CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Candesartan cilexetil Torrent 2 mg, 4 mg, 8 mg, 16 mg and 32 mg tablets
Torrent Pharma GmbH, Germany

candesartan cilexetil

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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/2068/001-005/DC
Registration number in the Netherlands: RVG 107854 - 107857, 107870

20 April 2012

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA06
Route of administration:	oral
Therapeutic indication:	essential hypertension in adults; treatment of adult patients with heart failure and impaired left ventricle systolic function as add-on therapy to ACE inhibitors or when ACE-inhibitors are not tolerated
Prescription status:	prescription only
Date of authorisation in NL:	31 October 2011
Concerned Member States:	Decentralised procedure with DE, LT, RO and UK
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 (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Candesartan cilexetil Torrent 2 mg, 4 mg, 8 mg, 16 mg and 32 mg tablets, from Torrent Pharma GmbH. The date of authorisation was on 31 October 2011 in the Netherlands.

The product is indicated for:

- Essential hypertension in adults
- Treatment of adult patients with heart failure and impaired left ventricle systolic function (left ventricular ejection fraction ≤ 40%) as add-on therapy to ACE inhibitors or when ACE-inhibitors are not tolerated.

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

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a role in the pathogenesis of end organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (AT_1) receptor.
Candesartan cilexetil is a prodrug suitable for oral use. It is rapidly converted to the active substance, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist, selective for AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.
Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. There is no effect on ACE and no potentiation of bradykinin or substance P. In controlled clinical trials comparing candesartan with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the angiotensin II (AT_1) receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Atacand 2 mg, 4 mg, 8 mg, 16 mg and 32 mg tablets (NL License RVG 21703-21706 and 30755 respectively) which have been registered in the Netherlands by AstraZeneca since 13 October 1997 (2, 4, 8 and 16 mg) and 4 October 2004 (32 mg). In addition, reference is made to Atacand authorisations in the individual member states (reference product).

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 three bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Atacand 4 mg, 8 mg and 32 mg tablets from 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 these product types 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 candesartan cilexetil, an established active substance however not described in the European Pharmacopoeia (Ph. Eur.*). Candesartan is a white or almost white powder, practically insoluble in water, freely soluble in methylene chloride and slightly soluble in anhydrous ethanol. The drug substance shows polymorphism. In literature there are three forms: Form I, Form II and amorphous form. The drug substance from this source is Form I. The drug substance has one chiral centre. The drug substance from this source is a racemic mixture.

Manufacturing process
The manufacturing of candesartan cilexetil consists of eight steps. The first three steps are performed by two suppliers and the last five steps by the DMF holder. The last step of the synthesis is a purification step using acetone. Number 1 class organic solvents are used.

The Active Substance Master File (ASMF) procedure is used for the active substance. 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.

Quality control of drug substance
The drug substance specification is in line with the draft Ph. Eur. monograph, with additional requirements for heavy metals, azide content, XRD, residual solvents, particle size and microbial purity. The specifications are acceptable in view of the route of synthesis and the various ICH guidelines.
Batch analytical data of three full scale batches have been provided, demonstrating compliance with the specification. Data of three batches also demonstrated that the polymorphic form is consistent.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). Changes were observed in related substances and assay. All other parameters remain relatively stable at both conditions. Based on the provided stability data a retest period of 24 months without specific storage conditions can be granted. Stability studies will be continued up to 60 months at long term conditions as per submitted protocol.

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

Medicinal Product

Composition
Candesartan tablets are uncoated, immediate release tablets containing 2, 4, 8, 16 or 32 mg of candesartan cilexetil as the active substance. The tablets of all strengths are round and biconvex. Except for the 2 mg tablets which is plain on both sides, the tablet strengths of 4, 8 and 16 mg contain a breakline on one side and are plain on the other side, and the 32 mg formulation has a breakline on both sides. The tablets with a breakline can be divided into equal halves.

