

Public Assessment Report

Scientific discussion

**Converide 150 mg/12.5 mg, 300 mg/12.5 mg and
300 mg/25 mg film-coated tablets**

(irbesartan/hydrochlorothiazide)

NL/H/2910/001-003/DC

Date: 30 October 2014

This module reflects the scientific discussion for the approval of Converide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets. The procedure was finalised on 28 April 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 10-12.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Converide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets from Medochemie Limited.

The product is indicated for treatment of essential hypertension. This fixed dose combination is indicated in adult patients whose blood pressure is not adequately controlled on irbesartan or hydrochlorothiazide alone. 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 product CoAprovel 150/12.5 mg, 300/12.5 mg and 300/25 mg, film-coated tablets which have been registered through the centralised procedure by Sanofi Pharma Bristol-Myers Squibb SNC since 15 October 1998 (EU/1/98/086—EMA/H/C/000222). Further information can be found in the EPAR of CoAprovel (<http://www.ema.europa.eu/htms/human/epar/>).

The concerned member states (CMS) involved in this procedure were CY, EL, RO, BG (300 mg/12.5 mg and 300 mg/25 mg only), CZ (150 mg/12.5 mg and 300 mg/12.5 mg only), Lithuania (150 mg/12.5 mg and 300 mg/25 mg only) and Slovakia (300 mg/12.5 mg and 300 mg/25 mg only).

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

II. QUALITY ASPECTS

II.1 Introduction

Converide 150 mg/12.5 mg is a white, round, convex, film-coated tablet with diameter 9.5 mm. Converide 300 mg/12.5 mg is a pink, convex, film coated capsule-shaped tablet, scored on one side, embossed "MC" on the other side, with dimensions 17.5 x 8 mm. Converide 300 mg/25 mg is a white, convex, film coated capsule-shaped tablet, scored on one side, embossed "MC" on the other side, with dimensions 17.5 x 8 mm. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The film-coated tablets are packed in opaque PVC/PVDC-Alu blisters or transparent PVC/PE/PVDC-Alu blisters.

The excipients are:

Tablet core - lactose monohydrate, pregelatinised starch, colloidal anhydrous silica, croscarmellose sodium E468, cellulose microcrystalline PH-102, E460, magnesium stearate E572.

Film-coating - hypromellose E464, lactose monohydrate, macrogol 6000, titanium dioxide E171, red iron oxide E172 (only for the 300/12.5 mg strength).

The 150/12.5 mg is directly dose proportional to the 300/25 mg strength. For the 300/12.5 mg strength, the amount of core excipients is the same and the amount of filler (lactose monohydrate) is changed to account for the change in amount of active substance.

II.2 Drug Substances

Irbesartan

Irbesartan is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, crystalline powder, which is practically insoluble in water, sparingly soluble in methanol and slightly soluble in methylene chloride. The active substance shows polymorphism.

The Active Substance Master File (ASMF) procedure is used for one manufacturer of irbesartan. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of

the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

For the second manufacturer of irbesartan the CEP procedure is used. 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

For the drug substance manufactured by the ASMF holder a description of the process has been given. The process consists of two synthetic reaction steps and one purification step.

For the second supplier a CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The MAH's drug substance specification comprises the drug substance specification of the ASMF-holder and for drug substance from the CEP-holder. The specification also complies to the Ph. Eur. A number of additional parameters than those described in the Ph.Eur. are included; these are acceptable. Batch analytical data for batches tested by the MAH, demonstrating compliance with the proposed drug substance specifications, have been provided for five batches of irbesartan.

Stability of drug substance

Stability data on the active substance from the ASMF holder have been provided for three full-scale batches stored at 25°C/60%RH (48 months) and 40°C/75% RH (6 months). Furthermore, 1 month data is available for three additional batches stored at 25°C/60% RH. Based on the available stability data the proposed retest period of four without special storage conditions, can be granted.

The active substance from the CEP holder 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.

Hydrochlorothiazide

Hydrochlorothiazide is an established active substance described in the Ph.Eur. It is a white or almost white, crystalline powder, which is very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol. It dissolves in dilute solutions of alkali hydroxides. The active substance shows polymorphism. The CEP procedure is used for hydrochlorothiazide.

Manufacturing process

As a CEP has been submitted, no details on the manufacturing process have been included.

Quality control of drug substance

The proposed drug substance specification is acceptable. The drug substance specification is in line with Ph.Eur. All parameters mentioned on the CEP are tested. The proposed limit for particle size distribution is acceptable, based on the results of the biobatch and other drug substance batches.

Batch analytical data for batches tested by the MAH, demonstrating compliance with the proposed drug substance specifications have been provided for two batches of hydrochlorothiazide.

