Bundesinstitut
für Arzneimittel
und Medizinprodukte

PUBLIC ASSESSMENT REPORT

Decentralised Procedure

Cinacalcet-ratiopharm 30 mg; 60 mg; 90 mg Filmtabletten
Cinacalcet AbZ 30 mg; 60 mg; 90 mg Filmtabletten

Procedure Number: DE/H/4202-4203/001-003/DC

Active Substance:
Cinacalcet hydrochloride

Dosage Form:
film-coated tablets

Marketing Authorisation Holder in the RMS, Germany:
ratiopharm GmbH (DE/H/4202/001-003/DC)
AbZ-Pharma GmbH (DE/H/4203/001-003/DC)

Publication:
20.08.2019

This module reflects the scientific discussion for the approval Cinacalcet-ratiopharm / AbZ Filmtabletten. The procedure was finalised on 16.12.2015.

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Cinacalcet-ratiopharm 30 mg, 60 mg and 90 mg Filmtabletten, Cinacalcet AbZ 30 mg, 60 mg and 90 mg Filmtabletten	
Name of the drug substance (INN name)	Cinacalcet hydrochloride	
Pharmaco-therapeutic group (ATC)	H05BX01	
Pharmaceutical form and strength	30 mg, 60 mg and 90 mg film-coated tablets	
Reference Number for the Decentralised Procedure	DE/H/4202/001-003/DC DE/H/4203/001-003/DC	
Reference Member State	DE	
Concerned Member States	DE/H/4202/01-03/DC DE/H/4203/01-03/DC	AT, BG, CY, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, SE, SK, UK LU
Marketing Authorisation Holder (name and address)	*DE/H/4202/001-003/DC* ratiopharm GmbH Graf-Arco-Str. 3 89079 Ulm Germany *DE/H/4203/001-003/DC* AbZ-Pharma GmbH Graf-Arco-Str. 3 89079 Ulm Germany	
Names and addresses of all proposed manufacturer(s) responsible for batch release in the EEA	PLIVA Hrvatska d.o.o. (PLIVA Croatia Ltd.) Prilaz baruna Filipovica 25, 10000 Zagreb Croatia	

I INTRODUCTION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for Cinacalcet-ratiopharm 30, 60 and 90 mg Filmtabletten (DE/H/4202/001-003/DC) and Cinacalcet AbZ 30, 60 and 90 mg Filmtabletten (DE/H/4203/001-003/DC), indicated for

- Treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.
- Cinacalcet-ratiopharm / AbZ 30, 60 and 90 mg Filmtabletten may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate.
- 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

is approved.

II EXECUTIVE SUMMARY

II.1 About the Product

This decentralised application concerns a generic version of cinacalcet hydrochloride, under the trade names Cinacalcet-ratiopharm Filmtabletten (DE/H/4202/001-003/DC) and Cinacalcet AbZ Filmtabletten (DE/H/4203/001-003/DC) in the RMS. The different product names proposed during the procedure may be used interchangeably in this report. Marketed dose strengths for each product will be 30, 60 and 90 mg.

The originator product is Mimpara 90 mg Film-Coated Tablet (MA no. EU/1/04/292/009-012), Amgen Europe B.V, The Netherlands, registered centrally in the EU since 26 October 2004.

With DE as the Reference Member State in this Decentralised Procedure, ratiopharm GmbH and AbZ-Pharma GmbH applied for the Marketing Authorisations for Cinacalcet-ratiopharm Filmtabletten in the RMS and in AT, BG, CY, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, SE, SI, SK and UK; for Cinacalcet-AbZ Filmtabletten in the RMS and in LU.

Cinacalcet is a calcimimetic agent that increases the sensitivity to extracellular calcium of the calcium-sensing receptors of the parathyroid gland, which regulate parathyroid hormone secretion; this results in a reduction in parathyroid hormone secretion as well as a decrease in serum calcium. Cinacalcet hydrochloride is given orally in the treatment of secondary hyperparathyroidism (HPT) in patients with end stage renal-disease (ESRD) on maintenance dialysis therapy. It may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate. It is further indicated for the reduction of hypercalcaemia in patients with parathyroid carcinoma or 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.

Doses are expressed in terms of the base; cinacalcet hydrochloride 33 mg is equivalent to about 30 mg of cinacalcet.

In the treatment of secondary hyperparathyroidism, the initial dose is 30 mg once daily, increased at intervals of 2 to 4 weeks by 30 mg to a maximum of 180 mg daily.

For the treatment of hypercalcaemia in patients with parathyroid carcinoma or primary hyperparathyroidism, cinacalcet is given in an initial dose of 30 mg twice daily, increased sequentially at intervals of 2 to 4 weeks to a maximum of 90 mg three or four times daily.

II.2 General Comments on the Submitted Dossier

The application is submitted under article 10 (1), generic application of Council Directive 2001/83/EC, as amended, claiming to be a generic to the reference products Mimpara 90 mg Film-Coated Tablet (MA no. EU/1/04/292/009-012), Amgen Europe B.V, The Netherlands, registered centrally in the EU since 26 October 2004.

