

Public Assessment Report

Scientific discussion

Candesartan Reddy (candesartan cilexetil)

SE/H/2449/01-03/DC

This module reflects the scientific discussion for the approval of Candesartan Reddy. The procedure was finalised on 2024-09-02. 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, a marketing authorisation has been granted for Candesartan Reddy, 4 mg, 8 mg, 16 mg, 32 mg, Tablet.

The active substance is candesartan cilexetil. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Candesartan Reddy, 4 mg, 8 mg, 16 mg, 32 mg, Tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as the sole concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Atacand, 4 mg, tablet authorised in SE since 1997, with CHEPLAPHARM Arzneimittel GmbH as marketing authorisation holder.

The reference product used in the bioequivalence studies is Atacand, 8 mg, tablet and Atacand, 32 mg, tablet, both from DE with CHEPLAPHARM Arzneimittel GmbH as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of candesartan are well known. As candesartan is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)

There are marketed candesartan tablets in the RMS and CMS, respectively, and the fact that Reddy's generic product may substitute part of the existing marketed products, is not expected to lead to increased consumption or pose any additional risk to the environment. Hence, no further environmental risk assessment is deemed necessary.

There are no objections to approval of Candesartan Reddy from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Candesartan Reddy with the reference product Atacand.

Pharmacokinetic properties of the active substance

Absorption and distribution

Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The relative bioavailability of the tablet formulation compared with the same oral solution is approximately 34% with very little variability. The estimated absolute bioavailability of the tablet is therefore 14%. The mean peak serum concentration (C_{max}) is reached 3-4 hours following tablet intake. The candesartan serum concentrations increase linearly with increasing doses in the therapeutic dose range. No gender related differences in the pharmacokinetics of candesartan have been observed. The area under the serum concentration versus time curve (AUC) of candesartan is not significantly affected by food.

Candesartan is highly bound to plasma protein (more than 99%). The apparent volume of distribution of candesartan is 0.1 l/kg.

The bioavailability of candesartan is not affected by food.

Biotransformation and elimination

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on in vitro data, no interaction would be expected to occur in vivo with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.

Total plasma clearance of candesartan is about 0.37 ml/min/kg, with a renal clearance of about 0.19 ml/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of 14C-labelled candesartan cilexetil, approximately 26% of the dose is excreted in the urine as candesartan and 7% as an inactive metabolite while approximately 56% of the dose is recovered in the faeces as candesartan and 10% as the inactive metabolite.

Study C1B03057 (8 mg)

Methods

This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Candesartan Reddy, 8 mg, immediate release tablets with Atacand, 8 mg, immediate release tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of Candesartan were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max} . The study was conducted between 13 June 2023 and 10 July 2023.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, t_{max} median, range) for Candesartan, n=60.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	903.485 ± 328.596	92.514 ± 33.626	4.000 (1.500 - 6.000)
Reference	877.047 ± 281.542	89.603 ± 26.931	3.670 (1.500 - 6.000)
*Ratio (90% CI)	102.18 (97.49-107.09%)	101.54 (95.47-107.99%)	-
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 plasma concentration			

*calculated based on ln-transformed data

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Study C1B03058 (32 mg)

Methods

This was a single-dose, two-way crossover study conducted in 60 healthy volunteers, comparing Candesartan Reddy, 32 mg, immediate release tablets with Atacand PROTECT, 32 mg, immediate release tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of Candesartan were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max} . The study was conducted between 5 July 2023 and 13 July 2023.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 2 below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range) for Candesartan, n=60.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	3338.493 $\pm$ 933.349	301.480 $\pm$ 79.577	4.178 (2.00-8.00)
Reference	3299.051 $\pm$ 1127.339	297.054 $\pm$ 96.749	4.242 (2.00-7.00)
*Ratio (90% CI)	101.36 (96.42-106.56%)	103.46 (97.44-109.85%)	-
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 plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 4 mg and 16 mg.

Discussion and overall conclusion

The bioequivalence studies and their statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 4 and 16 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of Candesartan is linear in the therapeutic dose range (i.e. between 4 mg and 32 mg).

Based on the submitted bioequivalence studies, Candesartan Reddy is considered bioequivalent with Atacand.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Since bioequivalence with the originator product has been demonstrated, no additional data is deemed necessary.

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 Reddy.

Part II Safety specification

Summary of safety concerns	
Important identified risks	• Foetal toxicity
Important potential risks	• The potential to interfere with heart growth when used long term by children that have not completed their somatic growth
Missing information	• None

The summary of safety concerns is endorsed.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Foetal toxicity	<i>Routine risk minimisation measures:</i> SmPC section 4.6: where advice is given on stopping the AIIRAs and, if appropriate, alternative therapy should be started When pregnancy is diagnosed. SmPC section 5.3: exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, and hyperkalaemia). If exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. <i>Additional risk minimisation measures:</i> No risk minimisation measures	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</i> None <i>Additional pharmacovigilance activities:</i> None
Important potential risk		
The potential to interfere with heart growth when used long term by children that have not completed their somatic growth	<i>Routine risk minimisation measures:</i> SmPC section 5.1: where stated 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. <i>Additional risk minimisation measures:</i> No risk minimisation measures	<i>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</i> None <i>Additional pharmacovigilance activities:</i> None

Part VI Summary of the RMP

The Summary of the RMP is endorsed.

Conclusion RMP assessment

The submitted Risk Management Plan, version 0.3 signed 31 May 2024, is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Atacand 4 mg/8 mg/16 mg/32 mg tablets (SE/H/1865/001-004/DC) for content and to Sitagliptin 25 mg/50 mg/100 mg film-coated tablets (DE/H/6648/001-003/DC) for layout.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Candesartan Reddy, is found adequate. There are no objections to approval of Candesartan Reddy, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Candesartan Reddy, 4 mg, 8 mg, 16 mg, 32 mg, Tablet was positively finalised on 2024-09-02.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)