COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(cinacalcet hydrochloride)

NL/H/4345/001-003/DC

Date: 10 September 2019

This module reflects the scientific discussion for the approval of Cinacalcet Aristo 30 mg, 60 mg and 90 mg, film-coated tablets. The procedure was finalised on 10 June 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
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
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 Aristo 30 mg, 60 mg and 90 mg, film-coated tablets from Aristo Pharma GmbH.

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 section 4.4 of the SmPC).

Cinacalcet Aristo may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section 5.1 of the SmPC).

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 decentralised procedure concerns a generic application claiming essential similarity with the innovator product Mimpara 30 mg, 60 mg and 90 mg tablets, which has been registered in the EEA by Amgen Europe B.V. since 26 October 2004 through centralised procedure EMEA/H/C/000570.

The concerned member states (CMS) involved in this procedure were Austria, Czech Republic, Denmark, Finland, Germany, Italy, Norway, Poland, Portugal, Romania, Spain, Sweden, Slovakia 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 Aristo is a white to off-white, oval shaped film-coated tablets debossed with either '30', '60' or '90' on one side. Each film-coated tablet contains cinacalcet hydrochloride equivalent to 30 mg, 60 mg or 90 mg cinacalcet.

The film-coated tablet are packed in PVC/PVDC/Aluminium blisters.

The excipients are:
Tablet core - maize starch pregelatinised, crospovidone, microcrystalline cellulose, colloidal anhydrous silica, sodium stearyl fumarate
Film-coating - hypromellose, lactose monohydrate, titanium dioxide (E 171), triacetin, macrogol

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. The active substance is a white to off-white crystalline powder, which is soluble in methanol and ethanol and insoluble in water. Crystalline Form-I is used. Cinacalcet hydrochloride is not hygroscopic and has one chiral center. The R-enantiomer is produced.

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.

<u>Manufacturing process</u>
The manufacturing process of cinacalcet hydrochloride is divided into one synthesis line of five stages (four full chemical steps and one purification step), and a side synthesis line of 2 stages. For all steps adequate descriptions, adequate in-process controls and adequate specifications on intermediates are applicable. No class I solvents are used in the manufacturing process applied by both suppliers.

Quality control of drug substance
In-house drug substance specifications have been laid down by the ASMF-holder and MAH. A USP NF Draft Monograph appeared, in USP NF 42(4). In this monograph cinacalcet related compounds A-B-C-D-E are limited. These cinacalcet related compounds are sufficiently limited by the ASMF-holder.

Stability of drug substance
Six process validation batches are used in the stability studies. Data up to 36 months is available. The drug substance is relatively stable. No changes or significant trends could be observed. Based on the available stability data the claimed re-test period 36 months has been granted. The product does not need a specific storage temperature condition. Store in the original container in order to protect from moisture.

II.3 Medicinal Product

Pharmaceutical development
The development of the drug product has been described, the choice of excipients is justified and their functions are explained. The same excipients as in the reference product were selected, except for povidone, which is not present in the proposed drug product. Formulation development mainly consisted of reference product characterisation, optimisation of the formulation with regard to the selected excipients and their quantities and optimisation of the wet granulation manufacturing process.
A bioequivalence study has been performed with the 90 mg product strength. A biowaiver of strengths for the 30 mg and 60 mg strengths has been requested. For both the bioequivalence study as well as the biowaiver of strengths for the 30 mg and 60 mg strengths, comparative dissolution data have been provided. The results show that the all three tablet strengths have comparable dissolution characteristics throughout the physiological pH range. The biowaiver of the additional strengths is acceptable.

Manufacturing process
The manufacturing process consists of preblending, wet granulation, final blending, compression, coating and packaging. The process is considered a standard manufacturing process. The manufacturing process has been adequately validated according to the relevant European guidelines. Process validation data has been presented for two common blend batches of commercial scale, each split up into batches of the 30 mg – 60 mg – 90 mg strengths.

Control of excipients
The excipients comply with the Ph. Eur. requirements, except for the two film-coatings. The in-house specifications for the film-coatings are considered acceptable. The individual components of the film-coatings comply with the Ph. Eur.

Quality control of drug product
The drug product specification includes tests for description, water content, identification of the drug substance, uniformity of dosage units by mass variation, dissolution, assay, related

substances and microbial contamination. The release and shelf-life requirements and limits are identical, except for water content. The analytical methods have been adequately described and validated. Batch analytical data have been provided for two batches of each strength, demonstrating compliance with the release specifications.

Stability of drug product

Stability data on the drug product have been provided on two batches of each strength stored at 25°C/60% RH (18 months), 30°C/75% RH (6 months) and 40°C/75% RH (6 months). The batches were stored in blister packs of PVC/PVdC-Alu. For all conditions and time periods no significant changes and no clear trends were observed. Based on the available data and on extrapolation, a shelf-life of 30 months has been granted. This medicinal product does not require any special storage conditions.

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

The film-coating contains lactose monohydrate. BSE/TSE declarations have been provided, demonstrating compliance with the Note for Guidance on Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev 3). Sodium stearyl fumarate is synthetic: the raw material stearyl alcohol is of vegetable origin. Triacetin is made from rapeseed oil.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cinacalcet Aristo has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH committed to re-evaluate to water content at the end of shelf life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Cinacalcet Aristo 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 bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Cinacalcet Aristo 90 mg, film-coated tablet (Aristo Pharma 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
The choice of the reference product in the bioequivalence study is justified as the reference product was authorised in Europe through a centralised procedure. 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 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 data shows comparable dissolution.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 24-42 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 breakfast consisted of 40 g fried chicken, 2 Bomaby toast, 30 g French fries and 240 ml whole milk. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected 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, 6.5, 7, 7.5, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets should be taken with food. As such, the fed condition applied in the study is 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

Three subjects did not report to the clinical facility for Period II. The remaining 33 subjects completed in the study and were included in the analysis.

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

Treatment N=33	**AUC_{0-72}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	761 ± 323	--	92 ± 35	4.33 (2.0 – 7.0)	--
Reference	802 ± 365	--	99 ± 43	4.67 (2.0 – 7.0)	--
***Ratio (90% CI)**	0.97 (0.89-1.05)	--	0.95 (0.85-1.07)	--	--
CV (%)	21.0	--	27.4	--	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

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 Aristo 90 mg is considered bioequivalent with Mimpara 90 mg film-coated tablets.

Safety

There were 3 adverse events reported in 3 subjects during both phases of the study. All 3 adverse events were nausea. Two adverse events were reported after taking reference product while one adverse event was reported after taking test product. All adverse events were mild and were resolved. These adverse events were considered related to the study drugs.

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 Aristo.

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

Important identified risks	• Hypocalcaemia • Convulsions/seizures • Hypersensitivity reactions (including rash, urticaria and angioedema) • Hypotension and/or worsening heart failure • QT prolongation and ventricular arrhythmia secondary to hypocalcaemia
Important potential risks	• Fractures • Acute pancreatitis • Possible drug-related hepatic disorders • Nervous system disorders (excluding seizure) • Neoplastic events
Missing information	• Use in pregnant and breast-feeding 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

The package leaflet (PL) 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 2 rounds with 10 participants each.
The package leaflet passed the readability user test successfully. The interviews showed that the information of the PL was clear, readable and well understood by potential users.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cinacalcet Aristo 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 Aristo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 June 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