Stability of drug substance

The active substance from the CEP holder is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. During development the composition was optimised until the final formulation was

obtained. The choices of packaging and manufacturing process are justified. Breakability has not been demonstrated. The score line on the 300 mg/12.5 mg and 300 mg/25 mg tablets is not intended for dividing the tablet into equal doses.

The pharmaceutical development of the product has been adequately performed. The data to demonstrate dissolution *in vitro*, are valid to confirm the adequacy of waiving additional *in vivo* bioequivalence testing for the 150/12.5 and 300/12.5 mg strengths. The proposed biowaivers are acceptable from a chemical-pharmaceutical point of view.

Manufacturing process

The film-coated tablets are manufactured using a standard manufacturing process consisting of wet granulation, blending, tableting 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 one batch of the 150/12.5 mg, and two batches of the 300/12.5 mg and 300/25 mg strengths.

Control of excipients

All excipients comply with the Ph.Eur., except for red iron oxide, for which an in-house specification is used. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, average weight, disintegration, hardness, identification of actives and colorants, water content, uniformity of dosage units, dissolution, related substances, assay and microbiological control. The release and shelf life specifications are identical with the exception of the limit for water content, for which a wider end of shelf life limit is set. The drug product specification is considered acceptable.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site has been provided for a total of eight batches (two batches for the 150/12.5 mg, three batches for the 300/12.5 mg and three batches for the 300/25 mg strength), demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for a total of eight batches: one pilot-scale and one production-scale batch for the 150/12.5 mg, one pilot-scale and two production-scale batches for the 300/12.5 mg and one pilot-scale batch and two production-scale batches for the 300/25 mg. The batches were stored at $25\pm 2^\circ\text{C}/60 \pm 5\% \text{RH}$ (the pilot-scale batches for 24 months and the production-scale batches for 18 months) and $40\pm 2^\circ\text{C}/75\pm 5\% \text{RH}$ (for 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Opaque PVC/PVDC-Alu blisters and transparent PVC/PE/PVDC-Alu blisters. Based on the available data the proposed shelf life of 30 months is acceptable. Photostability studies showed that the drug product packed in the transparent blister shows slight sensitivity to light while the product packed in the opaque blister does not. The following storage conditions are applicable: "This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture." (Opaque PVC/PVDC-Alu blisters) and "store in the original package in order to protect from moisture and light." (transparent PVC/PE/PVDC-Alu blisters).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate and magnesium stearate are the only materials of animal origin used. For magnesium stearate two suppliers are used; for one of the suppliers a TSE statement has been provided, while for the second supplier a CEP issued by the EDQM has been submitted. For the supplier of lactose a TSE statement is provided. The theoretical risk of TSE can be considered negligible.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Converide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The results of the ongoing stability studies with the product up to the approved shelf-life will be submitted as they become available.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Converide is 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 CoAprovel, 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

Irbesartan and hydrochlorothiazide 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.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Converide 300 mg/25 mg (Medochemie Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Coaprovel 300 mg/25 mg film-coated tablets (Sanofi Pharma Bristol-Myer Squibb SNC, Sweden).

The Swedish reference product is acceptable, as CoAprovel is registered through the centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver has been granted for Converide 150 mg/12.5 mg and 300 mg/12.5 mg, because the following conditions are met:

- The bioequivalence study has been performed with the 300/25 mg strength and the pharmacokinetics for irbesartan and hydrochlorothiazide are linear.
- The 150/12.5 mg strength and the bioequivalence study strength are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and the compositions of the strengths are quantitatively proportional.
- The 300/12.5 mg strength and the bioequivalence study strength are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and for the 2 formulations the amount of core excipients are the same but the amount of filler is changed to account for the change in amount of active substance hydrochlorothiazide.

- A comparison between the dissolution profiles of the strengths applied demonstrates comparable dissolution in 3 different buffers.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male (21) and female (23) subjects, aged 19-37 years. Each subject received a single dose (300 mg/25 mg) of one of the 2 irbesartan/hydrochlorothiazide formulations. The tablet was orally administered after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Irbesartan/hydrochlorothiazide may be taken without reference to food intake. Therefore the study under fasting conditions is acceptable. The sampling scheme is both long enough and frequent enough.

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.

Results

As one subject dropped-out before dosing, there was a replacement with a back-up subject. Three more subjects dropped out due to personal reasons after the first period. A total of 41 subjects were included in pharmacokinetic and statistical analysis.

