CBG MEB

Public Assessment Report

Scientific discussion

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

(cinacalcet hydrochloride)

NL/H/3419/001-003/DC

Date: 24 October 2016

This module reflects the scientific discussion for the approval of Cinacalcet Sieger 30 mg, 60 mg and 90 mg, film-coated tablets. The procedure was finalised on 3 February 2016. 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 Sieger 30 mg, 60 mg and 90 mg, film-coated tablets from Sieger Pharma S.A.

The product is indicated for treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

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

Cinacalcet is also indicated for reduction of hypercalcaemia in 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 Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Cinacalcet Sieger is a green, oblong, biconvex film-coated tablet, engraved with '30', '60' or '90' on one side and plain on the other side. Each tablet contains as active substance 30 mg, 60 mg or 90 mg of cinacalcet hydrochloride.

The film-coated tablets are packed in transparent PVC/PVDC/Aluminium blisters and transparent PVC/PCTFE (Aclar)/Aluminium blisters.

The excipients are:
Tablet core – (partially) pregelatinised (maize) starch, microcrystalline cellulose (E460), croscarmellose sodium (E468), colloidal anhydrous silica (E551) and magnesium stearate (E470b).
Tablet coating - hypromellose 15cP (E464), lactose monohydrate, titanium dioxide (E171), triacetin, D&C Blue #2/Indigo carmine aluminium lake (E132) and yellow iron oxide (E172).

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is cinacalcet hydrochloride, a well known active substance not described in the European Pharmacopoeia (Ph.Eur.) or any national EU Pharmacopoeia. It is a white to off-white, non-hygroscopic crystalline powder. It is soluble in methanol and 95% ethanol and has a very low aqueous solubility, especially at basic pH (<0.001 mg/mL). Cinacalcet hydrochloride exhibits polymorphism. The anhydrous Form-I is used.
Cinacalcet hydrochloride has a single asymmetric carbon. Hence it shows optical isomerism; there are two isomers possible. Cinacalcet hydrochloride R-isomer is used for Cinacalcet 30, 60 and 90 mg film-coated tablets. The S-isomer is regarded as an impurity and controlled in the drug substance.

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
Acceptable specifications have been adopted for the starting materials, reagents and solvents. No class 1 solvents or metal catalysts are used. The manufacturing process is sufficiently described in the ASMF.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with that of ASMF holder, supplemented with an additional requirement for particle size distribution. The specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three commercial size batches.

Stability of drug substance
Stability studies have been conducted at accelerated conditions (40˚C/75% RH) for 6 months and long term conditions (30˚C/65% RH) for 36 months on three process validation batches. The retest period of 48 months, when stored below 30°C is acceptable.

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. All excipients are well known. Drug substance characterisation was performed and included particle size, chirality, polymorphism and solubility. Several formulations were tried and tested for manufacturability, dissolution and stability. The choices for the manufacturing process and packaging are justified. The pharmaceutical development of the product has been adequately performed.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Cinacalcet Sieger 90 mg, film-coated tablets and reference product, Mimpara 90 mg film-coated tablets. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. The composition of the 90 mg tablet batch used in the pivotal bioequivalence trial is identical to the final formulation chosen.

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. At pH 1.2 and 4.5 dissolution profiles are comparable between the 90 mg biobatch and the additional 30 mg and 60 mg strengths. However at pH 6.8 a difference in dissolution was observed between the 30 mg strength and the 90 mg biobatch. To demonstrate similar profiles at pH 6.8 the MAH compared 3 tablets of 30 mg and 1 tablet of 60 mg in 600 ml medium with the 90 mg test batch. Similarity was confirmed in both cases using multivariate comparison (MVC) by determining the Mahalanobsis distance. The overall data sufficiently confirm that dissolution of the 30 mg and 60 mg strengths is comparable to that of the 90 mg study test batch in pH 6.8 medium.

