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Public Assessment Report

Name of the Product:

Cencipral

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

(cinacalcet hydrochloride)

Procedure number: HU/H/0392/001-003/DC

Marketing authorisation holder:
PharOS – Pharmaceutical Oriented Services Ltd.

Date: 25 November 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of Cencipral 30 mg, 60 mg and 90 mg coated tablets. The holder of the marketing authorisation is PharOS – Pharmaceutical Oriented Services Ltd.

The active substance is cinacalcet. Each film-coated tablet contains 30 mg or 60 mg or 90 mg of cinacalcet (as hydrochloride), respectively.

The other ingredients are:

- tablet core: pregelatinised starch, Povidone K-30 (E1201), Crospovidone Type A (E1202), silica colloidal anhydrous, magnesium Stearate (E572) and water purified;
- tablet coating: Hypromellose 15 (E464), lactose monohydrate, triacetin (E1518), titanium dioxide (E171), iron oxide yellow (E172), indigo carmine (E132) and water purified.

Cencipral 30 mg tablets are light green, oval, film-coated tablets, marked with "30" on one side. The dimensions of the tablet are 8.1 mm x 5.2 mm ± 5%.

Cencipral 60 mg tablets are light green, oval, film-coated tablets, marked with "60" on one side. The dimensions of the tablet are 10.0 mm x 6.3 mm ± 5%.

Cencipral 90 mg tablets are light green, oval, film-coated tablets, marked with "90" on one side. The dimensions of the tablet are 11.6 mm x 7.3 mm ± 5%.

Cencipral is available in blisters or in bottles.

Cencipral works by controlling the levels of parathyroid hormone (PTH), calcium and phosphorous in your body. It is used to treat problems with organs called parathyroid glands. The parathyroids are four small glands in the neck, near the thyroid gland, that produce parathyroid hormone (PTH).

Cencipral is used:

- to treat secondary hyperparathyroidism in patients with serious kidney disease who need dialysis to clear their blood of waste products;
- to reduce high levels of calcium in the blood (hypercalcaemia) in patients with parathyroid cancer;
- to reduce high levels of calcium in the blood (hypercalcaemia) in patients with primary hyperparathyroidism who still have high calcium levels after removal of the parathyroid gland or when removal of the gland is not possible.

In primary and secondary hyperparathyroidism too much PTH is produced by the parathyroid glands. "Primary" means that the hyperparathyroidism is not caused by any other condition and "secondary" means that the hyperparathyroidism is caused by another condition, e.g., kidney disease. Both primary and secondary hyperparathyroidism can cause the loss of calcium in the bones, which can lead to bone pain and fractures, problems with blood and heart vessels, kidney stones, mental illness and coma.

What patients need to know before taking Cencipral?

Those who are allergic to cinacalcet or any of the other ingredients of this medicine, *should not take Cencipral.*

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking <Cencipral>.

Before starting to take Cencipral, patients must tell their doctor if they have or have ever had:
- seizures (fits or convulsions). The risk of having seizures is higher if you have had them before;
- liver problems;
- heart failure.

Life threatening events and fatal outcomes associated with low calcium levels (hypocalcaemia) have been reported in patients treated with Cencipral.

Low calcium levels can have an effect on your heart rhythm. Patients must consult their doctor if experiencing an unusually fast or pounding heartbeat, if having heart rhythm problems, or if taking medicines known to cause heart rhythm problems, while taking also Cencipral.

During treatment with Cencipral, patients must inform their doctor if starting or stopping smoking, as this may affect the way Cencipral works.

Children and adolescents

Children and adolescents under the age of 18 must not take Cencipral.

Other medicines and Cencipral

Patients must inform their doctor if taking the following medicines.

Medicines such as the followings can affect how Cencipral works:
- medicines used to treat skin and fungal infections (ketoconazole, itraconazole and voriconazole);
- medicines used to treat bacterial infections (telithromycin, rifampicin and ciprofloxacin);
- a medicine used to treat HIV infection and AIDS (ritonavir);
- a medicine used to treat depression (fluvoxamine).

Cencipral may affect how medicines such as the following work:
- medicines used to treat depression (amitriptyline, desipramine, nortriptyline and clomipramine);
- medicines used to treat changes in heart rate (flecainide and propafenone);
- a medicine used to treat high blood pressure (metoprolol).

Cencipral with food and drink

This medicine> should be taken with or shortly after food.

Pregnancy, breast-feeding and fertility

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

Cencipral has not been tested in pregnant women. In case of pregnancy, the doctor may decide to modify the treatment, as Cencipral might harm the unborn baby.

