CBG MEB

Public Assessment Report

Scientific discussion

Candesartan cilexetil/Hydrochloorthiazide Torrent 32 mg/12.5 mg and 32 mg/25 mg, tablets

(candesartan cilexetil/hydrochlorothiazide)

NL/H/2070/005-006/DC

Date: 9 December 2014

This module reflects the scientific discussion for the approval of Candesartan cilexetil/Hydrochloorthiazide Torrent 32 mg/12.5 mg and 32 mg/25 mg tablets. The procedure was finalised on 3 July 2014. 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 Candesartan cilexetil/Hydrochloorthiazide Torrent 32 mg/12.5 mg and 32 mg/25 mg tablets from Torrent Pharma GmbH.

The product is indicated for treatment of essential hypertension in adult patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide 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 product Atacand Plus. The first marketing authorisation in de EEA was obtained for Atacand Plus 8 mg/12.5 mg tablets in Sweden by Astra Zeneca in 1998. No reference products of the 32 mg/12.5 mg and 32 mg/25 mg strength are available in the Netherlands, but several generics in these strengths have been granted marketing authorisation.

This application is a line extension to Candesartan cilexetil/Hydrochloorthiazide Torrent 8 mg/12.5 mg and 16 mg/12.5 mg tablets for which Torrent Pharma GmbH obtained a registration in 2011 (procedure NL/H/2070/001-002/DC). The Public Assessment Report for this procedure is available on http://mri.medagencies.org/download/NL_H_2070_001_PAR.pdf.

The concerned member states (CMS) involved in this procedure were Germany and Lithuania.

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

II. QUALITY ASPECTS

II.1 Introduction

Candesartan cilexetil/Hydrochloorthiazide Torrent 32 mg/12.5 mg is a light yellow colored to yellow colored, oval, biconvex, bevel edged uncoated tablet with a breakline on both sides.
Candesartan cilexetil/Hydrochloorthiazide Torrent 32 mg/25 mg is a peach colored to light orange colored, oval, biconvex, bevel edged, uncoated tablet with a breakline on both sides.
Both tablets can be divided into equal halves.

The tablets are packed in Alu-Alu blisters, PVC/PVDC-Al blisters or HDPE bottles.

The excipients are: lactose monohydrate, maize starch, calcium stearate, hydroxypropyl cellulose (E463), disodium edetate, carmellose calcium (E466), ethyl cellulose (E462), microcrystalline cellulose (E460), ferric oxide yellow (E172); additionally for the 32/25 mg strength: ferric oxide red (E172).

The 32 mg/12.5 mg differs from the 32 mg/25 mg tablets in lactose monohydrate percentage to make up for the differences in active substances and colourants.

II.2 Drug Substance

Candesartan cilexetil
Candesartan cilexetil is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or off-white crystalline powder, which is insoluble in water, and soluble in methylene chloride and acetone. Candesartan cilexetil has one chiral centre and exists in three polymorphic forms (I, II and amorphous). The drug is manufactured as a racemic mixture as polymorphic form I.

The Active Substance Master File (ASMF) procedure is used for candesartan cilexetil. 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.

Manufacturing process
The manufacturing of candesartan cilexetil consists of eight steps. No class 1 organic solvents are used. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph with appropriate additional tests. 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 four full-scale batches for both manufacturing sites.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). At both storage conditions a slight increase of impurities was seen as well as a decrease in assay. No changes were seen in the other parameters and all results remained well within the specified limits. Based on the provided stability data, a retest period of 24 months without specific storage conditions was granted.

Hydrochlorothiazide
Hydrochlorothiazide (HCTZ) is an established active substance described in the Ph.Eur. It is a white to almost white crystalline powder, which is very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol. It shows polymorphism.

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
The drug substance specification is in line with the Ph.Eur. monograph, with additional requirements for residual solvents, particle size distribution and microbial quality. 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 two batches.

Stability of drug substance
The active substance 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. The main development studies the were optimization of the composition and the performance of comparative *in-vitro* dissolution studies. Dissolution profiles were demonstrated to be

similar. A bioequivalence study has been performed for both product strengths versus their respective reference product strength. The bioequivalence study test batches were manufactured according to the finalized manufacturing process and composition. The subdivision of the tablets complies with the relevant Ph. Eur. monograph. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacture are wet granulation, blending and compression, where candesartan cilexetil is dispersed in the granulation fluid. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches per strength. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
All excipients comply with the requirements of the European Pharmacopoeia or with USP-NF requirements (iron oxides). Dried microcrystalline cellulose is obtained by performing an additional drying step on the Ph.Eur. grade microcrystalline cellulose. The specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, resistance to crushing, water content, disintegration time, dissolution, uniformity of dosage units, subdivision of tablets, related substances, isopropyl alcohol, assay and microbial limits. Except for water content and related substances, the release and shelf-life requirements are identical. The specification is acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for two pilot-scale batches per strength stored at 25°C/60% RH (12-24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in HDPE bottles (with 30 and 500 tablets), Al/Al-blisters and PVC-PVdC/Al-blisters. At both storage conditions an increase of impurities is seen. Results for assay and water content are variable. No trends or changes were seen in any of the other parameters and all values were within the specified limits. Photostability data show that the drug product is not sensitive to light. The proposed shelf-life of 24 months without any special storage requirements is justified.
In-use stability data after 12 months and 24 months of storage has been provided demonstrating that the product remains stable for 90 days following first opening of the HDPE bottle.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is the only excipient of animal origin. A declaration is provided that the lactose is sourced from milk of healthy animals fit for human consumption in accordance with the guideline.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Candesartan cilexetil/ Hydrochloorthiazide Torrent 32 mg/12.5 mg and 32 mg/25 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH will apply a prospective process validation approach. The complete prospective validation scenario includes the first three production batches of finished product.
- The MAH committed to revise the limits for the individual related substances as well as the limit for total impurities at the end of shelf-life based on stability data.
- The MAH committed to continue the on-going long-term stability studies up to shelf-life.
- The MAH committed to include the first three production batches of each strength in the stability program.

- The MAH committed to study one batch of each strength in in-use stability studies after 12 months and 24 months of storage and that another batch will be studied after 18 months.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Candesartan cilexetil/Hydrochloorthiazide Torrent 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 Atacand Plus, 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

Candesartan cilexetil 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products Candesartan cilexetil/Hydrochloorthiazide Torrent 32 mg/12.5 mg and 32 mg/25 mg tablets (Torrent Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference products Atacand® PLUS 32 mg/12.5 mg and 32 mg/25 mg tablets (AstraZeneca GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified. The use of the reference products from Germany are acceptable since the reference products are not authorised in the Netherlands.
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.

Candesartan and HCTZ may be taken without reference to food intake, and therefere the studies under fasted conditions are appropriate.

Bioequivalence studies

Study I – 32 mg/12.5 mg tablet

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 18-45 years. Each subject received a single dose (32 mg/12.5 mg) of one of the 2 candesartan cilexetil/hydrochlorothiazide formulations. The tablet was orally administered after an overnight fast of at least 8 hours with 200 mL water. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 4.33, 4.66, 5, 5.33, 5.66, 6, 7, 9, 12, 18, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable, the washout and sampling period were long enough and the sampling scheme adequate to estimate the pharmacokinetic parameters.

Results
One subject was medically withdrawn from the study due to vomiting in period I. Thirty-nine subjects completed the study and were included in the pharmacokinetic analysis.