The 2 mg tablets are white to off-white with a diameter of 5 mm, the 4 mg tablets are white to off-white with a diameter of 7.1 mm, the 8 mg tablets are pink to reddish brown colored with a whitish mosaic appearance and have a diameter of 8 mm, the 16 mg tablets are light pink to pale red colored and have a diameter of 7.1 mm, and the 32 mg tablets are light pink to pale red colored and have a diameter of 9.5 mm.

The tablets are packed in Al/OPA-Al-PVC blisters or in transparent PVC/PVDC-Al blisters.

The excipients are: lactose monohydrate, maize starch, hypromellose 2910 (E464), calcium stearate, hydroxypropyl cellulose (E463), disodium edetate and cellulose microcrystalline (E460). The 8, 16 and 32 mg tablets also contain ferric oxide red as colorant.

All tablet strengths contain the same excipients except for the ferric oxide red colorant that is not present in the 2 mg and 4 mg tablets. The 16 mg and 32 mg tablets are fully dose proportional to each other, which is also the case for the 2 mg with the 4 mg tablets. The 8 mg tablet is not dose proportional to the other strengths. The excipients in candesartan tablets and the materials used for the primary packaging are well known and widely used for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were regarding the characterisation of the originator product, optimization of the formulation and comparative dissolution studies. The choices of the packaging and manufacturing process are justified.
Bioequivalence studies were performed with the 4 mg, 8 mg and 32 mg tablets. The BE batches were manufactured according to the finalized composition and process. Subdivision testing (not for 2 mg) has been satisfactorily performed in line with Ph. Eur. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of dry mixing, wet granulation, drying, blending and lubrication, compression and packaging. 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 scaled batches will be performed post authorization.

Control of excipients

The excipients except Ferric oxide comply with Ph. Eur. or in-house requirements. These specifications are acceptable. Lactose is sourced from milk of healthy animals fit for human consumption in accordance with the guideline (EMEA/410/01rev2). Ferric oxide complies with EC Directive 2009/35/EC and USP-NF*.

Quality control of drug product

The product specification includes tests for description, tablet dimension, identification, average weight, water content, dissolution, uniformity of dosage units, subdivision of tablets, related substances, assay and microbial quality. Except for water content and related substances, the release and shelf-life limits 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, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on two pilot scale batches per strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). For the 2, 4 and 8 mg tablets batches packed in Al-Al blisters were also stored at 30°C/65% RH (12 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al-Al and PVC/PVDC-Al blister packs. An increase of impurities is seen at all three storage conditions that is most pronounced at accelerated conditions. Out-of specification results for impurities are seen for the lower strengths of drug product (2, 4 and 8 mg tablets) at accelerated conditions. The results show a decrease in assay at all conditions. No trends or changes are seen for the other parameters. The proposed shelf-life of 24 months

for the 16 and 32 mg tablets without any special storage requirements and of 21 months for the 2 mg, 4 mg and 8 mg tablets with storage condition “Store below 30°C” are justified.The MAH committed to continue the ongoing stability studies at least up to the proposed shelf-life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only material used in the formulation which is of animal origin, is lactose monohydrate. It is ensured that it does not contain and is not derived from specified risk materials, thus presents no concern with respect to TSE/BSE. Lactose is sourced from milk of healthy animals in the same conditions as milk collected for human consumption. All other materials are synthetic or vegetable sources.

** USP-NF = United States Pharmacopoeia National Formulary*

II.2 Non clinical aspects

This product is a generic formulation of Atacand, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 candesartan cilexetil 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

