

Public Assessment Report

Scientific discussion

**Cinacalcet Devatis 30 mg, 60 mg and 90 mg
film-coated tablets**

(cinacalcet hydrochloride)

NL/H/3388/001-003/DC

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This module reflects the scientific discussion for the approval of Cinacalcet Devatis 30 mg, 60 mg and 90 mg film-coated tablets. The procedure was finalised on 12 October 2015. 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 Devatis 30 mg, 60 mg and 90 mg film-coated tablets, from Devatis GmbH.

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

Cinacalcet Devatis 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

Cinacalcet Devatis is not indicated for use in children and adolescents. 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 Devatis is a light green, oval film-coated tablet, marked with “30”, “60” or “90” on one side. Each tablet contains 30 mg, 60 mg or 90 mg cinacalcet hydrochloride.

The product is packed in clear PVC/PCTFE-Aluminium blister packs.

The excipients are:

Tablet core

- Pre-gelatinised starch (maize)
- Microcrystalline cellulose [E460]
- Crospovidone [E1202]
- Colloidal anhydrous silica [E551]
- Magnesium stearate

Tablet coat

- Hypromellose [E464]
- Titanium dioxide [E171]
- Lactose monohydrate
- Triacetin/glycerol triacetate
- Iron oxide, yellow [E172]
- Indigo carmine aluminium lake [E132]
- Macrogol [E1520]

The three tablets 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 manufactured. The active substance has a single asymmetric carbon. Hence it shows optical isomerism; there are two isomers possible. The R-isomer is used. 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

The synthesis of cinacalcet hydrochloride involves 2 main steps. The manufacturing process is sufficiently described in the ASMF.

Quality control of drug substance

The drug substance specification of the MAH is in line with that of ASMF holder, supplemented with an additional requirement for particle size distribution. For the added test on particle size distribution the MAH has given an upper limit. Justification has been provided why an additional lower limit is not deemed necessary.

Batch analytical data demonstrating compliance with this specification have been provided for two commercial size batches.

Stability of drug substance

The ASMF holder has conducted stability studies at accelerated conditions ($40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$) for 6 months and long term conditions ($30 \pm 2^\circ\text{C}/65 \pm 5\% \text{RH}$) for 36 months on three process validation batches. The drug substance is intended to be stored at room temperature. The approved retest period is 48 months.

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. All excipients are well known. Drug substance characterization was performed and included particle size, chirality, polymorphism and solubility. 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 Devatis 90 mg film-coated tablets and reference product, Mimpara 90 mg film-coated tablets obtained from The Netherlands. The bioequivalence study test batch was manufactured according to the finalized 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 (>85% in 15 minutes) 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 description of the manufacturing process is sufficiently detailed. The process includes weighing, sieving, dry mixing, granulating, drying, sieving of granules, mixing with pre-lubrication mix, mixing with lubricant, compression of lubricated granules, preparation of coating solution, film coating in two steps and packaging.

With regard to process validation, data on the product have been presented for three full 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 inactive ingredients of Cinacalcet Devatis comply with the Ph.Eur. monographs, with the exception of the coating materials which are non-compendial excipient mixtures. These coating premixes contain ingredients that meet appropriate compendial requirements for their intended uses. The specifications are acceptable.

Quality control of drug product

The product 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. The release and shelf-life requirements/limits are identical except for the proposed limits for water content and total impurities. The limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on seven batches: two full scale batches of 30 mg and one at half scale; one full scale batch of 60 mg; and two full scale batches of 90 mg and one at half scale. All batches demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on seven batches stored at 25°C/60% RH (12 months), 30°C/65% RH (12 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 6/12-months storage period. In general, the content of cinacalcet remains stable over time and no increase in impurity levels is seen. The drug product is stable against UV and day light.

A shelf life of 24 months is assigned. The claimed storage condition 'This medicinal product does not require any special storage conditions' is accepted.

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 Devatis 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 Devatis 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 Devatis 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 Devatis 90 mg film-coated tablet (Devatis GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Mimpara 90 mg film-coated tablet (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 pharmaceutical products are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance is the same for all strengths
- Appropriate *in vitro* dissolution data confirms the adequacy of waiving:
 - Dissolution tests have been performed in pH 1.2, pH 4.5 and pH 6.8. Comparable dissolution is shown at pH conditions.

