

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Sildenafil 8 mg, 16 mg and 32 mg, tablets
Laboratorios Liconsa S.A., Spain**

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/2270/002-004/DC
Registration number in the Netherlands: RVG 109133-109135**

11 July 2012

Pharmacotherapeutic group:	angiotensin II antagonists, plain
ATC code:	C09CA06
Route of administration:	oral
Therapeutic indication:	essential hypertension; treatment of 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:	19 June 2012
Concerned Member States:	Decentralised procedure with ES, IT, PT
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 Silardaf 8 mg, 16 mg and 32 mg, tablets from Laboratorios Liconsa, S.A. The date of authorisation was on 19 June 2012 in the Netherlands.

The product is indicated for:

- Essential hypertension
- Treatment of adult patients with heart failure and impaired left ventricle systolic function (left ventricular ejection fraction \leq 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-angiotensinaldosterone 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 (AT1) 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 AT1 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 (AT1) 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 product Atacand 8 mg, 16 mg and 32 mg tablets (NL License RVG 21704-21706) which has been registered in the Netherlands by AstraZeneca since 13 October 1997 (8-16 mg) and 4 October 2004 (32 mg) through MRP UK/H/0197/003-005. 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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Atacand 32 mg, registered in Spain. 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 candesartan cilexetil, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white to off-white powder, which is insoluble in water and isopropyl alcohol, slightly soluble in methanol and sparingly soluble in 0.1N NaOH. Candesartan cilexetil has one chiral centre and exists in three polymorphic forms (I, II and amorphous). The substance is manufactured as a racemic mixture as polymorphic form I.

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

Manufacturing process

The manufacturing of candesartan cilexetil consists of three or five steps, depending on the manufacturer. No class 1 organic solvents are used. The starting material from both manufacturers is acceptable.

Quality control of drug substance

For both manufacturers the drug substance specification is in line with the Ph.Eur. monograph. Batch analytical data have been provided on three batches from each manufacturing site.

Stability of drug substance

For one manufacturer, no changes at long term (12 months) or accelerated conditions (6 months) were observed. Therefore a re-test period of 24 months can be granted.

For the second drug substance supplier, stability data have been provided for seven full-scale batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). All parameters remain relatively stable at both conditions. The proposed retest period of 30 months was granted. The proposed storage condition is accepted: Store in a refrigerator, store in original packaging.

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

Medicinal Product

Composition

Silardaf 8 mg is a pink bevelled round scored tablet, with a diameter of 6.5 mm.

Silardaf 16 mg is a pink round scored tablet with a diameter of 7.0 mm.

Silardaf 32 mg is a pink round scored tablet with a diameter of 9.5 mm.

The tablets can be divided into equal halves

The tablets are packed in transparent ALU/PVC blister packs.

The excipients are: hydroxypropyl cellulose (E463), lactose monohydrate, maize starch, diethylene glycol monoethyl ether (transcutol), magnesium stearate, ferric oxide red (E172).

The 16 mg tablet is fully dose proportional to the 32 mg tablet. The 8 mg tablets differ from the 16 mg tablets in lactose monohydrate percentage to make up for the differences in active substance and colourant.

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 the characterisation of the originator product, comparative dissolution studies and optimising the manufacturing process. The subdivision of all the tablet strengths was tested during process validation. All strengths comply with the relevant Ph.Eur. monograph.

A bioequivalence study was performed with the 32 mg strengths of drug product. The batch used in the bioequivalence studies has the same composition and is manufactured in the same way as the future commercial batches. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is divided into the following steps: sifting, dry mixing, wet granulation, drying, sifting, 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 three pilot-scale batches of each strength. Process validation for larger batches sizes will be performed post authorization. This is considered to be acceptable. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph.Eur., USP-NF or in-house requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification of drug substance, identification of colorant, water content, dissolution, uniformity of dosage units (content uniformity), related substances, assay, breakability and microbial limits. The release and shelf-life limits are identical except for related substances. The analytical methods have been adequately described and validated, and are stability indicating.