Manufacturing process
The manufacturing process uses wet granulation followed by compression. The process also includes dry mixing, drying, sizing, mixing, lubrication, coating, quality control and packaging. The product is manufactured with conventional manufacturing techniques. Process validation data on the product have been presented for two commercial and one pilot scaled batch. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
All inactive ingredients of Cinacalcet Sieger film-coated tablets comply with the Ph.Eur. monographs, with the exception of the coating material which is a non-compendial excipient mixture. The coating premix contains ingredients that meet appropriate regulatory/compendial requirements for their intended uses. 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 appearance, disintegration, identification of active substance, identification of the colorants, uniformity of dosage units, water content, dissolution, assay, related substances and microbiological examination. 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 each strength (two small commercial scale and one pilot) from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided on 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. All results comply over the 24-months storage period. No increase in impurity levels and no microbiological growth on storage conditions is seen. The tablets are not sensitive to light. The proposed shelf life of 36 months with storage condition 'This medicinal product does not require any special storage conditions' is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material from animal origin. BSE/TSE certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cinacalcet Sieger 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 Sieger 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.

The MAH has submitted a bioequivalence study for Cinacalcet Sieger 90 mg. For the other strengths (30 mg and 60 mg) a biowaiver is applied for. Both the bioequivalence study and the biowaiver are discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Cinacalcet Sieger 90 mg, film-coated tablets (Sieger Pharma 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 carried out the bioequivalence studies on the highest strength (90 mg). A biowaiver is requested for other strengths (30 mg and 60 mg) as cinacalcet hydrochloride exhibits linear kinetics in the studied dose range and as all the following general biowaiver criteria are 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 a pH 1.2, 4.5 and 6.8 shows comparable dissolution

Cinacalcet Sieger 30 mg and 60 mg tablets comply with the general requirements for a biowaiver. A biowaiver for these strengths was granted.

Design
A randomised, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fed conditions in 40 healthy male (n=38) and female (n=2) subjects, aged 20-44 years. Each subject received a single dose (90 mg) of one of the 2 cinacalcet formulations. The tablet was orally administered with 240 ml water after the start of intake of a high fat, high caloric breakfast. There were 2 dosing periods, separated by a washout period of 17 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets should be taken with food. Administration of cinacalcet hydrochloride with food results in an approximate 50–80% increase in cinacalcet hydrochloride bioavailability. Increases in plasma cinacalcet hydrochloride concentration are similar, regardless of the fat content of the meal. As such, the fed conditions applied in the study are considered 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
24 subjects completed the study and were eligible for pharmacokinetic analysis. A high number of subjects dropped out (n=16), mostly due to adverse events related to the treatment, like vomiting (n=15). Vomiting is also the most reported adverse event in patients. One subject dropped out due to a personal reason.

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

Treatment N=24	**AUC_{0-72}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	341 ± 126	361 ± 133	35 ± 15	4.5 (2.0 – 7.0)
Reference	349 ± 127	379 ± 154	36 ± 14	3.75 (1.50 – 7.0)
***Ratio (90% CI)**	1.00 (0.93 – 1.09)	--	0.99 (0.85 - 1.15)	--
CV (%)	15.8	--	29.9	--

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

**ln-transformed values*

Safety
A total of 15 adverse events were reported during the entire course of the study. Out of 15, 5 adverse events were observed in test product treated subjects. 8 adverse events were observed in reference product treated subjects. One adverse event was reported in the subject who did not receive any of the treatments. One adverse event was reported just before dosing of period II. As the subject had completed the washout period, it was difficult to attribute this adverse event to the treatment given in period I. The reported adverse events were either probably related to or not related to the study medication, were mild to moderate in severity and were followed up till resolution. No serious adverse event or significant adverse event was observed during the entire course of the study.

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 Sieger 90 mg, film-coated tablets 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 Sieger.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hypersensitivity reactions (including rash, urticarial

	and angioedema) • Seizures • QT prolongation and ventricular arrhythmias secondary to hypocalcaemia • Hypocalcaemia • Hypotension and/or worsening heart failure
Important potential risks	• Fracture • Acute pancreatitis • Possible drug-related hepatic disorders • Myocardial ischemia • Nervous system disorders (excluding seizure) • Neoplastic events
Missing information	• Pregnant women • Lactating women • Paediatric patients 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

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 test consisted of: a pilot test, followed by two rounds with 10 participants each. The 15 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Cinacalcet Sieger 30 mg, 60 mg and 90 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form 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 Sieger with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 February 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in product name in Slovakia due to MAH transfer.	NL/H/3419/1-3/IB/001	IB	7-9-2016	7-10-2016	Approval	N
Introduction of pharmacovigilance system of new MAH in Slovakia due to approved MAH transfer.	NL/H/3419/1-3/IA/002	IA	16-9-2016	12-10-2016	Approval	N