Candesartan cilexetil is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH submitted three bioequivalence studies: one with the 32 mg strength at the initial application and two other studies with the 4 mg strength and the 8 mg strength in response to the questions of the RMS at Day 106 of the procedure. In the initial application the MAH proposed a biowaiver for the 2, 4, 8 and 16 mg formulation. The argumentation for the biowaiver was not accepted by the MEB for the three lower strengths. In the three bioequivalence studies the pharmacokinetic profile of the test products Candesartan cilexetil Torrent 4 mg, 8 mg and 32 mg tablets is compared with the pharmacokinetic profile of the reference products Atacand 4 mg, 8 mg and 32 mg tablets.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Candesartan cilexetil may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of candesartan cilexetil. Therefore, a food interaction study is not deemed necessary. The bioequivalence studies under fasting conditions are in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioequivalence study I: 4 mg tablet, fasted conditions
Study design
A single-dose, open label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 19-42 years. Each subject received a single dose (4 mg) of one of the 2 candesartan cilexetil formulations. The tablet was orally administered with 200 ml water after under fasting conditions. There were 2 dosing periods, separated by a washout period of 6 days.

Blood samples were collected pre-dosing and at 0.75, 1.5, 2.0, 2.33, 2.66, 3.0, 3.33, 3.66, 4.0, 4.33, 4.66, 5.0, 5.5, 6.0, 6.5, 7.0, 9.0, 12.0, 18.0, 24.0 and 36.0 hours after drug administration.

Analytical/statistical methods
The analytical method is adequately validated and 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
Three subjects dropped out from the study. Two subjects were found positive in urine screen for drug abuse and one subject one did not report to study facility. Therefore samples of 29 subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N=29	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	449 ± 162	470 ± 169	50 ± 22	4.33(2.00-6.00)	8.32 ±2.2
Reference	459 ± 204	485 ± 211	50 ± 28	4.00 (2.00-5.5)	8.42 ±2.2
***Ratio (90% CI)**	0.99 (0.92-1.07)	-	1.01 (0.92-1.11)	-	-
CV (%)	18	-	22	-	-

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. The size of the extrapolated area of the AUC exceeded 20% in one subject, but as the sampling period covers approximately 4 half-lives this is acceptable. Based on the pharmacokinetic parameters of candesartan cilexetil under fasted conditions, it can be concluded that Candesartan cilexetil Torrent 4 mg tablets and Atacand 4 mg are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II: 8 mg tablet, fasted conditions
Study design
A single-dose, open label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 19-44 years. Each subject received a single dose (8 mg) of one of the 2 candesartan cilexetil formulations. The tablet was orally administered with 200 ml water after under fasting conditions. There were 2 dosing periods, separated by a washout period of 8 days.
Blood samples were collected pre-dosing and at 0.75, 1.5, 2.0, 2.33, 2.66, 3.0, 3.33, 3.66, 4.0, 4.33, 4.66, 5.0, 5.5, 6.0, 6.5, 7.0, 9.0, 12.0, 18.0, 24.0 and 36.0 hours after drug administration.

Analytical/statistical methods
The analytical method is adequately validated and 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

Two subjects where withdrawn from the study, one due to an adverse event in period 1 and one did not report to the study facility in period 2. Therefore samples of 30 subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N=30	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	984 ±287	1028 ±304	110 ±36	4.33(2.00-6.50)	8.28 ±1.3
Reference	992 ±276	1036 ±291	106 ±28	3.83 (2.00-6.00)	8.23 ± 1.4
***Ratio (90% CI)**	0.99 (0.92-1.07)	-	1.02 (0.92-1.14)	-	-
CV (%)	17	-	24	-	-

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t} 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 candesartan cilexetil under fasted conditions, it can be concluded that Candesartan cilexetil Torrent 8 mg tablets and Atacand 8 mg are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study III: 32 mg tablet, fasted conditions

Study design

A single-dose, open label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 20-43 years. Each subject received a single dose (32 mg) of one of the 2 candesartan cilexetil formulations. The tablet was orally administered with 200 ml water after under fasting conditions. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dosing and at 0.75, 1.5, 2, 2.3, 2.7, 3.0, 3.3, 3.7, 4, 4.3, 4.7, 5, 5.5, 6, 6.5, 7, 9, 12, 18, 24, and 36 hours after drug administration.

