobin and/or hematocrit – Cardiac disorder

	– Elevation of liver function values – Hypersensitivity reactions incl. angioedema and serum sickness – Renal impairment
Important missing information	– Exposure during breastfeeding – Exposure in children

Routine risk minimisation activities are considered sufficient for this product.

Product information

SmPC
The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Diovan.

Readability test
The package leaflet has not been evaluated via a user consultation study. Instead, reference is made to the successfully used tested PL for another procedure. This concerned another Valsartan 40 mg, 80 mg and 160 mg product. The test consisted of a pilot test with 3 participants, followed by two rounds with 5 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The leaflet had a high score: 100% for locating the information necessary to answer the questions very easily or easily and 100% for understanding of this information. Herewith the leaflet passed the defined success criteria. The MAH provided an acceptable justification statement, declaring that the user tested PL is highly similar tot the one for Valsacell.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Valsacell 40 mg, 80 mg and 160 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Diovan 40 mg, 80 mg and 160 mg. 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Valsacell 40 mg, 80 mg and 160 mg, film-coated tablets were authorised in the Netherlands on 28 August 2013.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to continue the on-going stability studies at least up to the shelf-life of 36 months.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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