COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cinacalcet Rafarm 30 mg, 60 mg, 90 mg film-coated tablets

(cinacalcet hydrochloride)

NL/H/4148/001-003/DC

Date: 28 March 2019

This module reflects the scientific discussion for the approval of Cinacalcet Rafarm 30 mg, 60 mg, 90 mg film-coated tablets. The procedure was finalised at 30 January 2019. 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
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
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 Rafarm 30 mg, 60 mg, 90 mg film-coated tablets from Rafarm S.A.

The product is indicated for:

Secondary hyperparathyroidism (HPT)

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

Paediatric population
Treatment of secondary 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 SmPC section 4.4).

Cinacalcet Rafarm may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see SmPC section 5.1).

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, 90 mg film-coated tablets which has been registered in the EEA by Amgen Europe B.V. since 26 October 2004 through centralised procedure EMEA/H/C/000570.

The concerned member states (CMS) involved in this procedure were Cyprus and Greece.

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

II. QUALITY ASPECTS

II.1 Introduction

Cinacalcet Rafarm is a light green, oval shaped, film-coated tablet, engraved with "30", "60" or "90" marked on one side.

Each tablet contains as active substance 30 mg, 60 mg or 90 mg of cinacalcet, as 33.06 mg, 66.12 mg or 99.18 mg of cinacalcet hydrochloride.

The film-coated tablets are packed in clear PVC/PCTFE/Aluminium blisters.

The excipients are:
Tablet core
- Pre-gelatinised starch (maize)
- Microcrystalline cellulose E460
- Crospovidone E1202
- Magnesium stearate E470b
- Colloidal anhydrous silica E551

Tablet coat
- Hydroxypropylmethyl Cellulose E464
- Titanium dioxide E171
- Lactose monohydrate
- Treacetin E1518
- Iron oxide, yellow E172
- Indigo carmine aluminium lake E132
- Macrogol E1521

The tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is cinacalcet hydrochloride, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). The active substance is soluble in dichloromethane, methanol, and ethanol and slightly soluble in water. The polymorphic form I is used. Cinacalcet hydrochloride is not hygroscopic and has one chiral centre. The R-enantiomer is used in the production of the drug product.

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.

Manufacturing process

The manufacturing process of cinacalcet hydrochloride is divided into three stages consisting of seven steps in total. The drug substance starting materials used are considered to be acceptable. No class I solvents have been used in the manufacturing process.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The specification has been established in-house by the MAH with requirements for appearance, solubility, identification, water content, sulphated ash, heavy metals, chiral purity, related substances, assay, chloride content, residual solvents, particle size distribution, and microbial contamination. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three full scaled batches stored at 30°/65% RH (48 months) and 40°C/75% RH (6 months). All parameters remained stable during the time tested and no significant changes were seen. Based on the presented stability data, a re-test period of 60 months with the storage conditions “store in well closed container below 30°C, excursions are permitted up to 40°C” is considered acceptable. However, the MAH applied for a re-test period of 36 months, and the storage conditions “Store in a well closed container at 15-25°C’’. This is granted.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The same excipients as in the reference product were selected, except for povidone, which is not present in the proposed drug product. Formulation development mainly consisted of reference product characterisation, optimisation of the formulation with regard to the selected excipients and their quantities and optimisation of the wet granulation manufacturing process. A bioequivalence study has been performed with the 90 mg product strength, and a biowaiver of strengths, for the 30 mg and 60 mg strengths, can be accepted based on the provided comparative dissolution profiles.

Manufacturing process

The manufacturing process consists of pre blending, wet granulation, final blending, compression, coating and packaging. The process is considered to be a standard manufacturing process. The manufacturing process has been adequately validated according to the relevant European guidelines. Process validation data has been presented for three

common granule batches of commercial scale, three batches of the upper (90 mg) and the lower (30 mg) strength and one batch of the middle (60 mg) strength.

