COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Calcedem 30 mg, 60 mg and 90 mg film-coated tablets

(cinacalcet)

NL/H/5236/001-003/MR

Date: 3 March 2021

This module reflects the scientific discussion for the approval of Calcedem 30 mg, 60 mg and 90 mg film-coated tablets. The procedure was finalised at 16 October 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
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 Calcedem 30 mg, 60 mg and 90 mg film-coated tablets, from Demo S.A.

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 SmPC section 4.4).

The product 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 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 centralised procedure EMEA/H/C/000570.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Calcedem is a green, oval biconvex film-coated tablet, debossed with "C9CC" on one side and either "30", "60" or "90" on the other side. Each tablet contains 30 mg, 60 mg or 90 mg cinacalcet hydrochloride.

The film-coated tablet is packed in PVC/PE/PVDC/Al transparent blisters.

The excipients are:
Tablet core – pre-gelatinised starch (maize), microcrystalline cellulose (E460), povidone (K-29/32), crospovidone (type A and B), magnesium stearate (572) and colloidal anhydrous silica
Tablet coat – polyvinyl alcohol-partially hydrolysed (E1203), titanium oxide (E171), macrogol (L 4000), talc (E553b), 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 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 very slightly soluble in disodium phosphate buffers at pH 1-3 and insoluble at pH 7-11. The active substance exhibits polymorphism. The anhydrous Form-I is manufactured. Cinacalcet hydrochloride has a single asymmetric carbon. Hence it shows optical isomerism; there are two isomers possible. The R-isomer is used.

For both manufacturers, 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 manufacturers 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 synthesis of cinacalcet hydrochloride involves 3 (manufacturer-I) or 7 (manufacturer-II) main steps. The manufacturing processes are sufficiently described in the ASMF procedures.

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 3 batches.

Stability of drug substance

Manufacturer-I

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 3 process validation batches. Based on the presented stability data, a re-test period of 48 months is considered acceptable with the proposed storage condition: "in a well closed container below 30°C, excursions are allowed up to 40°C".

Manufacturer-II

Stability studies have been conducted at accelerated conditions (40˚C/75% RH) for 6 months and long term conditions (25˚C/60% RH) for 9 months on 3 process validation batches. Based on the presented stability data, a re-test period of 9 months without special storage conditions is considered 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. During the development, studies were performed such as characterization of batches of the originator, *in vitro* dissolution of originator tablets and investigations of formulations and process parameters. The batches used in the formulation development studies are acceptable.

One *in vivo* bioequivalence study was submitted to demonstrate bioequivalence between Calcedem and reference product, Mimpara. The bioequivalence study test batch was 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 has been validated according to relevant European/ICH guidelines. The main steps in the manufacturing process are: dispensing of the raw materials, preparation of the granulate, preparation of the pre-compression blend, tablet compression and film-coating. Process validation data on the product have been presented for 3 small scale 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 comply with the Ph.Eur. The 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, identity, assay, related substances, uniformity of dosage units, dissolution, and microbiological purity. 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 3 small scale batches per product strength from one of the proposed production sites have been provided, demonstrating compliance with the specification. The MAH committed to provide batch analysis data of full commercial scale batches.

Stability of drug product
Stability data on the product are included for three minimal production scale batches, per product strength. The batches have been stored according to the ICH stability guideline up to 36 months at 25°C/60% RH, and 6 months at 40°C/75% RH. The batches were stored in the proposed packaging. All parameters were well within the specification limits. A photostability study has been performed, according to ICH guidelines; showing that the tablets are light resistant. A shelf-life of 3 years, without special storage conditions, in the proposed packaging is justified.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Calcedem 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 Calcedem 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 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 Calcedem 30 mg, 60 mg and 90 mg film-coated tablets (Demo S.A., Greece) is compared with the pharmacokinetic profile of the reference product Mimpara 30 mg, 60 mg and 90 mg tablets (Amgen, UK).

The choice of the reference product in the bioequivalence study 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 this study can be extrapolated to the lower strengths, as the criteria for waiving 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

Bioequivalence study

Design

A single-dose, two-treatment, two-period, randomised, crossover comparative bioequivalence study was carried out under fed conditions in 60 healthy subjects (31 males and 29 females), aged 18-49 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. The meal

comprised of approximately 240 ml whole milk, 2 large eggs, 4 ounces of hash brown potatoes (2 potato patties), 1 English muffin with approximately 4.5 g of butter and two strips of bacon. This meal consisted 34 g of protein (136 kcal), 71 g of carbohydrate (284 kcal) and 57.5 g of fat (518 kcal) for a total of 938 kcal. There were 2 dosing periods, separated by a washout period of 14 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, 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.

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
22 subjects discontinued the study; 2 for personal reasons not related to clinical events, 2 for personal reasons related to clinical events, 14 due to emesis within the restriction period, 2 due to protocol violation (breakfast not completed within 30 minutes), 1 due to an out-of-range blood calcium result prior to drug administration, and 1 for safety reasons. Therefore 38 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=38	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	343 ± 152	30 ± 15	5.25 (2.0 – 10.0)
Reference	342 ± 145	30 ± 12	5.0 (1.50 – 12.0)
***Ratio (90% CI)**	1.00 (0.96 – 1.04)	0.95 (0.88 - 1.03)	--
CV (%)	9.7	20.9	--

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

**ln-transformed values*

Safety

A total of 131 adverse events (AE) were reported by 44 (73%) of the 60 participated in this study. Of these events, 64 occurred after administration of the test product and 67 occurred after administration of the reference product. Overall, most of the AEs were deemed mild (102/131, 78%) and moderate (29/131, 22%) in severity. No severe or serious AEs were reported for any of the subjects enrolled in the study.

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC0-72 and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Calcedem is considered bioequivalent with Mimpara.

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 Calcedem.

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

Important identified risks	- Hypocalcaemia - Seizures/convulsions - QT prolongation and ventricular arrhythmias secondary to - hypocalcaemia
Important potential risks	None
Missing information	- 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 making reference to the originator product 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

Calcedem 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 Calcedem with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 16 October 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