

Public Assessment Report

Scientific discussion

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

(cinacalcet hydrochloride)

NL/H/4342/001-003/DC

Date: 22 April 2020

This module reflects the scientific discussion for the approval of Cinacalcet CF 30 mg, 60 mg and 90 mg, film-coated tablets. The procedure was finalised at 21 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 CF 30 mg, 60 mg and 90 mg, film-coated tablets, from Centrafarm B.V.

The product is indicated for:

Secondary hyperparathyroidism

Adults

Treatment of secondary hyperparathyroidism (HPT) in 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.

The product 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)

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

This mutual recognition 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 a centralised procedure (EMA/H/C/000570).

The concerned member states (CMS) involved in this procedure were Austria, Czech Republic, Germany, Denmark, Spain, Finland, France, Ireland, Iceland, Italy, Norway, Sweden and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Cinacalcet CF is a green, oval biconvex film-coated tablet. The 60 mg strength is embossed with a line on one side which is not intended for breaking the tablet. Each tablet contains 30 mg, 60 mg or 90 mg cinacalcet hydrochloride.

The film-coated tablets are packed in clear, transparent PVC-PCTFE-PVC/Al blisters.

The excipients are:

Tablet core – microcrystalline cellulose, maltodextrin, crospovidone, colloidal anhydrous silica, sodium starch glycolate and magnesium stearate

Tablet coat – hypromellose, titanium dioxide (E171), triacetin, iron oxide yellow (E172) and indigotine aluminium lake (E132)

The three tablet strengths are fully dose proportional.

II.2 Drug Substance

The active substance is cinacalcet hydrochloride, a well known active substance however, not described in the European Pharmacopoeia (Ph.Eur.) or any national EU Pharmacopoeia. It is a white to off-white, non-hygroscopic crystalline powder. Cinacalcet hydrochloride is soluble in methanol and 95% ethanol and slightly soluble in water. Cinacalcet hydrochloride has one asymmetric centre. Hence it shows optical isomerism; there are two enantiomers possible. The R-enantiomer is used in the production of the drug product. Cinacalcet hydrochloride can be in crystalline form and in amorphous form. The drug substance cinacalcet hydrochloride is sourced from two suppliers. Both manufacturers declare that they consistently produce the same polymorphic form I and that polymorphic form is stable.

The Active Substance Master File (ASMF) procedure is used for the active substance from both suppliers. 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 processes are sufficiently described in the ASMF procedures for both manufacturers. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for a total of three batches.

Stability of drug substance

Stability data on the active substance have been provided for a total of ten full-scale or validation batches (from both manufacturers) stored at 25°C/65% RH (60 months) and 40°C/75% RH (6 months). All the parameters remained stable during the time tested and no significant changes were observed. The proposed retest period of 5 years for both manufacturers in the proposed packaging with the storage condition for the drug substance from one manufacturer "Store in well closed container below 30°C, excursions are allowed up to 40°C" and without any special storage condition for the other manufacturer are justified. No additional stability data are needed to fully support the claimed retest period and storage conditions.

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 explained. The batches used in the formulation development studies are acceptable.

One pilot and three pivotal *in vivo* bioequivalence studies were submitted to demonstrate bioequivalence between Cinacalcet CF and reference product, Mimpara. The bioequivalence study test batches were manufactured according to the finalised manufacturing process and composition. Sufficient comparative dissolution data between the test and reference product have been provided.

For the lower strengths a biowaiver is requested. The 30 mg and 60 mg tablets are fully dose proportional film-coated tablets. Comparative dissolution data in media with different pH (1.2, 4.5, and 6.8) between 90 mg tablets and the other two strengths (30 mg and 60 mg) have been provided. The results show that the all three tablet strengths have comparable dissolution characteristics throughout the physiological pH range.

Manufacturing process

The manufacturing process is a standard process and consists of fluid bed granulation followed by compression and film coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scaled batches per product strength in accordance with

the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients, except for the film-coating, comply with the Ph.Eur. For the Opadry coating an adequate specification has been provided. The analytical procedures are in accordance with the Ph.Eur. and the excipients making up the film-coating also comply with the Ph.Eur.

