LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Candesartan Devatis
(candesartan cilexetil)

SE/H/2685/001-004/DC

This module reflects the scientific discussion for the approval of Candesartan Devatis. The procedure was finalised at 2026-01-28. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Candesartan Devatis, 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.

II. EXECUTIVE SUMMARY

II.1 About the product

Candesartan Devatis 4 mg, 8 mg, 16 mg and 32 mg tablets contain candarsartan cilexetil (an angiotensin II antagonist), as active substance. The proposed indications are for the treatment of primary hypertension in adults, treatment of hypertension in children and adolescents aged 6 to <18 years and treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) when ACE inhibitors are not tolerated, or as adjunctive therapy to ACE inhibitors in patients with symptomatic heart failure despite optimal therapy when mineralocorticoid receptor antagonists are not tolerated.

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 diseases. It also has a role in the pathogenesis of target organ hypertrophy and damage. The main physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water balance and stimulation of cell growth, are mediated via the type I- (AT1-) receptor.

In hypertension, candesartan causes a dose-dependent, long-term reduction in arterial blood pressure. The antihypertensive effect is due to a decrease in systemic peripheral resistance without a reflex increase in heart rate. There is no evidence of severe or profound hypotension after the first dose or rebound effect after discontinuation of treatment.

Candesartan cilexetil is a prodrug suitable for oral use. It is rapidly converted into the active substance, candesartan, via ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin-II receptor antagonist, selective for AT1- receptors, with strong binding to and slow dissociation from the receptor. It is without agonist activity.

Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and breaks down bradykinin. There is no effect on ACE and no enhancement of bradykinin or substance P. In controlled clinical studies comparing candesartan with ACE inhibitors, the frequency of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to play an important role in cardiovascular regulation. Angiotensin II-(AT1-) receptor antagonism results in dose-related increases in plasma renin levels, angiotensin I- and angiotensin II- levels and a decrease in plasma aldosterone concentration.

In the treatment of hypertension, the recommended starting dose and usual maintenance dose is 8 mg once daily, with most of the antihypertensive effect achieved within 4 weeks. In treatment of heart failure, the usual recommended starting dose is 4 mg once daily. In the treatment of heart failure, titration to the target dose of 32 mg once daily (maximum dose) or to the maximum tolerated dose is done by doubling the dose at intervals of at least 2 weeks.

II.2 General comments on the submitted dossier

The application for Candesartan Devatis, 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 and NL as concerned member states (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 Sweden since 1997, with Cheplapharm Arzneimittel GmbH as marketing authorisation holder.

The reference products used in the bioequivalence studies are Atacand, 4 mg, tablet, and Atacand PROTECT, 32 mg, tablet, from Germany with Cheplapharm Arzneimittel GmbH as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP aspects
A statement on the application of appropriate GCP standards in the submitted studies has been provided. No issues regarding GCP have been identified. The clinical facility and bioanalytical facility were inspected by several authorities during the period 2021-2024, i.e. MHRA (2021), FDA (2022), WHO (2023) and EMA (2021 and 2024.) The inspection reports revealed no critical quality concerns. No inspection of the submitted bioequivalence studies is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

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.

Drug 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.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of candesartan cilexetil are well known. As candesartan cilexetil 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)
The applicant has presented an so called ”Art-10 ERA” document (i.e., an document that identifies a standard ERA from another product as a reference ERA) for Candesartan Devatis 4, 8, 16 and 32 mg Tablets.

- The treatment of primary hypertension in adults.

- The treatment of hypertension in children and adolescents aged 6 to <18 years.

- The treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤40%) when Angiotensin Converting Enzyme (ACE)-inhibitors are not tolerated or as add-on therapy to ACE-inhibitors in patients with symptomatic heart failure, despite optimal therapy, when mineralocorticoid receptor antagonists are not tolerated.

The recommended initial dose and usual maintenance dose of Candesartan Devatis 4, 8, 16 and 32 mg tablets is 8 mg once daily.

In the submitted Art-10 ERA the applicant has identified an approved reference ERA for Candesartan Medical Valley (approved in DK/H/3424/01-05/DC). The applicant has provided a justification outlining that the conclusions from this reference ERA are still valid.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Candesartan Devatis (Candesartan Cilexetil) with the reference product Atacand, one with the 4 mg strength and one with the 32 mg strength.

Pharmacokinetic properties of the active substance
Absorption: Following oral administration, candesartan cilexetil is converted to the active substance candesartan. The estimated absolute bioavailability of the tablet is 14%. The bioavailability of candesartan is not affected by food. The mean peak serum concentration (C_{max}) is reached 3-4 hours following tablet intake.

Linearity: The candesartan serum concentrations increase linearly with increasing doses in the therapeutic dose range.

Elimination: The terminal half-life of candesartan is approximately 9 hours.

Study 0445-23 - 4 mg strength
Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Candesartan Cilexetil, 4 mg, tablet with Atacand, 4 mg, tablet 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 a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 09 February 2024 and 19 February 2024.

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for candesartan, n=45.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**459.0 ± 139.9**	**50.7 ± 16.2**	**4.000 (2.000-6.000)**
Reference	**454.4 ± 124.1**	**52.5 ± 14.9**	**4.333 (2.000-6.000)**
***Ratio (90% CI)**	**100.5 (94.58-106.86)**	**96.1 (89.39-103.35)**	**-**
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 0153-23 - 32 mg strength
Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing

Candesartan Cilexetil, 32 mg, tablet with Atacand PROTECT, 32 mg, tablet 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 a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 20 December 2023 and 30 December 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 ± SD, t_{max} median, range) for candesartan, n=47.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**2839.8 ± 861.2**	**286.9 ± 102.1**	**4.333 (2.667-8.000)**
Reference	**2892.2 ± 676.1**	**292.2 ± 73.2**	**4.333 (2.000-7.000)**
***Ratio (90% CI)**	**96.2 (90.68-102.04)**	**95.5 (88.66-102.77)**	**-**

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 strengths of 8 mg and 16 mg.

Discussion and overall conclusion
The bioequivalence studies and the 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) and ICH Guideline M13A on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/2022). The bioanalytical methods were adequately validated.

Bioequivalence studies have been conducted with the 4 mg and 32 mg strengths. The 16 mg and 32 mg tablets and 4 mg and 8 mg are considered proportional with regard to the composition of the core of the tablet, according to criteria in the bioequivalence guideline. In that case, the 8 mg strength should have been selected for the bioequivalence study instead of the 4 mg, but there is no concern raised since the highest strength 32 mg has also been studied.

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

Absence of studies with the additional strengths of 8 mg and 16 mg is acceptable, as all conditions for biowaiver for additional strength(s), 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 between 4 mg and 32 mg.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. As bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: Devatis GmbH (SE, DE, NL)

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Devatis.

Part II Safety specification
The Summary of safety concerns is aligned with the EU RMP of the reference product Atacand and is thus endorsed.

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

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.

Part VI Summary of the RMP
The applicant has adequately summarised the proposed RMP.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 2025-07-22, 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.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Candesartan Devatis, is found adequate. There are no objections to approval of Candesartan Devatis, 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.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

Post approval commitments
N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

- **Additional risk minimisation measures (including educational material)**

  N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

  N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with Article 22 of Directive 2001/83/EC**

  N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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 language used for the purpose of user testing the PL was English. Assessment of the User Testing is attached in Appendix I.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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