It is not known whether Cencipral is excreted in human milk. The doctor will discuss with the patient if she should discontinue either breast-feeding or treatment with Cencipral.

Driving and using machines

No studies on the effects on the ability to drive and use machines have been performed. Dizziness and seizures have been reported by patients taking Cencipral. If experienced these, the ability to drive or operate machinery may be affected.

Cencipral contains lactose

Those who have been told by their doctor that they have an intolerance to some sugars, contact the doctor before taking this medicinal product.

How to take Cencipral

Cencipral must be taken orally, with or shortly after food. The tablets must be taken whole and are not to be divided.

The doctor will take regular blood samples during treatment to monitor the progress and will adjust the dose if necessary.

For patient being treated for secondary hyperparathyroidism the usual starting dose for Cencipral is 30 mg (one tablet) once per day.

For patients being treated for parathyroid cancer or primary hyperparathyroidism the usual starting dose for Cencipral is 30 mg (one tablet) twice per day.

What to do if more Cencipral have been taken than should it should be?

Patients having taken more Cencipral than prescribed must contact their doctor immediately. Possible signs of overdose include numbness or tingling around the mouth, muscle aches or cramps and seizures.

What to do if taking Cencipral has been forgotten?

Double dose to make up for a forgotten dose should never be taken. If taking a dose of Cencipral has been forgotten, the next dose should be taken as normal.

Possible side effects

Like all medicines, Cencipral film-coated tablets can cause side effects, although not everybody experiences them.

If the patient starts to get numbness or tingling around the mouth, muscle aches or cramps and seizures, he/she should tell it to the doctor immediately. These may be signs that your calcium levels are too low (hypocalcaemia).

Very common side effects (that may affect more than 1 in 10 people) are nausea and vomiting, these side effects are normally quite mild and do not last for long.

Common side effects (that may affect up to 1 in 10 people) include
- dizziness,
- numbness or tingling sensation (paraesthesia),
- loss (anorexia) or decrease of appetite,
- muscle pain (myalgia),
- weakness (asthenia),
- rash,
- reduced testosterone levels,
- high potassium levels in the blood (hyperkalaemia),
- allergic reactions (hypersensitivity),
- headache,
- seizures (convulsions or fits),
- low blood pressure (hypotension),
- upper respiratory infection,
- breathing difficulties (dyspnoea),
- cough,
- indigestion (dyspepsia),
- diarrhea,
- abdominal pain, abdominal pain – upper,
- constipation,
- muscle spasms,
- low calcium levels in the blood (hypocalcaemia).

Not known (their frequency cannot be estimated from available data) are
- hives (urticaria),
- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema),
- unusually fast or pounding heart beat which may be associated with low levels of calcium in your blood (QT prolongation /ECG[f1][PT2]/ and ventricular arrhythmia secondary to hypocalcaemia).

After taking Cencipral a very small number of patients with heart failure had worsening of their condition and/or low blood pressure (hypotension).

Additional side effects in children[f3] and adolescents

The use of Cencipral in children and adolescents has not been established. A fatal outcome was reported in an adolescent clinical trial patient with very low calcium levels in the blood (hypocalcaemia).

How to store Cencipral

This medicinal product does not require any special temperature storage conditions but keep it out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Cencipral 30 mg, 60 mg and 90 mg film-coated tablets. The procedure was finalised at 17 August 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member state, CMS: Cyprus) concerned the generic version of cinacalcet 30 mg, 60 mg and 90 mg film-coated tablets.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The applicant has adequately demonstrated bioequivalence between the product applied for and the reference products.

The originator (reference) products were Mimpara 30 mg, 60 mg and 90 mg film-coated tablets by Amgen Europe B.V. Netherlands. Cinacalcet was first approved in the Community on 22 October 2004 via centralised procedure.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Cencipral 30 mg, 60 mg and 90 mg film-coated tablets (PharOS – Pharmaceutical Oriented Services).

The products are indicated for the treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy and for the reduction of hypercalcaemia in patients with parathyroid carcinoma and primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

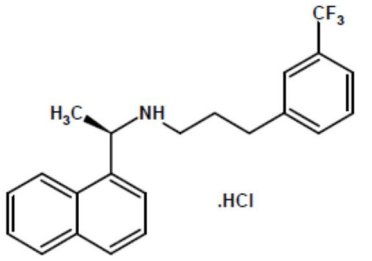
The chemical-pharmaceutical assessment report concerns the application of Cencipral 30 mg, 60 mg, 90 mg film-coated tablets via a decentralized procedure according to Article 10 (1) of Directive 2001/83/EC (i.e. a generic application).