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 appearance, identity, average mass, uniformity of dosage units, dissolution, assay, related substances and microbiological quality. 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 for three pilot scaled batches per product strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product are included for three pilot scaled batches, per product strength stored at 25°C/60% RH (up to 36 months) and at 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 clear, transparent Al-PVC/PCTFE/PVC blister packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

At accelerated conditions an increase in water content and an increase in average mass was observed. Disintegration time and resistance to crushing decreased significantly in all strengths. All results remained within the specifications. At long term conditions similar trends were observed although less pronounced.

The proposed storage conditions 'This medicinal product does not require any special temperature storage conditions. Store in original package in order to protect from humidity.' are acceptable. Based on the provided stability data a shelf life of 48 months can be granted.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cinacalcet CF 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 CF 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 pilot and three pivotal bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

The MAH conducted one pilot study and three pivotal bioequivalence studies in which the pharmacokinetic profile of the test product Cinacalcet CF 90 mg, film-coated tablet (Centrafarm B.V., NL) is compared with the pharmacokinetic profile of the reference product Mimpara 90 mg film-coated tablet (Amgen, UK).

Based on the results of study I and study II, the film-coated tablets were reformulated by means of increasing the particle size of the active substance. Two new bioequivalence

studies (study III and study IV) were performed using the same biobatch of the new formulation.

The choice of the reference product

The choice of the reference product in the bioequivalence studies has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH has carried out a bioequivalence study on the highest strength (90 mg). The results of the studies can be extrapolated to the lower strengths, as the criteria for biowaiving additional strengths have been fulfilled:

- The tablets are dose proportional
- The tablets are manufactured by the same manufacturer and manufacturing process
- Over the 30–180 mg dose range, cinacalcet shows linear pharmacokinetics
- Dissolution at pH 1.2, 1.3, 4.5 and 6.8 shows comparable dissolution

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in these studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – pilot study under fed conditions

In this pilot study with a 3-way, 3-period crossover design, 14 subjects received 90 mg of each of two batches of the test formulation and 90 mg of the Mimpara reference formulation under fed conditions. The washout period was 14 days. Three subjects were withdrawn due to vomiting. Blood samples were taken over 72 hours. As the confidence intervals for both AUC and C_{max} were outside the range of 80-125%, bioequivalence could not be proven for both test batches.

Bioequivalence study II – pivotal study under fed conditions

In this study with a 2-way, 2-period crossover design, 52 subjects received either 90 mg of the test formulation or 90 mg of the Mimpara reference formulation under fed conditions. The washout period was 14 days. Four subjects were withdrawn during the study. Blood samples were taken over 72 hours.

The study was designed as a two stage design study: 94.12% CI were calculated after completion of stage 1, in order to obtain the intra-subject CV and to estimate the required sample size for the second stage. The interim analysis using data of 48 subjects revealed that bioequivalence could not be achieved in the second stage in compliance with the study protocol due to a difference in C_{max} between the test and reference formulations being 14%. Bioequivalence could not be proven with a power of 80% and with a maximum planned sample size of 96 subjects.

From the results of the pivotal study it appeared that 90% CI for C_{max} was outside the normal criteria of 80 - 125%. Based upon these study results, the 90 mg test tablet was reformulated, i.e. the particle size of the active substance was increased, and two new bioequivalence studies were carried out using a new biobatch.

Bioequivalence study III – Pivotal three-period study under fed conditions

Design

A single-dose, three-way, three-period, semi-replicative, randomised, crossover comparative bioequivalence study was carried out under fed conditions in 69 healthy subjects, aged 18-52 years. Each subject received a single dose (90 mg) of one of the 2 cinacalcet formulations. The tablet was orally administered within 30 min after start of intake of a high fat, high caloric breakfast, in solid form with 240 ml water. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Cinacalcet should be taken with food or shortly after a meal, as studies have shown that bioavailability of cinacalcet is increased when taken with food. As such, the fed conditions applied in the study are considered adequate.