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

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3027±966	3095 ± 996	270± 81	4.3 (2.0-7.0)	7.8±1.2
Reference	2950 ± 856	3013 ± 883	261 ± 98	4.3 (1.7-7.0)	7.9 ±1.5
***Ratio (90% CI)**	1.01 (0.93-1.11)	--	1.05 (0.94-1.17)	--	--
CV (%)	24	--	30	--	--

$AUC_{0-\infty}$ 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*

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

Treatment N=39	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	625 ± 166	649 ± 166	90 ±23	1.7 (1.0-4.7)	8.5 ± 1.1
Reference	634 ± 144	657 ± 146	94 ± 21	1.7 (1.0-4.7)	8.6 ± 1.1
***Ratio (90% CI)**	0.97 (0.92-1.03)	**--**	0.95 (0.89-1.01)	--	--
CV (%)	15	--	15	--	--

$AUC_{0-\infty}$ 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*

Study II – 32 mg/25 mg tablet

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20-44 years. Each subject received a single dose (32 mg/25 mg) of one of the 2 candesartan cilexetil/hydrochlorothiazide formulations. The tablet was orally administered after an overnight fast of at least 8 hours with 200 mL water. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 4.33, 4.66, 5, 5.33, 5.66, 6, 7, 9, 12, 18, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable, the washout and sampling period were long enough and the sampling scheme adequate to estimate the pharmacokinetic parameters.

Results
Three volunteers dropped out of the study and two were withdrawn. Three volunteers did not report to facility for Period II. Two subjects were medically withdrawn from the study due to vomiting in period I. Thirty-five subjects completed the study and were included in the pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of candesartan under fasted conditions.

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	3856 ± 1290	3946 ±1327	377 ± 210	3.66 (1.33-5.66)	8.21 ± 1.7
Reference	3911 ± 1001	3988 ± 1025	373 ± 128	4.33 (1.33-7.00)	8.21 ± 1.4
***Ratio (90% CI)**	0.97 (0.89-1.07)	--	0.99 (0.86-1.13)	--	--
CV (%)	23	--	34	--	--

$AUC_{0-\infty}$ 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*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydrochlorothiazide under fasted conditions.

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1584 ± 364	1623 ± 388	229 ± 58	1.33 (0.66-4.33)	9.22 ±1.1
Reference	1580 ± 375	1616 ± 393	221 ± 67	1.33 (0.66-4.66)	9.20 ± 1.0
***Ratio (90% CI)**	1.00 (0.97-1.04)	--	1.05 (0.97-01.13)	--	--
CV (%)	10	--	19	--	--

$AUC_{0-\infty}$	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 bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80-1.25. Based on the submitted bioequivalence studies Candesartan cilexetil/ Hydrochloorthiazide Torrent 32 mg/12.5 mg and 32 mg/25 mg tablets are considered bioequivalent with Atacand® PLUS 32 mg/12.5 mg and 32 mg/25 mg tablets.

In the first study a total of 5 adverse events (AE) were reported. In the second study. A 7 AEs were reported in five volunteers. All adverse events were mild in nature and resolved completely.

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).

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 Candesartan cilexetil/Hydrochloorthiazide Torrent.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hyperkalaemia Hypotension
Important potential risks	Elevation of liver function values Renal impairment Hypersensitivity reactions incl. angioedema Decrease in hemoglobin and/or hematocrit
Missing information	--

Only routine pharmacovigilance activities will be performed. No additional pharmacovigilance activities and no risk minimisation activities have been planned. This is acceptable for this product.

The MAH committed to implement the outcome of the art.31 referral (EMEA/H/A-31/1370) reviewing the benefit/risk balance of the concomitant use of Angiotensin-II inhibitors, ACE inhibitors and aliskiren, once finalised.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Atacand® PLUS. 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 not been evaluated via a user consultation study. The PL submitted for NL/H/2070/005-006/DC is, except for the QRD-related text, similar to the PL as user tested for the lower strengths (NL/H/2070/001-004/DC). The results of the user testing were satisfactory. Therefore, no new consultation study is required. The justification of the MAH for not submitting a new user testing is accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Candesartan cilexetil/Hydrochloorthiazide Torrent 32 mg/12.5 mg and 32 mg/25 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Atacand Plus 32 mg/12.5 mg and 32 mg/25 mg tablets. Atacand Plus 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 Candesartan cilexetil/Hydrochloorthiazide Torrent 32 mg/12.5 mg and 32 mg/25 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 July 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