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

Treatment N=41	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	20096 \pm 9867	23080 \pm 10133	3750 \pm 1113	1.0 (0.5-3.5)	--
Reference	19940 \pm 10415	22988 \pm 10896	3605 \pm 1064	1.0 (0.5-4.0)	--
*Ratio (90% CI)	1.02 (0.95-1.10)	--	1.04 (0.97-1.12)	--	--
AUC_{0-∞} 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					

**In-transformed values*

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

Treatment N=41	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	892 \pm 195	983 \pm 209	161 \pm 46	1.5 (0.5-4.0)	--
Reference	923 \pm 209	1014 \pm 224	159 \pm 43	1.5 (1.0-3.5)	--
*Ratio (90% CI)	0.97 (0.93-1.00)	--	1.01 (0.96-1.06)	--	--

AUC_{0-∞}	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				

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.8-1.25. Based on the submitted bioequivalence study Converde 300 mg/25 mg is considered bioequivalent with CoAprovel 300 mg/25 mg 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 Converde.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> • Hyperkalaemia • Hypotension • Foetotoxicity
Important potential risks	<ul style="list-style-type: none"> • Elevation of liver function values • Renal impairment • Hypersensitivity reactions incl. angioedema • Decrease in haemoglobin and/or hematocrit
Missing information	<ul style="list-style-type: none"> • Use in children <18 years • Exposure during breastfeeding

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 CoAprovel. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is 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

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 testing process involved: one pilot test on four participants followed by two main tests on ten participants each. Nineteen questions

about the most critical parts of the package leaflet and three general questions about the package leaflet were used. The package leaflet has not been adapted between two tests or after the last test. There were sufficient questions about the critical sections. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

Taking into account the results for each question more than 90% of the participants finds the section and answered the question correctly. 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

Converide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of CoAprovel 150/12.5, 300/12.5 and 300/25 mg tablets. CoAprovel 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 Converide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/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 28 April 2014.

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

Summary Public Assessment Report

Generics

**Converide 150 mg/12.5 mg, 300 mg/12.5 mg
and 300 mg/25 mg film-coated tablets**

(irbesartan and hydrochlorothiazide)

NL/H/2910/001-003/DC

Date: 30 October 2014

Summary Public Assessment Report

Generics

Converide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets

Active substances: irbesartan and hydrochlorothiazide

This is a summary of the public assessment report (PAR) for Converide. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Converide film-coated tablets.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Converide and what is it used for?

Converide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg are 'generic medicines'. This means that they are similar to 'reference medicines' already authorised in the European Union (EU) called CoAprovel 150/12.5 mg, 300/12.5 mg and 300/25 mg, film-coated tablets.

This medicine is used in adults who have essential hypertension (high blood pressure) that is not adequately controlled by irbesartan or hydrochlorothiazide alone. 'Essential' means that the hypertension has no obvious cause.

How does this medicine work?

Converide contains two active substances, irbesartan and hydrochlorothiazide.

Irbesartan is an 'angiotensin II receptor antagonist', which means that it blocks the action of a hormone in the body called angiotensin II. Angiotensin II is a powerful vasoconstrictor (a substance that narrows blood vessels). By blocking the receptors to which angiotensin II normally attaches, irbesartan stops the hormone having an effect, allowing the blood vessels to widen.

Hydrochlorothiazide is a diuretic, which is another type of treatment for hypertension. It works by increasing urine output, reducing the amount of fluid in the blood and lowering the blood pressure.

The combination of the two active substances has an additive effect, reducing the blood pressure more than either medicine alone. By lowering the blood pressure, the risks associated with high blood pressure, such as having a stroke, are reduced.

How is this used?

The pharmaceutical form of Converide is a film-coated tablet and the route of administration is oral.

The medicine can only be obtained with a prescription.

The dose to be used depends on the dose of irbesartan or hydrochlorothiazide that the patient was taking before. Doses higher than 300 mg irbesartan and 25 mg hydrochlorothiazide once a day are not recommended. This medicine may be added to some other treatments for hypertension.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

How has this medicine been studied?

Because Converide is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, CoAprovel. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of this medicine?

Because Converide is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with this medicine, see section 4 of the package leaflet.

Why is this medicine approved?

It was concluded that, in accordance with EU requirements, this medicine has been shown to have comparable quality and to be bioequivalent to CoAprovel. Therefore, the Medicines Evaluation Board decided that, as for the reference medicine, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of this medicine?

A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Converide, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about this medicine

The marketing authorisation for Converide 150 mg/12.5 mg, 300 mg/12.5 mg and 300 mg/25 mg film-coated tablets was granted on 26 May 2014.

The full PAR for this medicine can be found on the website <http://mri.medagencies.org/Human>. For more information about treatment with Converide, read the package leaflet (http://mri.medagencies.org/download/NL_H_2910_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in October 2014.