Batch analytical data have been provided on three pilot-scaled batches of each strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided on three pilot-scale batches of each strength stored at 25°C/60% RH (24 months), at 30°/65% RH (6 months) and at 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 PVC-Alu blisters.

Increases in impurities were observed in all strengths and at all conditions, however stayed within the specifications. Photostability results demonstrated that the tablets are not light sensitive. Based on the observed trends, the proposed shelf-life of 24 months was granted without special storage conditions packed in PVC/Al blisters.

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

Lactose monohydrate is the only excipient of animal origin. Statements of the suppliers of the drug substances and excipients regarding BSE/TSE safety have been provided.

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 has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Silardaf 32 mg (Laboratorios Liconsas, S.A, Spain) is compared with the pharmacokinetic profile of the reference product Atacand 32 mg tablets (AstraZeneca Farmacéutica Spain, S.A.).

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.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy subjects (17 males/15 females), aged 18-44 years. Each subject received a single dose (32 mg) of one of the 2 candesartan formulations. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours. There were 2 dosing periods, separated by a washout period of 12 days. The study was performed in compliance with ICH-GCP guidelines. The study design is agreed.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

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

All 32 volunteers completed the study.

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

Treatment N=32	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	2839 \pm 761	3023 \pm 824	234 \pm 80	3.3 (2.0-6.0)	14 \pm 7
Reference	2857 \pm 891	2990 \pm 921	231 \pm 72	3.8 (2.3-6.0)	11 \pm 6
*Ratio (90% CI)	1.00 (0.91-1.10)	1.02 (0.93-1.12)	0.99 (0.87-1.15)	--	--

CV (%)	23	23	33	--	--
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*

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

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 study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to other strengths

The bioequivalence study was carried out with the highest dose (32 mg). The results of this study can be extrapolated to the other dose strengths (8 mg and 16 mg) as the conditions of section 4.1.6. of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 rev. 1) are fulfilled:

- The pharmaceutical products are manufactured at the same site by the same manufacturer and manufacturing process,
- Linear pharmacokinetics, i.e. proportional increase in AUC and C_{max} with increased dose, over the therapeutic dose range
- The qualitative composition of the different strengths is the same.
- The composition of the strengths is quantitatively proportional for the 16 and 32 mg tablet strength. As the amount of the active substance(s) is less than 5 % of the tablet core weight of the Candesartan 8 mg tablets (the amount of active substance is 4.97% in these tablets) and the amount of a filler (lactose monohydrate) is changed to account for the change in amount of active substance. The other core excipients content is the same for the concerned strengths (apart from ferric oxid red, but for immediate release products, colour agents are not required to follow this rule). And therefore the MAH concluded that the results from the bioequivalence study with the high dose, Silardaf 32 mg, can be extrapolated to the other dose strengths (8 mg and 16 mg). This is agreed.
- Appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

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).

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 SPC is identical to the art. 30 referral SPC for candesartan containing products.

Readability test

The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability.

The 1st round of testing showed that, for each question, >90% of participants were able to find the correct section, and >90% of the participants were able to answer the questions correctly. No changes were made after the first round of testing. The 2nd round of testing showed the same outcome. No changes were made after the second round of testing.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Sildenafil 8 mg, 16 mg and 32 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Atacand 8 mg, 16 mg and 32 mg 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Sildenafil 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 15 February 2012. Sildenafil 8 mg, 16 mg and 32 mg, tablets were authorised in the Netherlands on 19 June 2012.

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

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

Quality - medicinal product

- The MAH committed that in the future process validation product batch data, also blend uniformity data will be included.
- The MAH committed that validation of the manufacturing process of the candesartan 8 mg/16 mg/32 mg tablets will be performed with three of the first production batches of each site manufactured at industrial scale.
- The MAH committed that the first three batches of the largest batch size of each product strength will be put into the stability program.
- The MAH committed that production batch data will be reviewed with a view to tightening the limit for water content and tightening the dissolution limit.
- The MAH committed that during the manufacturing of the three first industrial batches it will be demonstrated that tablets within the proposed hardness range (lowest, medium and highest hardness) meet the friability specification.

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 _{1/2}	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