Control of excipients

The excipients comply with the Ph. Eur. requirements, except for the Sheffcoat and Opadry film-coatings. The in-house specifications for the film-coatings are considered acceptable. The individual components of the film-coatings comply with the Ph. Eur., except for the colouring agents which comply with EU Regulation 231/2012. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, water content, disintegration, identification of the drug substance, identification of colourants, uniformity of dosage units by mass variation, dissolution, assay, related substances and microbial contamination. The release and shelf-life requirements and limits are identical, except for water content and total impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from three batches of the upper and lower strengths and one batch of the middle strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the drug product have been provided on three batches of the upper and lower strengths and one batch of the middle strength stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months). The conditions applied in the stability studies are according to the ICH stability guideline. Except for water content, no significant changes or up or downward trends were observed for any of the tested parameters at both storage conditions. For all tested batches a slight increase in water content is observed when stored at both storage conditions. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of four years, without any storage condition.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Except for the Sheffcoat film-coating, no materials derived from animal and/or human origin are used in the manufacture of the proposed drug product. BSE/TSE declarations have been provided. For the Sheffcoat film-coating compliance with the Note for Guidance on Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev 3) has been stated as the film-coating contains material derived from bovine milk.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cinacalcet Rafarm 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 Rafarm 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 Rafarm 90 mg film-coated tablets (Rafarm S.A., Greece) 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 has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH has requested a biowaiver for the other strengths of 30 mg and 60 mg based on the bioequivalence study of Cinacalcet Rafarm 90 mg film-coated tablets.

The following prerequisites for requesting a biowaiver for the strength of 30 mg and 60 mg based on the bioequivalence study with the strength of 90 mg are met:

- The strength have been manufactured by the same manufacturing process
- The qualitative composition of the strengths is the same and the composition of the strengths is quantitatively proportional
- The pharmacokinetics of cinacalcet can be considered dose linear within the dose range of 30-180mg
- Comparable dissolution has been shown by the MAH at three pHs for all three strengths of the drug product.

All biowaiver criteria are considered fulfilled and therefore the biowaiver of strengths can be granted.

Bioequivalence studies

Design

An open label, balanced, randomized, two-treatment, three-period, three-sequence, single oral dose, partial replicate, crossover bioequivalence study was carried out under fed conditions in 74 healthy male subjects, aged 30.6 ±6.88 years. Each subject received a single dose (90 mg) of one of the two cinacalcet hydrochloride formulations. The tablet was orally administered with 240 ml water after serving a high fat and high calorie breakfast after an overnight fast of at least ten hours. There were three dosing periods. Subjects were assigned to one of the three treatment sequences according to a schedule generated using the SAS (version 9.3 or higher, SAS Institute Inc., USA): R-R-T, T-R-R or R-T-R, whereas “R” is the Reference Product and “T” is the Test Product. Periods were separated by a washout period of at least 15 days and a maximum of 25 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.5, 2.0, 2.3, 2.7, 3.0, 3.3, 3.7, 4.0, 4.3, 4.7, 5.0, 5.3, 5.7, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the tablets should be taken with food. As such, the fed condition applied in the study is considered adequate. The wash-out period of 17-25 days is sufficient. The sampling period and sampling times are adequate.

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
In total 31 subjects were withdrawn from the study:

- Ten subjects were withdrawn due to emesis (within 12 hours after the dosing)
- Eleven subjects were withdrawn due to medical reasons
- Five subjects were withdrawn due to their own will (no-show for check-in)
- Five subjects were withdrawn due to protocol deviations (non-compliance with the diet and/or personal of the trial).

Therefore, 41 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=41	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**t_{max}** (h)
Test	373 ± 130	26.9 ± 10.2	6 (1.5-10)
Reference	366 ± 138.9	29.5 ± 12.6	6 (1.5-10)
***Ratio (90% CI)**	1.02 (0.95-1.09)	0.93 (0.85-1.01)	--
CV (%)	19	23.5	--

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

**ln-transformed values*

Safety
In general, test and reference product were well tolerated by the majority of healthy subjects in this study. Twenty-five adverse events were reported by 22 subjects during the conduct of the study. All the AEs were mild in nature except for the adverse event in one subject (Dizziness in Period-II) which was moderate in nature and all the subjects were followed up until resolution of their adverse events.

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Cinacalcet Rafarm 90 mg is considered bioequivalent with Mimpara 90 mg.

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 Rafarm.

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

Important identified risks	• Hypocalcaemia • Convulsion/seizures • Hypotension and worsening of cardiac failure • QT prolongation and ventricular arrhythmias secondary to hypocalcaemia • Hypersensitivity reactions (including rash, urticarial, angioedema)
Important potential risks	• Fracture • Acute pancreatitis • Possible drug-related hepatic disorders • Myocardial ischemia • Neoplastic events • Nervous system disorders
Missing information	• Use in pregnancy, lactation • Use in children and adolescents

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 making reference to Mimpara. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cinacalcet Rafarm 30 mg, 60 mg, 90 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Mimpara 30 mg, 60 mg, 90 mg film-coated 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 Rafarm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 January 2019.

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