COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cinacalcet Hetero 30 mg, 60 mg and 90 mg, film-coated tablets

(cinacalcet hydrochloride)

NL/H/4390/001-003/DC

Date: 14 September 2020

This module reflects the scientific discussion for the approval of Cinacalcet Hetero. The procedure was finalised on 29 April 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cinacalcet Hetero 30 mg, 60 mg and 90 mg, film-coated tablets from Hetero Europe S.L.

The product is indicated for:

Secondary hyperparathyroidism
Adults
Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

Paediatric population
Treatment of secondary hyperparathyroidism (HPT) in children aged 3 years and older with end-stage renal disease (ESRD) on maintenance dialysis therapy in whom secondary HPT is not adequately controlled with standard of care therapy (see section 4.4).

Cinacalcet Hetero may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate.

Parathyroid carcinoma and primary hyperparathyroidism in adults
Reduction of hypercalcaemia in adult patients with:

- parathyroid carcinoma.
- primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Mimpara 30 mg, 60 mg and 90 mg tablets which have been registered in the EEA by Amgen Europe B.V. since 26 October 2004 through centralised procedure EMEA/H/C/000570.

The concerned member state (CMS) involved in this procedure was Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

Cinacalcet Hetero is a light green, oval, biconvex film-coated tablet marked with "H" on one side and "C6", "C7" and "C8" on the other side. Each tablet contains cinacalcet hydrochloride equivalent to 30 mg, 60 mg or 90 mg cinacalcet.

The film-coated tablet is packed in PVC/Aclar-Aluminum blisters or High Density Polyethylene (HDPE) bottle with a cotton coil, and a child-resistant polypropylene cap with an induction seal.

The excipients are:
Tablet core - microcrystalline cellulose, pre-gelatinised starch (maize), crospovidone, talc and magnesium stearate
Tablet coating - hypromellose, lactose monohydrate, titanium dioxide (E171), triacetin, Indigo carmine aluminium lake (E132), iron oxide yellow (E172), macrogol

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is cinacalcet hydrochloride, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). It is a white to off-white, non-hygroscopic crystalline powder. It is freely soluble in methanol and ethanol, while it is poorly soluble in aqueous solutions. Cinacalcet hydrochloride exhibits polymorphism and anhydrous Form-I is manufactured. Cinacalcet hydrochloride has a single asymmetric carbon and shows optical isomerism; two isomers are possible. The R-isomer is used for the drug product, while the S-isomer is regarded as an impurity and controlled in the drug substance. The drug substance is micronised.

The Active Substance Master File (ASMF) procedure is used for 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.

<u>Manufacturing process</u>
The active substance is manufactured in a two-step synthesis followed by salt formation and purification steps. Acceptable specifications have been adopted for the starting materials, reagents and solvents. No class 1 solvents or metal catalysts are used.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches. All three batches analysed by the drug product manufacturer have been used for the manufacture of the drug product, including the test biobatch for the bioequivalence study.

Stability of drug substance

Stability data of at least three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months) have been provided for the non-micronised drug substance. The retest period is 48 months. It has been demonstrated that stability of the drug substance does not change due to micronisation.

II.3 Medicinal Product

Pharmaceutical development

The development of the products has been described, the choice of excipients is justified and their functions explained. The main development studies concerned the characterisation of the reference product, optimisation of the formulation and manufacturing process and dissolution method development. The discriminatory nature of the dissolution method has been adequately shown. The choices of the packaging and manufacturing process are justified.

A bioequivalence study has been performed with the highest product strength. The 90 mg test product used in the bioequivalence study was manufactured according to the final composition and manufacturing process. The dissolution studies in support of the biowaiver of additional strengths are acceptable.

Manufacturing process

A flow chart and a description of the manufacturing process have been provided, including in-process controls. Process validation data on the product have been presented for three commercial-scale batches. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients

All excipients comply with the Ph.Eur. monographs, with the exception of the coating material which is a non-compendial excipient mixture. The coating premixes contain ingredients that meet appropriate regulatory/compendial requirements for their intended uses. These specifications are acceptable.

