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Public Assessment Report

Scientific discussion

Casaro 8 mg, 16 mg, 32 mg
Candesartan cilexetil

SK/H/0266/001-003/DC

Date: May 2022

This module reflects the scientific discussion for the approval of Casaro. The procedure was finalised at 20 May 2022. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Casaro, tablets, 8 mg, 16 mg, 32 mg, from Medreg s.r.o., Czechia.

Casaro is indicated for
- 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 (see sections 4.2, 4.4, 4.5 and 5.1).

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

This decentralised procedure concerned a generic application claiming essential similarity with the reference medicinal product Atacand (8 mg, 16 mg, 32 mg, tablets by Cheplapharm, Arzneimittel GmbH) authorised in Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Casaro is coloured, round, biconvex uncoated tablets with breakline on one or both sides. Drug substance candesartan cilexetil is present in drug product with a strength of 8 mg, 16 mg and 32 mg. The used excipients are lactose monohydrate, maize starch, hypromellose, calcium stearate, hydroxypropyl cellulose, disodium edetate, cellulose microcrystalline and iron oxide red.

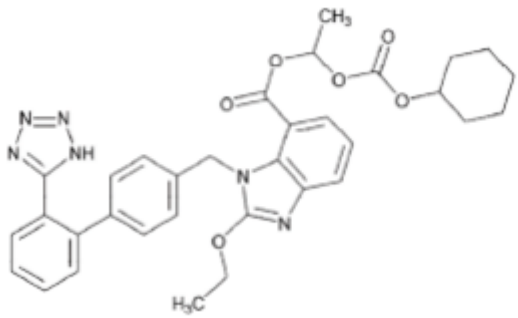
Casaro is packed in a blister packs (OPA/Al/PVC/Al blister or PVC/PVdC/Al blister).

Casaro is available in following pack sizes: 7, 14, 28, 30, 56, 70, 90 and 98 tablets.

II.2 Drug Substance

INN
candesartan cilexetil

Structural formula



Appearance
White or almost white powder, practically insoluble in water, freely soluble in methylene chloride and slightly soluble in anhydrous ethanol.

Chirality
Candesartan cilexetil has a chiral centre, exhibiting isomerism and exists in two polymorphic forms. Manufacturer consitently produces crystalline form 1 proved by X-ray crystallographic pattern.

Manufacturing
The active substance - candesartan cilexetil - is a well-known substance described in the Ph.Eur Monograph No. 01/2020:2573.

The manufacturing of a drug substance, candesartan cilexetil, was assessed in two procedures:
Certificate of Suitability (CEP) procedure:
Zhejiang Huahai Pharmaceutical Co., Ltd, China, who is a *CEP* holder
CEP is to certify the compliance of a material with the requirements laid down in the relevant monograph of the European Pharmacopoeia. Active pharmaceutical ingredients for which a Certificate of Suitability has been granted are suitable for use in medicinal products.

Active substance master file (ASMF) procedure
Torrent Pharmaceuticals Limited, India, who is a ASMF holder.
The main objective of the ASMF 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 products, the quality and quality control of the active substance. Competent Authorities thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal products.

Specifications
The specification for candesartan cilexetil has been set based upon the results obtained by multiple batch analyses and represent the quality that can be guaranteed, comply with Ph. Eur. monograph 2573.

Stability
Stability data on the active substance have been provided in accordance with applicable European guidelines demonstrating the stability of the active substance both at long term as well as at accelerated storage conditions. Based on the data submitted, retest period for 60 months (CEP)/5 years (ASMF) was granted.

II.3 Medicinal Product

The development of the product
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 were justified. The highest strength of drug product (strength 32 mg) was included in the BE study. Additional BE study on the strength 8 mg has been performed as well. The BE batches was manufactured according to the finalised composition and process. The biowaiver for the additional strength 16 mg was justified.

The manufacturing process
It consists of dry mixing, wet granulation, drying, blending and lubrication, compression and packaging. The manufacturing process was adequately validated on two pilot scale batches per strength.

The product specification

It includes tests for description, identification, average weight, dimension, water content, dissolution, uniformity of dosage units, related substances, assay and microbial quality. In general, the proposed specification is acceptable and in line with the general requirements of the Ph.Eur. and relevant guidelines.

Stability data on the product
It has been provided on two of three production scale batches stored at 25°C/60% RH (24/18/12 months), 40°C/75% RH (6 months) and for some batches also at 30°C / 65% (12 months). The conditions used in the stability studies are according to the ICH stability guideline. Sufficient data has been submitted to support the proposed shelf-life of **24 months** and storage condition **"*Do not store above 30 °C*".**

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Casaro has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic and pharmacokinetic properties of candesartan are well-known. As candesartan is widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Non-clinical overview based on literature review was, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Summary of main study results

Substance (INN/Invented Name): Candesartan cilexetil			
CAS-number (if available): 145040-37-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	log Dow = 2.11 (pH 5) log Dow = -0.675 (pH 7) log Dow = -0.902 (pH 9)	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default/refined	0.16/0.18	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OPPTS guideline 835.1110	Did not show significant adsorption to sewage sludge (a Kd value was not determined)	
Ready Biodegradability Test	OECD 301F	<5% biodegradation after 28 days Not readily biodegradable	
Aerobic and Anaerobic	OECD 308	• Mass Balance 100 ± 10% • There was no evidence of degradation in the	

Transformation in Aquatic Sediment systems		water phase • The dissipation half-lives from the water phase were 222 and 95 days for the high and low organic matter vessels, respectively. • There was very little evidence of degradation or dissipation in the sediment phase and specific sediment half-lives could not be calculated.			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Toxicity to green algae, growth inhibition test	OECD 201	NOEC	72 hour NOEC(yield) = 32 mg/L 72 hour LOEC(yield) = 56 mg/L 72 hour EC50(yield) = 56 mg/L 72 hour NOEC(growth rate) = 32 mg/L 72 hour LOEC(growth rate) = 56 mg/L 72 hour EC50(growth rate) > 56 mg/L	mg/L	*Pseudokirchinella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	21 day NOEC (reproduction, survival, length) = 10 mg/L 21 day LOEC (reproduction, survival, length) > 10 mg/L	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	32 day NOEC (hatch, survival, length and weight) = 1.0 mg/L 32 day LOEC (hatch, survival, length and weight) > 1.0 mg/L	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	3 hour EC50 >100 mg/L 3 hour NOEC = 100 mg/L	mg/L	

Conclusions on studies:
Candesartan cilexetil is not a PBT (Persistent, Bioaccumulative and Toxic) substance.

Considering the above data, candesartan cilexetil is not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

No new non-clinical studies were submitted as this was a generic MAA.
The applicant has submitted the ERA report of candesartan and it could be concluded that this generic product is unlikely to cause unacceptable risks to the aquatic environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

Applicant submitted bioequivalence studies with candesartan cilexetil 32 mg (PK-09-184) and 8 mg tablets (PK-10-190) and requested biowaiver for additional 16 mg strength.

IV.2 Pharmacokinetics

Descriptive Statistics of Formulation Means For Candesartan (32mg) in study PK-09-184

PK Parameters [N=25][1]	Candesartan Test(A)		Candesartan Reference(B)	
	Mean	± SD	Mean	± SD
[2]Tmax (hr)	4.00	2.00 – 5.50	4.33	2.33 – 6.50
Cmax (ng/mL)	282.910	153.69	266.309	135.76
AUC(0-t) (hr.ng/mL)	2694.236	992.11	2691.984	964.90
AUC(0-inf) (hr.ng/mL)	2844.591	1023.05	2890.157	1020.34
AUC_%Extrap (%)	5.433	3.26	6.794	4.45
Kel (1/hr)	0.083	0.02	0.078	0.02
T half (hr)	8.80	2.5	9.65	3.1

[1]Total evaluated subjects for Pharmacokinetic and statistical analyses.
[2]For Tmax, Median is presented instead of Arithmetic Mean &
Range (Min-Max) is presented instead of Standard Deviation.

Geometric Least Square Mean Ratios and 90% Confidence Interval for candesartan 32 mg

PK Parameters [N=25]	90% Confidence Interval (Lower limit-Upper limit)	Geometric LSM Ratio (%) (Test/Reference)	Intra Subject CV%
Ln(Cmax)	94.25 -118.05	105.48	23.51
Ln(AUC(0-t))	90.20 -111.08	100.10	21.70

Descriptive Statistics of Formulation Means For Candesartan (8 mg) in study PK-10-190

Pharmacokinetic parameter [N=30]	Arithmetic Mean (±SD)			
	Candesartan Test (A)		Candesartan Reference (B)	
	Mean	±SD	Mean	±SD
Cmax (ng/mL)	110.256	36.05	106.101	28.38
$AUC_{(0-t)}$ (hr. ng/mL)	983.953	287.17	992.153	275.64
AUC_{0-inf} (ng.hr/mL)	1028.062	303.68	1036.063	290.77
[1]Tmax (hour)	4.33	2.00 - 6.50	3.83	2.00 - 6.00
AUC%Extrap (%)	4.233	1.85	4.105	1.66
Kel (1/hr)	0.086	0.01	0.086	0.01
Thalf (hr)	8.28	1.3	8.23	1.4
[1]For Tmax, Median is presented instead of Arithmetic Mean & Range (Min-Max) is presented instead of Standard Deviation				

Geometric Least Square Mean Ratios and 90% Confidence Interval for Candesartan 8 mg

PK Parameters [N= 30]	90% Confidence Interval (Lower limit-Upper limit)	Geometric LSM Ratio (%) (Test/Reference)	Intra Subject CV%
Ln(Cmax)	92.20 - 113.59	102.34	24.02
Ln(AUC(0-t))	92.10-106.88	99.22	17.03

AUC_{0-t} *Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products*
$AUC_{0-\infty}$ *Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}*
C_{max} *Maximum plasma concentration*
t_{max} *Time until C_{max} is reached*

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Casaro is considered bioequivalent with Atacand.

The results of study PK-09-184 with Casaro 32 mg formulation can be extrapolated to other strength 16 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Casaro.

- Summary table of safety concerns as approved in RMP

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

IV.4 Discussion on the clinical aspects

Two bioequivalence studies were performed using 8 mg and 32 mg tablets (i.e. Casaro 8 mg vs Atacand 8 mg and Casaro 32 mg vs Atacand 32 mg). The bioequivalence has been demonstrated for both strengths. The results of the bioequivalence study performed with 32 mg strength were extrapolated for 16 mg strength.

V. USER CONSULTATION

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 PIL was English.
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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Casaro 8 mg, 16 mg and 32 mg have a proven chemical-pharmaceutical quality and are generic forms of Atacand 8 mg, 16 mg and 32 mg. Atacand 8 mg, 16 mg and 32 mg are well-known medicinal products with established favourable efficacy and safety profiles. Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.
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 Casaro with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 May 2022.