Analytical/statistical methods

The analytical method is adequately validated and 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
One subject withdrew consent due to personal reasons. Therefore samples of 25 subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2694 ± 992	2845 ±1023	283 ± 154	4.0 (2.0-5.5)	8.8 ± 2.5
Reference	2692 ± 965	2890 ±1020	266 ± 136	4.3 (2.3-6.5)	9.7 ± 3.1
***Ratio (90% CI)**	1.00 (0.90-1.11)	-	1.05 (0.94-1.18)	-	-
CV (%)	22	-	24	-	-

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t} 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 candesartan cilexetil under fasted conditions, it can be concluded that Candesartan cilexetil Torrent 32 mg tablets and Atacand 32 mg are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation to other strengths
Additional bioequivalence studies for the 2 mg and 16 mg formulations are not necessary as:

- All the strengths are manufactured by same manufacturer, at the same site and following the same manufacturing process.
- The qualitative composition of 2 mg and 4 mg strengths, and for the 16 mg and 32 mg strengths are the same.
- The 2mg and 4mg strengths and the 16 mg and 32 mg are quantitatively proportional.
- Appropriate in-vitro dissolution has confirmed for waiving additional in vivo bioequivalence testing.

On the basis of the pharmaceutical formulation design and as section 5.4 requirements of Guideline CPMP/EWP/QWP/1401/98 are met the PK-parameters can be extrapolated from the 4 mg test formulation to the 2 mg formulation and from the 32 mg test formulation to the 16 mg formulation.

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
Candesartan was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of candesartan 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 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. Routine pharmacovigilance activities are

sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Atacand (MRP UK/H/0197/001-005) and is up to date and in line with the Article 30 referral text for candesartan.

Readability test
The PIL is in line with the recently agreed text during the Art 30 referral procedure (June 2010). 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 with 2 participants, followed by two rounds with 10 participants each. The test population consisted of an equal amount of men and women, aged 25 to 68 years, 50%. Inclusion and exclusion criteria were specified in the protocol. The test was performed in English. Educational levels correspond with the inclusion criteria set in the protocol.
The test was performed by face-to-face interviews. The developed questionnaire contained 18 questions specific to Candesartan Torrent tablets and 3 questions specific to the format of the package leaflet. Before formulating the questions, all key safety messages in the PIL were indentified and then questions were designed around those issues that would ensure a patient's comprehension and ability to act upon.
There were sufficient questions about the critical sections, and the areas concerning traceability, comprehensibility and applicability were sufficiently covered.
A satisfactory test outcome is when, for each question, 90% of all participants are able to find the information requested within the PL, and 90% of all participants can show that they understand and can act upon it. The data showed that all 18 questions met these passing criteria in the first and second round. Based on quantitative and qualitative results, there were no revisions to the PL after the first and second round of testing.
The results of the test were satisfactory. The readability test has been sufficiently performed.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Candesartan cilexetil Torrent 2 mg, 4 mg, 8 mg, 16 mg and 32 mg tablets have a proven chemical-pharmaceutical quality and are a generic form of Atacand 2 mg, 4 mg, 8 mg, 16 mg and 32 tablets. Atacand 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 SPC 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Candesartan cilexetil Torrent 2 mg, 4 mg, 8 mg, 16 mg and 32 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 28 September 2011. Candesartan cilexetil Torrent 2 mg, 4 mg, 8 mg, 16 mg and 32 mg tablets were authorised in the Netherlands on 31 October 2011.

The date for the first renewal will be: 1 March 2016

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

Quality - active substance

- The MAH committed to continue stability studies up to 60 months at long term conditions as per submitted protocol.

Quality - medicinal product

- The MAH committed to continue the ongoing stability studies at least up to the proposed shelf-life.

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
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
XRD	X-Ray Diffraction

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
Addition packaging size of 7 tablets	NL/H/2068/ 001-005/IB/001	IB	26-01-2012	08-03-2012	Approval	N
Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State; Change to in-process tests or limits applied during the manufacture of the active substance; Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance.	NL/H/2068/ 001-005/IA/002	IA	07-02-2012	22-03-2012	Approval	N