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

Design

A single-dose, randomised, two-treatment, three-period, crossover, partial-replicate, comparative bioequivalence study was carried out under fed conditions in 74 healthy male subjects, aged 19-44 years. Each subject received a single dose (90 mg) of one of the 2 formulations. The tablets were orally administered 30 min after start of intake of a high fat, high caloric breakfast, in solid form with 240 ml water. There were three dosing periods, separated by a washout period of 17 days. The test formulation was administered once, and the reference product was given twice to each subject.

Blood samples were taken 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, 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.

A partial-replicate design was applied to use the observed intra-subject variability for C_{max} of the Reference for scaling the 90% confidence intervals. The bioequivalence acceptance criteria were based on intra-subject variability of reference product as follows:

- If the intra-subject coefficient of variability (CV) for C_{max} parameter was >30% for reference product in the study, then the product was considered as highly variable and limit for bioequivalence for C_{max} was applied based on scaled average bioequivalence approach. However, in this case the point estimate (T/R) should fall between 80-125%.
- If the intra-subject CV for C_{max} parameter was <30% for reference product in the study, then conventional bioequivalence limit was considered for C_{max} . In that case, the test product was considered to be bioequivalent to the reference product if the 90% CI for the ratio of the geometric least square means of natural log transformed C_{max} of test and reference formulations fall within 80% to 125%.

In any case, the conventional average bioequivalence criteria using 90% confidence intervals (CI) was to be considered as 80.00% to 125.00% for AUC_{0-72} .

Results

41 subjects completed the study and were eligible for pharmacokinetic analysis. A high number of subjects dropped out (n=31), mostly due to adverse events related to the treatment, like vomiting (n=10). Vomiting is also the most reported adverse event in patients.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of cinacalcet hydrochloride 90 mg under fed conditions.

Treatment N=41	AUC_{0-72} ng.h/ml	C_{max} ng/ml	t_{max} h
Test	373 ± 130	27 ± 10	-6.0 (1.5 – 10.0)
Reference	366 ± 139	29 ± 13	-6.0 (1.50 – 10.0)
*Ratio (90% CI)	1.02 (0.95 – 1.09)	0.93 (0.85 – 1.01)	--
CV (%)	19	23.5	--
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			

**In-transformed values*

Conclusion on bioequivalence study:

A replicate design was applied. However, as the intra-subject variability was below 30%, scaling had not to be applied. The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} were inside the normal range of acceptability (0.80 – 1.25). Based on the submitted bioequivalence study Cinacalcet Devatis 90 mg tablet is considered bioequivalent with the Mimpara 90 mg tablet.

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 Devatis film-coated tablets.

Summary table of safety concerns as approved in RMP:

Important identified risks	<ul style="list-style-type: none"> • Hypocalcemia • Convulsions/seizures • Hypersensitivity reactions (including rash, urticarial, angioedema) • Hypotension and/or worsening of heart failure • QT prolongation and ventricular arrhythmias secondary to hypocalcemia
Important potential risks	<ul style="list-style-type: none"> • Fracture • Acute pancreatitis • Possible drug-related hepatic disorders • Myocardial ischemia • Nervous system disorder (excluding seizure) • Neoplastic events
Missing information	<ul style="list-style-type: none"> • Pregnant women • Lactating women • Paediatric patients

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 film-coated tablets. 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 the originator product Mimpara. The only differences between the PL for Cinacalcet Devatis and the PL for Mimpara were administrative differences, layout differences and differences relating to the composition. The latter are the product-specific descriptions listed in chapter 5 and 6 of the PL, i.e. the appearance of the tablets, pack-sizes, listing of excipients and storage conditions. These chapters are usually not subject of the user testing. The differences, are considered not to impact the readability. The lay-out differences are in line with previous successful user tests of the MAH. Therefore the results of this test can be bridged to the PL for Cinacalcet Devatis. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cinacalcet Devatis 30 mg, 60 mg and 90 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Mimpara 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 Devatis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 October 2015.

There were no post-approval commitments made during the procedure.

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 the address of manufacturer/importer of the finished product.	NL/H/3388/001 /IA/001/G	IA	5-2-2016	6-3-2016	Approval	No
Change in the name of the medicinal product for nationally authorised products in accordance with the change in MAH.	NL/H/3388/001 /IB/001/G	IB	5-2-2016	6-3-2016	Approval	No