The reference products are Mimpara 30mg, 60 mg and 90 mg film-coated tablets (containing 30mg, 60 mg and 90 mg cinacalcet hydrochloride as active ingredient, respectively) which were the original products of Amgen Europe B.V.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: cinacalcet hydrochloride
Chemical name: N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-amino propane hydrochloride
Structure:



The active substance is a white or almost white crystalline powder which is slightly soluble in water, soluble in methanol and 95% ethanol. The molecule has one asymmetric centre and shows polymorphism. The manufacturer consistently produces the correct enantiomer and the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by UV, FT-IR, MS, 1H-NMR, 13C-NMR, elemental analysis, DSC, TGA and XRPD. The impurity profile of the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Cinacalcet hydrochloride is not official in any pharmacopoeia. Therefore, an in-house specification has been set for the active substance, which includes the following tests: description,

identification of cinacalcet hydrochloride (by IR and HPLC), polymorphic form, solubility, water content, sulphated ash, heavy metals, chloride content, chiral purity, related substances including a specified genotoxic impurity, assay of cinacalcet hydrochloride and residual solvents, catalysator metal content and microbiological purity. Additionally, particle size is also tested by the finished product manufacturer.

The testing methods are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

The drug substance is in white opaque HDPE bag twist tied with one-way strip seal. This bag is placed inside a second black PE bag and also twist tied with one-way strip seal. This double PE bag is placed into Al foil bag sealed with hot seal and placed in a well-closed HDPE container. Finally the drums are sealed with tamper evident seal.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable, if stored below 30°C in well closed container.

Good Manufacturing Practice (GMP) compliance of the active substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop tablets containing cinacalcet hydrochloride as drug substance in 30mg, 60 mg and 90 mg doses bioequivalent and pharmaceutically equivalent to the reference medicinal product Mimpara 30mg, 60 mg and 90 mg film-coated tablets, the branded original products of Amgen Europe B.V.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

Cencipral 30 mg film-coated tablets are light green, oval, film-coated tablets, marked with “30” on one side. The dimensions of the tablet are 8.1 mm x 5.2 mm ± 5%.

Cencipral 60 mg film-coated tablets are light green, oval, film-coated tablets, marked with "60" on one side. The dimensions of the tablet are 10.0 mm x 6.3 mm ± 5%.

Cencipral 90 mg film-coated tablets are light green, oval, film-coated tablet, marked with "90" on one side. The dimensions of the tablet are 11.6 mm x 7.3 mm ± 5%.

The excipients used in the finished product are pregelatinised maize starch, povidone K-30, crospovidone (Type A), colloidal anhydrous silica, magnesium stearate, purified water (which evaporates during the coating process), hypromellose 15, lactose monohydrate, triacetin, titanium dioxide, iron oxide yellow, indigo carmine. All excipients used comply with their respective European Pharmacopoeia (Ph. Eur.) monograph, except from the colouring agents. Iron oxide yellow and indigo carmine meet the requirements of Regulation (EU) No 231/2012. Compliance of the product with the general monograph of the Ph. Eur. *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Conference on Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is triplex aluminium//PVC/PE/PVDC blisters or white HDPE bottles with screwed mouth that are stoppered with white child-resistant PP cap, in box.

Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years in blisters and 30 months in HDPE bottles with the storage condition **"**This medicinal product does not require any special temperature storage conditions." is approved.

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From quality aspects the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of cinacalcet are well known. It has been a generic application. As cinacalcet is a widely used, well-known active substance, no further studies are required and the applicant has provided none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, cinacalcet.

III.2 Pharmacology

The drug product Cencipral contains as active substance cinacalcet. It belongs to the pharmacotherapeutic group of calcium homeostasis, anti-parathyroid agents. Cinacalcet is a calcimimetic agent which directly lowers PTH levels by increasing the sensitivity of the calcium sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.

The active substance is a well-known compound. No further information was provided regarding the pharmacology of cinacalcet.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

No new toxicity studies were submitted by the applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Cencipral 30 mg, 60 mg and 90 mg film-coated tablets are 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.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

Pharmacodynamics, pharmacokinetics and toxicology of cinacalcet are well-known. As Cencipral 30 mg, 60 mg and 90 mg film-coated tablets is a generic product there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of cinacalcet is well known.