One pivotal bioequivalence study was submitted. The reference product used in these studies was Mimpara 90 mg Film-Coated Tablet (MA no. EU/1/04/292/009-012), Amgen Europe B.V, The Netherlands, sourced from the German market. The applicant requested a biowaiver for the additional strengths of 30 mg and 60 mg.

This approach is accepted, and no further clinical data are required.

The clinical overview was well written and it refers publications up to the year 2014.

Together with the submitted documentation the information given in the submitted dossier is sufficient for this generic application.

II.3 General Comments on Compliance with GMP, GLP, GCP and Agreed Ethical Principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

It is stated in the study report that the bioequivalence study was conducted in accordance with GCP. During the assessment, there were no indications for non-compliance with GCP.

III SCIENTIVIC OVERVIEW AND DISCUSSION

III.1 Quality Aspects

Introduction

The chemical-pharmaceutical documentation is of sufficient quality in view of the present European regulatory requirements.

Drug Substances

The active ingredient of Cinacalcet 30 mg, 60 mg and 90 mg FCTs is Cinacalcet hydrochloride which is not monographed.

The documentation of the active substance Cinacalcet hydrochloride is presented as an Active Substance Master File (ASMF). Additional data has been presented from the drug product manufacturer.

The synthesis is sufficiently described; all requirements of the ASMF Guideline are fulfilled.

Although the synthesis is only a two-step-synthesis p, the synthesis is accepted due to the fact that both starting material are simple molecules and the introduction of the chiral center (here resolution of a racemate) is under GMP control.

Cinacalcet hydrochloride and its identified impurities have been sufficiently characterised.

The possible impurity profile of drug substance has been discussed in detail.

The active substance specification is in line with the General Monograph "Substances for

pharmaceutical use" 04/2013:2034 and ICH Q3A and Q6A guidelines.

The methods used are described in detail. The validation data provided are in accordance with the requirements of the relevant ICH guidelines.

The information about reference standards and container closure system is considered adequate.

The stability program is carried out according to ICH guidelines on stability testing. Results of eight production batches were all within specifications and no significant changes are observed with exception of same impurity results (no degradation impurities). This was explained sufficiently. The re-test period of the substance is 5 years in (into polyethylene bag, tied with a cable and introduced into an aluminium laminated bag) material is acceptable.

Drug Product

The goal of pharmaceutical development was to develop an immediate-release solid dosage form in three strengths, which are stable and essentially similar to the reference product Mimpara® 30 mg, 60 mg and 90 mg film-coated tablets marketed by Amgen Europe B.V. The new medicinal product will be marketed in three strengths: Cinacalcet 30, 60 and 90 mg FCTs. The development work of the formulation has been shortly described.

The dissolution method has been sufficiently developed. The discriminatory power of the dissolution test method has been evaluated by comparing dissolution profiles of the test product with some modifications. The choice of the speed rate and the dissolution media is justified for the QC testing.

Sufficient dissolution profiles of the reference and the test products of all strengths have been presented (speed rate 75 rpm, in 0.05N HCl, release media at pH 4.5 and pH 6.8). All dissolution profiles are comparable. The higher speed rate of 75 rpm has been justified.

The drug products are manufactured by the same manufacturing process; the qualitative composition of the different strengths is the same; the composition of the strengths is quantitatively proportional, and the dissolution profile is similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study. The extrapolation of the results from the bioequivalence study conducted with 90 mg strength to the lower strengths of 30 mg and 60 mg could be acceptable from the quality point of view.

The composition of the drug product is satisfactorily described.

The manufacturing process of the finished product has been sufficiently described. Holding times are adequately set. The IPCs used are acceptable specified. The validation results presented indicate that the process is robust and reproducible.

The presented specification is suitable to control the quality of the drug product.

All methods have been described in detail. The validation data provided are in accordance with the requirements of the relevant ICH guidelines.

Satisfactory batch analyses have been presented. The batch analyses data together with the results obtained from the validation study and stability testing confirm consistency and uniformity of the product based on the parameters tested and indicate the reproducibility of the manufacturing process for the drug product.

The suitability of the working standards has been shown.

The drug products are packed in PVC/ACLAR/PVC - Alu blister packs, in PVC/ACLAR/PVdC/PVC - Alu blister packs, and in HDPE bottles with or without silica gel desiccant. The applied primary packaging systems are standard for solid oral formulations. The provided specifications and information for the proposed container closure systems are considered as sufficient.

The conditions used in stability studies are according to the ICH stability guideline. Test results of stability testing at long-term and intermediate conditions up to 24 months and accelerated conditions up to 6 months have been provided for the new medicinal products. The results of in-use stability are acceptable.

Based on the obtained results, a shelf-life of 24 months with no special storage conditions can be accepted.

III.2 Nonclinical Aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Cinacalcet are well known. As Cinacalcet is a well-known substance, the Applicant refers to published literature.

From a non-clinical point of view there are no objections against a marketing authorisation.

Environmental Risk Assessment (ERA)
Since Cinacalcet-ratiopharm / AbZ 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.3 Clinical Aspects

One bioequivalence study was submitted. The study was a single-dose, randomized, two-period, two-sequence, two-treatment, crossover bioequivalence study under fed conditions with a period of washout of at least 14 calendar days between the two periods in order to prevent a carry-over effect. A single dose study in fed condition is adequate and in line with the recommendations of the Guideline on the investigation of Bioequivalence [CPMP/EWP/QWP/1401/98 Rev. 1/Corr** (BE-GL), as the SmPC recommend intake of the reference medicinal product only in the fed state.

Beside others, subjects in presence of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease were excluded.

The study population included healthy volunteers from 18 to 74 years of age, with a BMI from 21.0 to 29.2 kg/m^2. Each subject received one tablet of the test product or the reference product in each study period. A period of washout of at least 14 days was left between the two periods in order to prevent a carry-over effect. The reference product was Mimpara film-coated tablets, Amgen Europe B.V., The Netherlands (Source DE), approved centrally in the EU (MA no. EU/1/04/292/009-012).

Of the 42 healthy male and female subjects who were included in the study (FAS), 37 subjects received a single oral dose of the assigned formulation on day 1 and day 15 and 34 subjects completed the study (PPS).

The concentration of cinacalcet in human plasma samples was determined according an HPLC-MS/MS method. The compounds (cinacalcet HCL and cincaclcet-D4 HCL as internal standard) were identified and quantified over a theoretical concentration range of 0.250 ng/mL to 100.000 ng/mL. The validation was performed in compliance with the relevant EMA guidelines. From the results of the pre- and within-validation studies could be concluded that the method has adequate sensitivity, precision, accuracy and selectivity to determine cinacalcet in plasma at the concentration levels expected in real samples.

The main pharmacokinetic parameters of cinacalcet are displayed in the following table:

Table 1: Pharmacokinetic parameters (n=34)
(non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-72h} [ng/ml/h]	$AUC_{0-\infty}$ [ng/ml/h]	C_{max} [ng/ml]	t_{max} [h]	$T_{1/2}$ [h]
Test	318.737 ±157.489	342.167 ±175.368	30.183 ±16.758	4.00 (2.00 – 7.00)	24.55
Reference	330.268 ±152.112	355.302 ±170.058	32.580 ±15.715	4.5 (1.00 – 12.00)	25.03
***Ratio (90% CI)**	96.00 (91.57 – 100.66)	95.76 (91.34-100.40)	91.20 (84.37 – 98.59)		
CV (%)	11.6	11.6	19.1		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration (median (min, max))
$T_{1/2}$ half-life
* ln-transformed values

With regard to the submitted results of the bioequivalence study for the 90 mg strength, bioequivalence of Test 90 mg and Mimpara 90 mg has been shown. The applicant requested a biowaiver for the additional strengths of 30 mg and 60 mg. The Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98Rev.1/Corr**) states in section 4.1.6 "Strength to be investigated" that if several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and other product related issues. As 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 is quantitatively proportional, the drug input has been shown to be linear over the therapeutic dose range and the dissolution profile is similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study, the extrapolation of the results from the bioequivalence study conducted with 90 mg strength to the lower strengths of 30 mg and 60 mg is acceptable. The informative texts of the SmPC and PL including the therapeutic indication are in line with the originator Mimpara.

Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk management Plan

Summary of safety concerns	
Important identified risks	• Hypocalcaemia • Convulsions/seizures • Hypersensitivity reactions (including rash, urticaria, and angioedema) • Hypotension and/or worsening heart failure • QT prolongation and ventricular arrhythmias secondary to hypocalcemia
Important potential risks	• Fractures • Acute pancreatitis • Possible drug-related hepatic disorders • Myocardial ischemia • Nervous system disorders (excluding seizure) • Neoplastic events
Missing information	• Pregnant women • Lactating women • Paediatric patients

The Applicant has provided an RMP v. 1.3 within the new format of GVP module V.

Neither additional pharmacovigilance measures nor additional risk minimisation measures were proposed for the safety concerns, which is acceptable.

The RMP version 1.3 is approvable.

Periodic Safety Update Report (PSUR)

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal

Common renewal date
A common renewal date of 5 years after finalisation of the procedure was accepted.

Legal status
Medicinal product subject to medical prescription.

User Test
The results of this test indicate that the PIL provides a set of comprehensible information enabling the use of the medicinal product safely and appropriately. Some interviewees considered e.g. that the leaflet "*should be more concise and would like the use of more bullet points*" and that there are "*too much information*", this is due to the fact that the safety information cannot be shortened without losing safety relevant content which can also be found in the SmPC.

IV BENEFIT RISK ASSESSMENT

Approval can be recommended from a clinical and non-clinical point of view. The informative texts of the SmPC and PL including the therapeutic indication are in line with the originator Mimpara.

Approval can also be recommended from the quality point of view.

The application is approved. For intermediate amendments see current product information.

VI. PROPOSED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

VI.2 Final list of recommendations not falling under Article 21a/22 of Directive 2001/83 / positive benefit risk assessment

Description	Due date
The Applicant and restricted parts of the EU DMF version of Cinacalcet Hydrochloride will be updated.	after completion of the DCP procedures