Results

Twelve subjects terminated the trial prematurely. Six subjects were withdrawn due to vomiting with the first 12 hours post-dose in trial period and were replaced. Another six subjects were withdrawn from the trial either due to an adverse event or on their own request in the second and third period. Therefore, a total of 57 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=57 for Test N=115 for Reference	AUC ₀₋₇₂ ng,h/ml	C _{max} ng/ml	t _{max} h
Test	269 \pm 113	27 \pm 11	3.5 (1.0-7.5)
Reference	272 \pm 116	26 \pm 12	3.5 (1.0-7.0)
*Ratio (90% CI)	0.99 (0.94-1.04)	1.03 (0.96-1.10)	--
CV (%)	18.4	27.2	--
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 CV coefficient of variation			

Based on the submitted bioequivalence study the Cinacalcet CF 90 mg tablet is considered not bioequivalent with the Mimpara 90 mg tablets. Data from one subject were excluded, as for the test formulation no cinacalcet plasma concentrations were observed. Such data may not be excluded from the statistics, and bioequivalence can not be calculated and this hampers a conclusion on proof of bioequivalence. Therefore, the MAH submitted an additional study which is discussed below.

Bioequivalence study IV – Pivotal two-period study under fed conditions

Design

A single-dose, two-treatment, two-period, randomised, crossover comparative bioequivalence study was carried out under fed conditions in 76 healthy subjects aged 18-52 years. Each subject received a single dose (90 mg) of one of the 2 cinacalcet formulations. The tablet was orally administered within 30 min after start of intake of a high fat, high caloric breakfast, in solid form with 240 ml water. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Cinacalcet should be taken with food or shortly after a meal, as studies have shown that bioavailability of cinacalcet is increased when taken with food. As such, the fed conditions applied in the study are considered adequate.

Results

Two subjects terminated the trial prematurely. Four subjects were withdrawn due to vomiting and three subjects were withdrawn on their own request. Two subjects were replaced by standby subjects. Therefore, 38 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of cinacalcet under fed conditions.

Treatment N=69	AUC ₀₋₇₂ ng.h/ml	C _{max} ng/ml	t _{max} h
Test	299 \pm 123	34 \pm 16	2.5 (1.0-12.0)
Reference	297 \pm 122	32 \pm 18	2.5 (1.0-8.0)
*Ratio (90% CI)	1.01 (0.96-1.06)	1.09 (0.99-1.19)	--
CV (%)	17.7	32.1	--
AUC₀₋₇₂ area under the plasma concentration-time curve from time zero to 72 hours C_{max} maximum plasma concentration t_{max} time for maximum concentration CV coefficient of variation			

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for bioequivalence study IV for AUC₀₋₇₂ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Cinacalcet CF is considered bioequivalent with Mimpara.

The results for the 90 mg strength can be extrapolated to the lower 30 and 60 mg strengths, as the criteria for biowaiving of additional strengths have been fully fulfilled.

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 CF.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> - Hypocalcaemia - Convulsions/seizures - Hypotension and/or worsening of cardiac failure - Hypersensitivity reactions (including rash, urticarial, angioedema) - QT prolongation and ventricular arrhythmias secondary to hypocalcaemia
Important potential risks	<ul style="list-style-type: none"> - Fractures

	<ul style="list-style-type: none"> - Acute pancreatitis - Possible drug-related hepatic disorders - Nervous system disorders (excluding seizure) - Neoplastic events
Missing information	<ul style="list-style-type: none"> - Use during pregnancy and lactation

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 an approved PL for a comparable product in a previous procedure. The PL for this product has been accepted. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cinacalcet CF 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, 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 CF with the

reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 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
NL/H/4342 /1-3/IB/001	Change in type of container or addition of a new container	PL, Label and SmPC	20-01-2020	Approved	-