Except for demonstrating bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

After oral administration of cinacalcet to healthy humans, maximum concentrations of cinacalcet occur within 2 to 6 hours. Based on between-study comparisons, the absolute bioavailability of cinacalcet in fasted subjects has been estimated to be about 20-25%. Administration of cinacalcet with low- or high-fat meals increases exposure, (AUC∞) 1.5 to 1.8-fold. Cinacalcet was well absorbed with greater than 74% oral bioavailability.

The volume of distribution is high (approximately 1000 litres) indicating extensive distribution. Cinacalcet is approximately 97% bound to plasma proteins and distributes minimally into red blood cells. After absorption, cinacalcet concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady state levels of cinacalcet are achieved within 7 days with minimal accumulation. The pharmacokinetics of cinacalcet does not change over time. In HD patients bioavailability may decrease at doses greater than 200 mg, which may be a result of incomplete dissolution of the larger doses of cinacalcet in the gastrointestinal tract (the solubility of cinacalcet is reduced at pH>5.0). Median t_{max} of cinacalcet at all doses is 2 to 3 hours and steady state is achieved at approximately 4 days.

The pharmacokinetics are linear over 25- to 200 mg once-daily dose range, with no substantial increase in exposure at greater than 200 mg.

Cinacalcet is metabolised extensively in humans. *In vitro*, it undergoes NADPH dependent oxidative metabolism in the presence of human liver microsomes, resulting in the formation of multiple metabolites.

Cinacalcet is metabolized by multiple enzymes, predominantly CYP3A4 and CYP1A2 (the contribution of CYP1A2 has not been characterized clinically). The major circulating metabolites are inactive. The primary routes of metabolism of cinacalcet are *N*-dealkylation leading to carboxylic acid derivatives and oxidation of naphthalene ring

system to form dihydrodiols. The oxidative metabolites are conjugated before elimination. Urinary elimination is the predominant route of excretion of cinacalcet in healthy humans. After oral cinacalcet dosing to healthy humans approximately 80-83% of its inactive metabolites are excreted in urine and 13-17% in feces.

II.2.2 Bioequivalence study

The applicant declared that the bioequivalence study had been performed in accordance with GCP requirements (ICH/CPMP/135/95).

In order to compare the rate and extent of absorption between cinacalcet PharOS and Mimpara film-coated tablets a bioequivalence study was conducted using Mimpara® 90 mg film-coated tablets as reference product from the German market (marketing authorisation holder is Amgen Europe B.V. Netherlands).

The relative oral bioavailability of cinacalcet PharOS 90 mg film-coated tablets and the European brand product Mimpara 90 mg film-coated tablets was established by comparing the single dose pharmacokinetics of cinacalcet from the two formulations, under fed conditions, in a randomised crossover study.

Biowaiver

The applicant claimed for biowaiver for the 30 mg and 60 mg dose strengths on the basis of general biowaiver requirements („*If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, in vivo bioequivalence studies for additional strength(s) can be waived.*"

The applicant stated that all requirements of the *Note for Guidance on Investigation of bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1 Corr**) concerning biowaivers were met.

The general biowaiver criteria are as follows:
a) Cinacalcet PharOS exhibits linear pharmacokinetics in the range of 30 mg - 90 mg daily dose. So the results of the study of 90 mg can easily be extrapolated to the other doses of cinacalcet hydrochloride
b) All the three strengths (30, 60 and 90 mg) of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process.
c) The qualitative composition of Cinacalcet PharOS 30 mg and 60 mg tablets is same as that of Cinacalcet PharOS 90 mg tablets.
d) The composition of all the strengths are quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance is the same for all the 3 strengths.
e) The in-vitro dissolution profile is similar under identical conditions for the additional strengths i.e. 30 mg and 60 mg, and the strength of batch used in the bioequivalence study i.e. 90 mg.

The biowaiver claim for the 30 mg and 60 mg dose-strengths is justified as general requirements for biowaiver are completely fulfilled.

The study

The title of the study was "*A pivotal, open label, balanced, randomised, two-treatment, two-sequence, four-period, single-oral dose, four-way replicate crossover bioequivalence study of Cinacalcet 90 mg film-coated tablets as test formulation of Pharmaceutical Oriented Services (PharOS) Ltd., Greece, with Mimpara® 90 mg film-coated tablets as reference formulation of Amgen Europe B.V., The Netherlands, in healthy adult, human male subjects under fed condition"*

A single oral dose of one tablet either Test or Reference formulations, both containing 90 mg cinacalcet (as hydrochloride), was administered along with water as per the randomization schedule in the morning under fed conditions during each period.

Cinacalcet in human plasma was measured by using a validated LC-MS/MS method.