Quality control of drug product

The drug product specification includes tests for description, identification of active substance, average mass, water content, dissolution, uniformity of dosage units (content uniformity), related substances, assay, microbiological examination and identification of

colourants. The release and shelf-life limits are different for water content, while identical for all other tests.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided for three full-scale batches of each strength. All batches demonstrated compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three batches of each strength stored at 25°C/60% RH (24 months) and 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 the proposed packaging (PVC/Aclar-Aluminium blisters and HDPE containers). Photostability has been demonstrated under ICH Q1B conditions. Based on the stability results a shelf life of 30 months has been granted without special storage conditions.
It was demonstrated that an in-use stability of 30 days in the HDPE containers is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate (present as component of the coating) is the only material from animal origin. BSE/TSE free certification from supplier has been submitted with regard to the lactose monohydrate being used.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cinacalcet Hetero has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Cinacalcet Hetero is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Mimpara, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology,

pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cinacalcet hydrochloride is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Cinacalcet Hetero 90 mg (Hetero Europe S.L., Spain) is compared with the pharmacokinetic profile of the reference product Mimpara 90 mg film-coated tablets (Amgen Europe B.V., the Netherlands).

The choice of the reference product in the bioequivalence study is justified as the reference product is registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver was requested for the additional 30 and 60 mg strengths. For a waiver for an additional strength to be granted, the following criteria should be fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process
b) the qualitative composition of the different strengths is the same
c) the composition of the strengths are quantitatively proportional
d) appropriate *in vitro* dissolution data among the different tablet strengths (i.e. 30, 60 and 90 mg biobatch) showing comparable dissolution
e) pharmacokinetics of should be linear in the therapeutic dose-range.

All requirements for a biowaiver of strengths have been fulfilled, and the bioequivalence conclusion obtained for the 90 mg strength can therefore be extrapolated to the other strengths.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 68 healthy male subjects, aged 20-43 years. All subjects were in a fasting state for at least 10 hours before scheduled time for high fat, high calorie breakfast. Each subject received a single dose (90 mg) of one of the 2 cinacalcet formulations with 240 ml of water. There were 2 dosing periods, separated by a washout period of 21 days.

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, 5.33, 5.67, 6, 6.5, 7, 8, 10, 12, 16, 20, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The procedures followed for a fed study are according to the bioequivalence guideline. The high calorie, high fat meal is in line with the recommended meal in the Bioequivalence guideline consisting of approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively.

The sampling period until 72 hours post-dose is sufficient to provide a reliable estimate of the extent of exposure as the absorption phase is covered for an immediate-release product.

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

Three subjects were withdrawn/dropped out in period 2 due to personal reason (n=1), withdrawn on his own accord (n=1) and due to difficulty in accessing veins before dosing (n=1). Sixty-five subjects completed the study and were included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of cinacalcet under fed conditions.

Treatment N=65	**AUC_{0-72}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	565.94± 250.99	--	70.41 ± 32.46	4.67 (2.00– 5.67)	--
Reference	541.55 ± 268.95	--	70.60 ± 37.85	4.67 (1.50– 6.00)	--
***Ratio (90% CI)**	1.06 (1.00–1.12)	--	1.01 (0.94 – 1.09)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Cinacalcet Hetero 90 mg is considered bioequivalent with Mimpara 90 mg film-coated tablets.

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).

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 Cinacalcet Hetero.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypocalcaemia • Convulsions/Seizures • Hypersensitivity reactions (including rash, urticaria and angioedema) • Hypotension and/or worsening heart failure • QT prolongation and ventricular arrhythmias secondary to hypocalcaemia
Important potential risks	• Fracture • Acute Pancreatitis • Possible drug-related hepatic disorders • Nervous system disorders (excluding seizures) • Neoplastic events
Missing information	• Use in pregnant or breastfeeding women

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Mimpara. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report. The MAH bridges the content (Key safety messages) with the Pl of the reference product Mimpara (EMEA/H/C/000570).The design and layout are bridges with another product of the proposed MAH: Levetiracetam Hetero (PT/H/0515/001-004). As the proposed PL is identical to the reference product, bridging for the content to the PL of the reference product is agreed.
Regarding the design and layout, the MAH made a comparison of the proposed PL with the PL of Levetiracetam Hetero (PT/H/0515/001-004). Critical issues, like font, text size and headings are the same in both PLs. Therefore bridging for the design and layout to the PL of Levetiracetam Hetero (PT/H/0515/001-004) is agreed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cinacalcet Hetero 30 mg, 60 mg and 90 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Mimpara 30 mg, 60 mg and 90 mg tablets. Mimpara 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 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 Cinacalcet Hetero with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 April 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse