STATE INSTITUTE FOR DRUG CONTROL
Kvetná 11, 825 08 Bratislava, Slovak Republic

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Public Assessment Report

Scientific discussion

Casaro HCT
Candesartan cilexetil/hydrochlorothiazide

SK/H/0267/001-002/DC

Date: May 2022

This module reflects the scientific discussion for the approval of Casaro HCT 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 HCT, tablets, 16 mg/12.5 mg and 32 mg/12.5 mg from Medreg s.r.o., Czechia.

The product is indicated for:
primary hypertension in adult patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy.

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 Plus (16 mg/12.5 mg and 32 mg/12.5, 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 HCT tablets are colored, oval, biconvex, uncoated, immediate release tablets with break line on both sides in two strengths 16 mg/12.5 mg and 32 mg/12.5 mg. The used excipients are:

Casaro HCT 16 mg/12.5 mg:
Lactose monohydrate
Maize starch
Hypromellose 2910
Calcium stearate
Iron oxide red (E172)
Iron oxide yellow (E172)
Hydroxypropyl cellulose
Disodium edetate
Cellulose microcrystalline, dried

Casaro HCT 32 mg/12.5 mg:
Lactose monohydrate
Maize starch
Calcium stearate
Iron oxide yellow (E172)
Hydroxypropyl cellulose
Disodium edetate
Carmellose calcium
Ethyl cellulose
Cellulose microcrystalline, dried

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

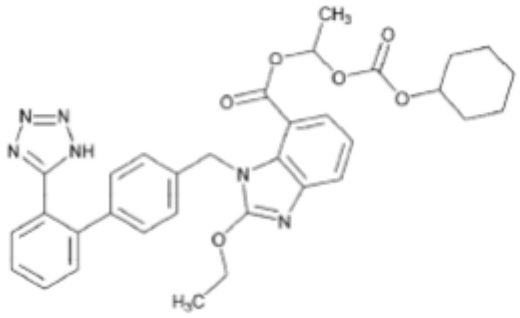
Casaro HCT is available in following pack sizes: 7, 14, 28, 30, 56, 70, 90 and 98 tablets.

II.2 Drug Substance

Candesartan

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. 2573.

The manufacturing of the 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.

Hydrochlorothiazide

INN
hydrochlorothiazide

Structural formula

Appearance
White to almost white crystalline powder, very slightly soluble in water, soluble in acetone, sparingly soluble in ethanol (96%). It dissolves in dilute solutions of alkali hydroxides.

Chirality
Achiral molecule

Manufacturing
The active substance - hydrochlorothiazide - is a well-known substance described in the Ph.Eur Monograph No. 0394.

The manufacturing of a drug substance, hydrochlorothiazide, was assessed in *Certificate of Suitability (CEP)* procedure:
Unichem Laboratories Limited, 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

Specifications
The specification for hydrochlorothiazide has been set based upon the results obtained by batch analyses and represent the quality that can be guaranteed, comply with Ph. Eur. monograph 0394.

Stability
Stability data on the active substance have been provided in accordance with applicable European guidelines demonstrating the stability of the active substance. Based on the data submitted, retest period of 5 years was granted.

II.3 Medicinal Product

The development of the product
The main development studies performed were regarding the characterization of the originator product, optimization of the formulation and comparative dissolution studies. The choice of the packaging and manufacturing process were justified.
Top spray granulation was the selected method of granulation for candesartan cilexetil and hydrochlorothiazide tablets.

The 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.

The product specification

The product specification includes tests for description, identification, average weight, 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

Stability data for 16/12.5 mg strength has been provided and 24 months long term results and 12 months intermediate results were submitted in both proposed packings, supplemented with 6 months long term data with candesartan cilexetil.
Long term stability data up to 24 months and accelerated data up to 6 months were provided for 32/12.5 mg strength in both packings.
The final shelf-life for both strengths is ***24 months.***
- with storage condition ***"Do not store above 30 °C"*** for 16 mg/12.5 mg strength
-without any special storage condition for 32 mg/12.5 mg strength.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Casaro HCT 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, pharmacokinetic and toxicological properties of candesartan as well as for hydrochlorothiazide are well known. As candesartan and hydrochlorothiazide are 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			(N)

class)					
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 Transformation in Aquatic Sediment systems	OECD 308	• Mass Balance 100 ± 10% • There was no evidence of degradation in the 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 7 2 hour NOEC(growth rate) = 32 mg/L 7 2 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	

Substance (INN/Invented Name): Hydrochlorothiazide			
CAS-number (if available): 58-93-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	Log Pow = 0.09 (pH 7)	Potential PBT (N)

Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surface\ water}$, default / refined	0.06 / 0.076	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	OECD106 OPPTS guideline 835.1110	Sludge 1 Kd(ads) = 11.9 Sludge 1 Koc(ads) = 28.9 Sludge 2 Kd(ads) = 14.2 Sludge 2 Koc(ads) = 33.0			
Ready Biodegradability Test	OECD 301B	36% degradation after 28 days Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	High organic carbon test system: Total System DT50 = 37.3 days (23.0 in Overlying Water, and 42.8 days in Sediment) 58% mineralization Low organic carbon test system: Total System DT50 = 34.7 days (23.2 in Overlying Water, and 55.5 days in Sediment) 70% mineralization Not persistent in the aquatic environment			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	Growth rate and yield: 72 hour NOEC = 100 mg/L 72 hour EC50 > 100 mg/L	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	Reproduction and length 21 day NOEC = 100 mg/L 21 day LOEC > 100 mg/L	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test	OECD 210 OPPTS 850.1400	NOEC	30 day NOEC = 10 mg/L 30 day LOEC > 10 mg/L	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	3 hour EC50 = >100 mg/L	mg/L	

Both candesartan and hydrochlorothiazide are not PBT (Persistent, Bioaccumulative and Toxic) substances.

Considering the above data, candesartan cilexetil and hydrochlorothiazide are 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 hydrochlorothizide 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 two bioequivalence studies with 32 mg/12.5 mg (**PK-11-059**) and 16 mg/12.5 mg (**PK-10-021**) strengths of Casaro HCT vs Atacand Plus tablets.

IV.2 Pharmacokinetics

Bioequivalence study PK-11-059

Descriptive Statistics of Formulation Means For Candesartan

PK Parameters [N=39][@]	Candesartan Test(A)		Candesartan Reference(B)	
	Mean	± SD	Mean	± SD
Tmax[#] (hr)	4.33	2.00-7.00	4.33	1.66-7.00
Cmax (ng/mL)	269.713	80.84	261.038	97.53
AUC(0-t) (hr.ng/mL)	3026.570	966.18	2950.173	855.88
AUC(0-inf) (hr.ng/mL)	3094.710	996.29	3013.294	883.18
AUC%Extrap (%)	2.161	1.57	2.044	1.13
Kel (1/hr)	0.09	0.0	0.09	0.0
Thalf (hr)	7.79	1.2	7.85	1.5

[@]N=Number of evaluated subjects
[#]For Tmax, Median is presented instead of Arithmetic Mean & Range (Min-Max) is presented instead of Standard Deviation.

Descriptive Statistics of Formulation Means For Hydrochlorothiazide

PK Parameters [N=39][@]	Hydrochlorothiazide Test(A)		Hydrochlorothiazide Reference(B)	
	Mean	± SD	Mean	± SD
Tmax[#] (hr)	1.66	1.00-4.66	1.66	1.00-4.66
Cmax (ng/mL)	89.838	22.83	93.818	21.47
AUC(0-t) (hr.ng/mL)	624.922	165.93	633.701	144.49
AUC(0-inf) (hr.ng/mL)	648.508	165.23	656.681	145.71
AUC%Extrap (%)	3.983	2.31	3.647	1.60
Kel (1/hr)	0.08	0.0	0.08	0.0
Thalf (hr)	8.50	1.1	8.55	1.1

[@]N=Number of evaluated subjects
[#]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 and Hydrochlorothiazide

PK Parameters [N=39]	90% Confidence Interval (Lower limit-Upper limit)	Geometric LSM Ratio (%) (Test/Reference)	Intra Subject CV%
Candesartan:			
Ln(Cmax)	93.69-117.31	104.84	30.06
Ln(AUC(0-t))	92.53-111.00	101.35	24.14
Hydrochlorothiazide:			
Ln(Cmax)	89.42-100.58	94.84	15.48
Ln(AUC(0-t))	91.85-102.97	97.25	15.04

Bioequivalence study PK-10-021

Summary Table of Pharmacokinetic Variables of Candesartan

Test : Candesartan							
Statistics:	**Tmax (hr)**	**Cmax (ng/mL)**	**AUC(0-t) (hr.ng/mL)**	**AUC(0-inf) (hr.ng/mL)**	**AUC_Extrap (%)**	**Kel (1/hr)**	**Thalf (hr)**
N	33	33	33	33	33	33	33
Mean	4.35	137.859	1490.704	1547.912	3.866	0.080	9.10
SD	1.0	46.77	518.78	531.98	2.33	0.02	2.4
Min	2.00	60.392	622.392	677.009	1.509	0.037	5.34
Median	4.33	131.969	1463.244	1508.835	3.239	0.078	8.86
Max	6.00	275.862	2920.443	2990.476	12.836	0.130	18.95
%CV	23.9	33.9	34.8	34.4	60.3	22.5	26.8
GM	4.22	130.649	1405.709	1462.673	3.387	0.078	8.84
Reference: Candesartan							
Statistics:	**Tmax (hr)**	**Cmax (ng/mL)**	**AUC(0-t) (hr.ng/mL)**	**AUC(0-inf) (hr.ng/mL)**	**AUC_Extrap (%)**	**Kel (1/hr)**	**Thalf (hr)**
N	33	33	33	33	33	33	33
Mean	4.45	132.925	1444.368	1498.295	3.859	0.080	9.12
SD	1.3	47.52	493.49	502.87	2.67	0.02	2.2
Min	2.00	46.459	562.078	635.071	1.186	0.044	6.00
Median	4.33	125.066	1396.129	1440.533	2.885	0.084	8.23
Max	7.00	224.394	2810.813	2906.566	11.494	0.116	15.88
%CV	30.3	35.8	34.2	33.6	69.2	20.9	24.0
GM	4.24	123.811	1365.422	1420.780	3.183	0.078	8.89

Geometric LSM ratio, 90% CI and Power for Study

PK Parameters [N=33]	Geometric LSM Ratio % (Test/Reference)	90% Confidence Interval (Lower limit-Upper limit)	Power
Candesartan			
Ln(Cmax)	106.12	92.05 -122.34	0.83
Ln(AUC(0-t))	103.20	93.89 - 113.44	0.99
Hydrochlorothiazide			
Ln(Cmax)	94.12	87.76 - 100.94	1.00
Ln(AUC(0-t))	95.80	90.06 - 101.91	1.00

Summary Table of Pharmacokinetic Variables of Hydrochlorothiazide

Test : Hydrochlorothiazide							
Statistics:	**Tmax (hr)**	**Cmax (ng/mL)**	**AUC(0-t) (hr.ng/mL)**	**AUC(0-inf) (hr.ng/mL)**	**AUC_Extrap (%)**	**Kel (1/hr)**	**Thalf (hr)**
N	33	33	33	33	33	33	33
Mean	2.58	76.642	563.816	586.993	4.182	0.073	9.69
SD	1.0	22.39	181.01	185.00	2.00	0.01	1.5
Min	1.00	38.574	225.349	249.020	2.159	0.050	7.32
Median	2.66	73.396	548.222	571.832	3.530	0.074	9.40
Max	4.33	131.056	1054.099	1097.037	9.566	0.095	13.79
%CV	38.2	29.2	32.1	31.5	47.8	14.6	15.4
GM	2.38	73.527	535.705	559.206	3.837	0.072	9.59
Reference: Hydrochlorothiazide							
Statistics:	**Tmax (hr)**	**Cmax (ng/mL)**	**AUC(0-t) (hr.ng/mL)**	**AUC(0-inf) (hr.ng/mL)**	**AUC_Extrap (%)**	**Kel (1/hr)**	**Thalf (hr)**
N	33	33	33	33	33	33	33
Mean	2.59	80.570	585.820	608.011	3.897	0.075	9.35
SD	1.2	19.39	172.78	174.63	1.71	0.01	1.2
Min	1.00	48.380	225.969	247.088	1.745	0.057	6.65
Median	2.66	81.930	586.291	605.857	3.349	0.073	9.50
Max	4.66	124.683	1029.168	1067.094	8.547	0.104	12.14
%CV	46.1	24.1	29.5	28.7	43.9	13.2	12.7
GM	2.30	78.229	559.989	582.787	3.584	0.075	9.28

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:
Bioequivalence between test and reference medicinal product has been shown appropriately for candesartan and hydrochlorothiazide (32 mg/12.5 mg and 16 mg/12.5 mg).

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 HCT.

- 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

Bioequivalence between Casaro HCT and Atacand Plus (32 mg/12.5 mg and 16 mg/12.5 mg) was established in both BE studies.

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 HCT 16 mg/12.5 mg and 32 mg/12.5 have a proven chemical-pharmaceutical quality and are generic forms of Atacand Plus 16 mg/12.5 mg and 32 mg/12.5 mg. Atacand Plus 16 mg/12.5 mg and 32 mg/12.5 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 HCT with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 May 2022.