Incurred sample reanalysis was performed according to the EMA bioanalytical guideline (*EMEA/CHMP/EWP/192217/2009*).

The pharmacokinetic (PK) parameters and statistical methods were as follows:
- primary parameters: $AUC_{(0-t)}$, C_{max},
- secondary target parameters: T_{max} $AUC_{0-\infty}$, %AUCextra, Kel, λz and $t_{1/2}$.

The statistical software used was ANOVA: SAS® Version 9.1.3 Institute Inc., Cary, NC, USA (PROC GLM); summary statistics for all plasma concentrations: Excel 2003; pharmacokinetic data: Kinetica 2000 Version 5.1, Innaphase, USA (using extravascular non-compartmental
analysis).

- All statistical tests were evaluated at the 95% significance level (α=0.05).
- All PK parameters were summarized by descriptive statistics: mean, median, minimum, maximum, standard deviation (SD), range, number of data points and %CV.
- The primary PK parameters were tested by analysis of variance (ANOVA) after logarithmic transformation. ANOVA was performed by the GLM-procedure (general linear model) using the SAS software module (PROC GLM) of SAS System.
- Total variance was split into components due to the following four factors: Period, Sequence, Subject (random) and Treatment.
- T_{max}, nonparametric confidence intervals were calculated (for median).
- The 90% confidence intervals for intra-individual ratios (LS-mean of test/LS-mean of reference) of primary parameters were determined.

Bioequivalence could be concluded if the 90% confidence intervals for the LS-means of intra-individual ratios (test/reference) for both the primary parameters were within the acceptance range of [80.00%; 125.00%] for ln-transformed values.

The results are summarised in the Table (next page).

PK parameter	Ratio, 90% Confidence interval and Intra-subject variation CV		
	Ratio of geometric means (T/R)	90% Confidence interval	Intra-subject variation %CV of the R
$AUC_{(0-t)}$	105.55 %	98.42% – 113.20%	12.67%
C_{max}	106.71 %	97.85% – 116.36%	18.50%

Conclusion on bioequivalence studies

The 90% confidence intervals for C_{max} and $AUC_{(0-t)}$ lie within the bioequivalence range of 80.00%-125.00%.

Essential similarity was demonstrated by means of a bioequivalence study between the test and reference product. The study has demonstrated that a single dose of the Applicant's Cinacalcet PharOS 90 mg film-coated tablets (Pharmaceutical Oriented Services Ltd. (PharOS), Greece, Batch No. 53521) *is bioequivalent* to a single dose of Mimpara® 90 mg film-coated tablets (Amgen Europe B.V., Netherlands, Batch No. 1032518).

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics of Cencipral 30 mg, 60 mg and 90 mg film-coated tablets were not performed.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The applicant has provided an adequate literature review to describe the efficacy profile of cinacalcet.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data. There was no death or other serious adverse event reported during the study. Severity of adverse events was mild or moderate. Single oral dose of one film-coated tablet containing 90 mg cinacalcet (as hydrocloride) was well tolerated when administered under fed conditions and no significant safety issues emerged.

The applicant has provided an adequate literature review to describe the safety profile of cinacalcet.

IV.6 Pharmacovigilance

IV.6.1 Summary of the 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 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

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

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns associated with cinacalcet 30, 60 and 90 mg film-coated tablets. No additional activities are proposed.

Routine risk minimisation measures (i.e. wording in SmPC, package leaflet and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to cinacalcet 30, 60 and 90 mg film-coated tablets. No additional activities are proposed.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of European Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

IV.7 Discussion on the clinical aspects

The application concerns a generic product. Abridged applications avoid the need for repetitive tests on humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

The indications are the treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy and for the reduction of hypercalcaemia in patients with parathyroid carcinoma and primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels.

To support the application the Applicant has adequately demonstrated bioequivalence between Cencipral 30 mg, 60 mg and 90 mg tablets and the reference product Mimpara 30 mg, 60 mg and 90 mg tablets .

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Cencipral 30 mg, 60 mg and 90 mg film-coated tablets, generic versions of cinacalcet. The applicant and the future holder of authorisation is PharOS – Pharmaceutical Oriented Services Ltd.

The indications are the treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy and for the reduction of hypercalcaemia in patients with parathyroid carcinoma and primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference products were Mimpara 30 mg, 60 mg and 90 mg tablets. The bio-equivalence of the test and reference products has been adequately demonstrated.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Cencipral 30 mg, 60 mg and 90 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and 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 language used for the purpose of user testing the patient information leaflet was Hungarian.

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. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached