24 September 2015
EMA/CHMP/695643/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cinacalcet Mylan

International non-proprietary name: cinacalcet

Procedure No. EMEA/H/C/004014/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ADR	Adverse Reaction
AE	Adverse Event
AESI	AEs of special interest
ALT	alanine aminotransferase
ANSM	National Agency for the Safety of Medicine and Health Products
Alu	Aluminium
AP	Applicant's Part of ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	aspartate aminotransferase
AUC	Area Under the plasma Concentration
AUC0-inf	Area Under the plasma Concentration-time curve from time zero to infinity
AUC0-t	Area Under the plasma Concentration-time curve from time zero to t hours
BCT	Blinded combination therapy
BE	Bioequivalence
BMI	Body Mass Index
BUN	blood urea nitrogen
CIOMS	Suspect Adverse Reaction Report Form
Cmax	maximum plasma concentration
CMH test	Cochran-Mantel-Haenszel test
CoA	Certificate of Analysis
CRO	Certified Research Organisation
DDI	Drug-drug interactions
DHCP	Direct Healthcare Professional Communication

DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
EC	European Commission
ECG	Electrocardiogram
EEG	electroencephalogram
EMA	European Madicines Agency
EoS	End os Study
ERA	endothelin receptor antagonist
ETA	endothelin receptor antagosinsts
EU	European Union
FAV	Final Assessment Visit
FEV1	Forced expiratory volume in one second
FPM	Finish Product Manufacturer
FT-IR	Fourier Transform Infrared Spectroscopy
GABA	Gamma-aminobutyric acid
GAD	Generalised Anxiety Disorder
GC	Gas Chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HCP	Health Care Professional
HCT	hematocrit
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography
HR	Hazard Ratio
CHMP	Committee for Human Medicine Products
ICD	Informed Consent Document
ICMR	Indian council of medical research
ICH	International Conference on Harmonisation of Technical

	Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IMP	Investigated Medicinal product
IMS	International Marketing Sales
INN	International Non-proprietary Name
IP	investigational product
IPC	In-process control test
IR	Incidence Rate
IR	Infrared
IRB	Institutional Review Board
ISR	Incurred Sample Reanalysis
ITT	Intention To Treat
KF	Karl Fischer titration
LFT	Liver Function tests
LLOQ	Lower Limit of Quantification
LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
LOQ	(1) Limit of Quantification, (2) List of Questions
LVEDP	Left ventricular end diastolic pressure
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
mg	milligram
MHRA	British National Competent Authority
mITT	Modified Intended To Treat
mPAP	Mean Pulmonary Artery Pressure
MR	Medical Representative
MRI	Magnetic resonance imaging
MS	Mass Spectrometry

MS	Mass Spectrometry
MWD	minute walk distance
N/A	Not Applicable
NAION	Non-Arteritic Anterior Ischemic Optic Neuropathy
NCA	National Competent Authority
ND	Not detected
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NSAID	Non-Steroidal Anti-Inflammatory Drug
OECD	Organisation for Economic Co-operation and Development
OOS	Out of Specifications
OTC	Over-the-counter
PAH	Pulmonary Arterial Hypertension
PCD	Photo-Contact Dermatitis
PCWP	pulmonary capillary wedge pressure
PDE	Permitted Daily Exposure
PDE-5	phosphodiesterase type-5
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PhV	Pharmacovigilance
PIL	Patient Information Leaflet
PK	pharmacokinetic
PMS	Post Marketing Surveillance
PP	Polypropylene
PS	Photo-Sensitivity
PSMF	Pharmacovigilance Systém Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTH	Pituitary thyroid hormone
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride

PVOD	Pulmonary Veno-Occlusive Disease
PVR	Pulmonary vascular resistance
QA	Quality Assurance
QC	Quality Control (samples)
QOS	Quality Overall Summary
QP	Qualified Person
Rf	Retention factor
RH	Relative Humidity
RMM	Risk Minimization Measure
RMS	Reference Member State
RR	Reporting Rate
RRT	Relative retention time
RSD	Relative standard deviation
Rt	Retention time
SAE	Severe Adverse Event
SAO2	oxygen saturation
SGOT	Serum glutamic oxaloacetic trnasaminase
SGPT	Serum glutamic pyruvic trnasmainase
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Querie
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
STD	Standard Deviation
T/R	Test/Reference
TGA	Thermo-Gravimetric Analysis
TLC	Total lung capacity
Tmax	time for maximum concentration (* median, range)
TSE	Transmissible spongiform encephalopathy
TSE	Transmissible spongiform encephalopathy
ULN	upper limit of normal

UV	Ultraviolet
WCI	Worst Case Imputation
WHO	World Health Organization
WRI	worst rank imputation
XRPD	X-ray powder diffraction

Not all the abbreviations might be used in the text.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant MYLAN S.A.S. submitted on 15 December 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cinacalcet Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 May 2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

"Treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

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

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."

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and two bioequivalence studies with the reference medicinal product Mimpara instead of non-clinical and clinical studies.

Information on paediatric requirements

Not applicable.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:
- Product name, strength, pharmaceutical form: Mimpara 30 mg, 60 mg and 90 mg film coated tablets
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22-10-2004
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/04/292/001-012

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Mimpara 30 mg, 60 mg and 90 mg film coated tablets
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22-10-2004
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/04/292/001-012

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Mimpara 90 mg film coated tablets
- Marketing authorisation holder: Amgen Europe B.V.
- Date of authorisation: 22-10-2004
- Marketing authorisation granted by:
  - Community
  - Community) Marketing authorisation number: EU/1/04/292/010
- Bioavailability study numbers: 712/14

Licensing status

The product was not licensed in any country at the time of submission of the application.

An application was filed in the following countries: USA and Canada.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Radka Montoniová

- The application was received by the EMA on 15 December 2014.
- The procedure started on 22 January 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 April 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 7 May 2015.
- During the meeting on 21 May 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 May 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2015.
- The following GCP inspection was requested by the CHMP and its outcome taken into consideration as part of the Efficacy assessment of the product:

  A GCP inspection at the study facility in India was carried out between 8 and 10 April 2015. The final inspection report was issued on 12.05.2015.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 August 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 September.
- During the meeting on 24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Cinacalcet Mylan.

2. Scientific discussion

2.1. Introduction

The active substance in the medicinal product in question is cinacalcet hydrochloride. The pharmacotherapeutic group of cinacalcet is calcium homeostasis, anti-parathyroid agents.

Cinacalcet is approved in the EU for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy, and for the treatment of hypercalcaemia in patients with parathyroid carcinoma or with primary hyperparathyroidism who are unable to undergo parathyroidectomy.

Cinacalcet is taken orally and comes in tablet form in three strengths (30 mg, 60 mg, and 90 mg). The tablet should not be split, chewed, or crushed. Cinacalcet should be taken with food or after a meal for increased absorption of the medication. Cinacalcet dosing is patient dependent and individualized.

Cinacalcet is a drug that acts as a calcimimetic (i.e. it mimics the action of calcium in the body) by allosteric activation of the calcium-sensing receptor that is expressed in various human organ tissues. The calcium-sensing receptors on the surface of the chief cell of the parathyroid gland are the principal regulator of parathyroid hormone (PTH) secretion. Cinacalcet increases the sensitivity of calcium receptors on parathyroid cells to reduce PTH levels and thus decrease serum calcium levels. The reduction in PTH levels also leads to a decrease in blood calcium levels. Reduction in PTH levels correlate with cinacalcet concentration.

The applicant did apply for all indications of the reference product:

Treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.

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

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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 30 mg, 60 mg or 90 mg of cinacalcet hydrochloride as active substance.

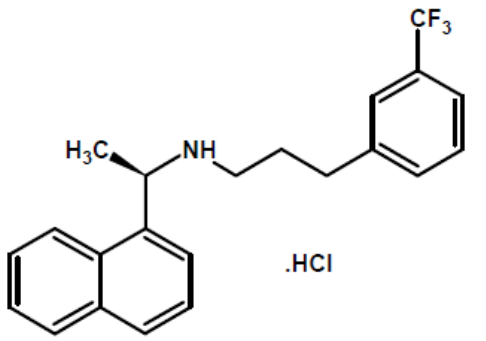
Other ingredients of the tablet core are: microcrystalline cellulose, colloidal anhydrous silica, povidone, crospovidone and magnesium stearate. Ingredients of the film-coat are hypromellose, titanium dioxide (E171), triacetin, indigo carmine aluminium lake (E132), and iron oxide yellow (E172).

The product is available in PVC/PVdC/Alu blisters for all film-coated tablets and high density polyethylene (HDPE) bottles with polypropylene (PP) screw cap closure with induction sealing liner for 30 mg strength.

2.2.2. Active substance

General information

The chemical name of cinacalcet hydrochloride is [(1R)-1-(naphthalen-1-yl)ethyl]({3-[3-(trifluoromethyl)phenyl]propyl})amine hydrochloride corresponding to the molecular formula $C_{22}H_{22}F_3N \cdot HCl$ and has a relative molecular mass 393.9. It has the following structure:



The active substance is a white to off-white, non-hygroscopic, crystalline powder, soluble in methanol and 95% ethanol, slightly soluble in water. It is insoluble at 25±2°C in pH buffers with pH 1.2, 4.5, and 6.8.

The chemical structure of cinacalcet hydrochloride has been adequately demonstrated by elemental analysis, UV, FT-IR, ^{1}H-NMR, ^{13}C-NMR, and MS.

Cinacalcet exhibits stereoisomerism due to the presence of a single chiral centre. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity. Enantiomeric purity is controlled routinely in the intermediates of the active substance synthesis and active substance specifications by chiral HPLC (both at release and during shelf-life).

Polymorphism has been observed for cinacalcet hydrochloride. Three different polymorphic forms and one amorphous form of the active substance have been identified in literature. Of these polymorphs, only one form is stable at ambient temperature, anhydrous Form I. Based on characterisation using XRPD, DSC, and TGA, it was demonstrated that the Form I used in the originator is the same as the one used in the product

development of this medicinal product.

Manufacture

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance intended for the proposed commercial process is obtained from a single manufacturer.

Cinacalcet hydrochloride is synthesized in six main chemical transformation steps using convergent synthesis, followed by salt formation and purification steps. During the evaluation procedure, the active substance starting materials were redefined to ensure full control of the quality of the active substance in line with ICH Q11. Commercially available well defined starting materials with acceptable specifications are used in the synthesis.

The following manufacturing steps were identified as critical for active substance quality: drying, milling, micronisation, blending, and sifting.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Reprocessing procedure of the active substance has been established and described in sufficient detail.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in a polythene bag, inserted in a second polythene bag, placed into aluminium foil bag sealed with hot seal and placed in a HDPE container. Primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance (visual examination), solubility, identity (IR, HPLC, and XRPD), water content (KF), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), chiral purity (HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), chloride content (potentiometric titration), and microbiological test (Ph. Eur.).

Several substances used in the synthesis of cinacalcet hydrochloride are showing potential genotoxic alerts, however it was demonstrated that these impurities are not detected in the batches of the active substance. Based on this justification, testing for these substances was omitted from the active substance specifications.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (n=5, commercial scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 48 months under long term conditions at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested*:* appearance (visual examination), identity (IR, HPLC, and XRPD), water content (KF), chiral purity (HPLC), related substances (HPLC), assay (HPLC), and microbiological test (Ph. Eur.). The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications and no significant changes were observed, both on long term and accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. Results on stress conditions (acid, alkali, peroxide, thermal, and photolytic degradation study) were also provided and demonstrate that the active substance is most sensitive to peroxide stress conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months when stored in in the proposed container below 30 ºC.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of pharmaceutical development was to develop a stable solid oral dosage formulation that is bioequivalent to the reference medicinal product Mimpara film-coated tablets.

During the pharmaceutical development, several attributes of the active substance affecting the finished product quality were considered.

It was demonstrated that the manufacturing process of the active substance consistently yields batches of a single, desired polymorphic form, which does not change during the manufacture and shelf-life of the finished product. Polymorphism is routinely controlled in the active substance specifications (both on release and during shelf-life).

The active substance is a powder with poor flow properties affecting finished product manufacturability which was addressed during formulation development using optimisation of excipients studies. Based on the studies evaluating the effect of particle size distribution of the active substance on dissolution, no significant influence was observed.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Excipients were selected based on the compatibility studies and the composition of the reference medicinal product.

The formulation used during clinical studies is the same as that intended for marketing.

The formulation of Cinacalcet Mylan is different from the formulation of the originator in the composition of the film-coating and in diluents used: whereas microcrystalline cellulose is used as a diluent in Cinacalcet Mylan, both microcrystalline cellulose and pregelatinised starch were used in Mimpara. These differences are not considered significant, which was demonstrated by comparable dissolution profiles as in the originator and performance *in vivo* (bioequivalence studies). The tablets of the different strengths are dose-proportional and manufactured from a common blend.

Two bioequivalence studies were performed showing bioequivalence between 90 mg tablets and the reference product.

A biowaiver for 30 mg and 60 mg tablet strengths was granted as all the requirements according to Bioequivalence guideline were fulfilled.

The discriminatory power of the dissolution method has been demonstrated. For finished product release and stability dissolution testing a paddle apparatus and standard acetate buffer without a surfactant are used.

The primary packaging is PVC/PVdC/Alu blisters for all film-coated tablets and high density polyethylene (HDPE) bottles with polypropylene (PP) screw cap closure with induction sealing liner for 30 mg strength. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of eight main steps: sifting, granulation, drying, dry screening, blending, compression, film-coating, and packaging. The process is considered to be a standard manufacturing process. The critical steps in the manufacturing process of the film-coated tablets include preparation of powder blend, compression, coating, and packaging.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual inspection), dimensions, identity (HPLC, UV), identity of colourants (chemical reaction), dissolution (HPLC), uniformity of dosage units (HPLC), assay (HPLC), related substances (HPLC), water content (KF), and microbiological test (Ph. Eur.). The omission of enantiomeric purity testing in the finished product specification was appropriately justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for 3 commercial scale batches for each of the tablet strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of 3 commercial scale batches for each of the tablet strength of finished product stored under long term conditions for 12 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance (visual inspection), dissolution (HPLC), assay (HPLC), related substances (HPLC), water content (KF), and microbiological test (Ph. Eur.). The analytical procedures used were the same as for release, except the method for assay (HPLC). All methods were shown to be stability indicating. Increased water content levels have been observed on a single batch during the on-going stability study under accelerated conditions, however the results were within the shelf-life specification acceptance criteria and it is not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

In addition, a single batch of 90 mg tablets was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. It was shown that the tablets are not photo-sensitive.

In-use stability studies on two batches of 30 mg strength tablets were performed. Based on the results, no specific in-use shelf life is recommended for this product.

Based on available stability data, the shelf-life of 2 years and without any special storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetic and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed in the quality part of the documentation and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Cinacalcet Mylan manufactured by Mylan Laboratories Limited is considered unlikely to result in any significant increase in the combined sales volumes for all cinacalcet containing products and the exposure of the environment to the active substance. Thus, the ER is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and no additional tests were required.

A valid justification for not submitting ERA is given.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Cinacalcet Mylan from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) and Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

This is an application for film-coated tablets containing cinacalcet hydrochloride. To support the marketing authorisation application the applicant conducted two bioequivalence studies with cross-over design under fed conditions.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community

were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

Justification for Biowaiver (for 30 mg and 60 mg strength)

The Bio-equivalence study has been conducted with the higher strength, i.e. Cinacalcet 90 mg film coated tablets. Biowaiver has been requested for both lower strengths, i.e. 30mg and 60mg with the justification summarized below.

According to the note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 rev.1), the bio-equivalence study results can also be extended to the lower strengths based on the following facts:

- All strengths of Cinacalcet hydrochloride 30mg, 60mg and 90mg film-coated tablets are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.
- The qualitative composition of all the strengths is same.
- The excipients included in the composition of the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected.
- The qualitative composition of the different strengths is the same. Cinacalcet hydrochloride 30 mg, 60 mg and 90 mg film-coated tablets are direct scale up/scale down formulations.
- Pharmacokinetics of Cinacalcet is linear over the dosage range of 30 mg – 180 mg.
- All the strengths exhibit similar in-vitro performance. So the dissolution profiles can be considered similar.

Since Cinacalcet 30mg and 60mg film-coated tablets fulfil all the requirements needed to waive bioequivalence studies for additional strengths as mentioned in CPMP guideline on the Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98-Rev 01 – January 2010, the bio-equivalence study results of Cinacalcet 90mg film coated tablets can be extended to Cinacalcet 30mg and 60mg film coated tablets.

Clinical studies

To support the application, the applicant has submitted two bioequivalence studies, of which the initial one (No.084-14) did not show bioequivalence; the company has therefore conducted another one (No. 712/14). Both studies have the same protocol; however as these two studies have been conducted in different CROs with different number of subjects, the assessment is provided for each study separately.

Tabular overview of (clinical) bioequivalence studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy subjects or Diagnosis of patients	Duration of Treatment	Study status; Type of Report
BA	Not Applicable								
BE	Project No. 084-14	Clinical Study Report & PK Report and Adverse Event Listing 5.3.1.2 CRFs and Individual Subject Listings 5.3.7 Literature References 5.4	**Efficacy:** To characterize the pharmacokinetic profile of the sponsor's test product in comparison to the reference product in healthy, adult, human subjects under fed conditions and to assess the bioequivalence. **Safety:** To monitor the adverse events and to ensure the safety of the subjects	**Study Design:** An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study in healthy, adult, human subjects under fed conditions **Type of Control:** No control groups	**Test Product T:** Cinacalcet Hydrochloride 90 mg Film Coated Tablets Dosage Regimen: 90 mg **Reference Product-R** Mimpara® (Cinacalcet) 90 mg Comprimes Pellicules (Film-Coated Tablets) Dosage Regimen: 90 mg Route of administration: Oral	Planned-44 Enrolled-46 Dosed-44 Completed-30 Analysed-37 Withdrawn / Discontinued -14	Healthy subjects	Single dose	Complete; Abbreviated

Type of the Study	Study Identifier	Location of Study Report	Study Design and Type of Control	Test Product Dose Regimen Route of Administration	No of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status and Type of Report
Bioequivalence Study	712/14	Determine bioequivalence between a drug (generic) product and a marketed reference product under fed conditions. Refer module 5.3.1.2, sections 1.0 to 15.0	An open label, balanced, randomized two-treatment, two-period, two-sequence single dose, crossover, two-stage oral bioequivalence study in healthy, adult, human subjects under fed conditions.	Cinacalcet 90 mg Film-coated Tablets administered orally	60 (52 subjects selected for pharmacokinetic and statistical analysis)	Healthy, adult, human subjects	Single oral dose of 90 mg tablet in each study period	Completed

2.4.2. Pharmacokinetics

Study No: 084-14

Methods

Study design (Study No. 084-14)

The study was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study in healthy, adult, human subjects under fed conditions, with a screening period of 28 days prior to dose administration in Period-I of the study.

After an overnight fast of at least 10 hours, the subjects were served high fat high calorie vegetarian breakfast, which they were required to consume within 30 minutes.

Note: Injection Ondansetron 4 mg intravenous as a concomitant medication was administered within 30 minutes prior to dose administration for the prevention of nausea and vomiting.

Test and reference products (Study No. 084-14)

Test Product-T		
Formulation	:	Cinacalcet Hydrochloride 90 mg Film Coated Tablets
Manufactured by	:	Mylan Laboratories Limited, F-4 & F-12, MIDC, Malegaon, Sinnar, Nashik 422 113, Maharashtra, India.
Batch No.	:	2002885
Batch Size	:	196,000 tablets
Manufacturing Date	:	03 / 2013
Expiry Date	:	02 / 2015
Storage Condition	:	Do not store above 25 °C.

Reference Product-R		
Formulation	:	Mimpara® (Cinacalcet) 90 mg Comprimes Pellicules (Film-Coated Tablets)
Manufactured by	:	Amgen Europe B.V., Minervum 7061, 4817 ZK Breda, The Netherlands / Nederland / Niederlande
Marketing Authorisation Holder	:	Amgen S.A.S, Neuilly Sur Seine, France.
Lot No.	:	1039913
Expiry Date	:	05 / 2016
Storage Condition	:	Do not store above 25 °C.

Population(s) studied (Study No. 084-14)

A total of 46 subjects including two additional subjects (Subject Nos. 1001-1044, X-1 & X-2) were enrolled and checked in for the study. Subject Nos. X-1 & X-2 were checked-in for the study, in order to compensate for any dropouts prior to dosing in Period-I. Both the additional subjects were checked out of the facility as none of the subjects discontinued / or were withdrawn from the study prior to dosing in Period-I.

Subjects participated in the study were healthy male adults, aged between 18 and 41 years of age (both inclusive); having BMI between 18.98 and 29.56 kg/m2 (both inclusive). All subjects were of Asian origin.

No female volunteers were enrolled in the study.

Hence, as per the protocol, forty-four (44) subjects (Subject Nos. 1001-1044) were dosed in Period-I of the study.

In overall, thirty (30) Subjects completed the study and there were fourteen subjects withdrawn from the

study.

Analytical methods (Study No. 084-14)

Cinacalcet in study samples was determined by HPLC method using tandem mass spectrometry detection. Cinacalcet and internal standard (cinacalcet-d3) were extracted from K3EDTA plasma by liquid-liquid extraction.

Certificates of analysis for cinacalcet hydrochloride and the internal standard were enclosed in the Attachment 1 to the Bioanalytical report.

Incurred sample reanalysis were performed on 10% for first 1000 samples and 5% on rest of the samples. Total number of 120 samples were reanalysed and 97.50% met the acceptance criteria specified in the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/1922177/2009 Rev1).

Bioanalytical method validation

The validation results of a high performance liquid chromatographic method using tandem mass spectrometry detection for determination of cinacalcet in human plasma are presented in the Validation Report. The method was validated. The long term stability data of cinacalcet in human plasma were submitted. Haemolysis effect and IS normalized matrix effect were assessed during partial method validation and reported in the bioanalytical report.

Pharmacokinetic Variables (Study No. 084-14)

Primary pharmacokinetic parameters: Cmax and AUC(0-72)

Secondary pharmacokinetic parameters: Tmax, λz and t1/2

These pharmacokinetic parameters were calculated for Cinacalcet by using non-compartmental model of WinNonlin Professional Software Version 5.3 (Pharsight Corporation, USA).

The pharmacokinetic variables are adequate and in line with the EMA Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr **.

Statistical methods (Study No. 084-14)

Descriptive statistics were calculated and reported for all pharmacokinetic parameters of Cinacalcet.

The conclusion of bioequivalence of the test product with the reference product was based on the results for ln-transformed pharmacokinetic parameters; Cmax and AUC(0-72). The ln-transformed pharmacokinetic parameters Cmax and AUC(0-72) were modelled by Analysis of Variance (ANOVA) for Cinacalcet. ANOVA model included categorical predictor variables Sequence, Subject (Sequence), Period and Formulation.

A F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha=0.05).

The outlier test was performed using studentized residual test (Lund's method) on ln-transformed pharmacokinetic parameters Cmax and AUC(0-72) using SAS Version 9.3.

No studentized residuals were found to be greater than the table value 2.96 for Cmax and AUC(0-72).

Originally (according to the protocol), the study was planned to have two-stage approach for the assessment of bioequivalence (in adherence to the procedure C of Potvin et al).This is acceptable approach and is in line with the bioequivalence guideline. However (according to the study report), as the statistical power after the

first stage was found to be sufficient, i.e. at least 80% (99.3% for lnCmax and 99.7% for lnAUC(0-72)), the study could not be extended to stage 2 and bioequivalence was not demonstrated using 90%CI at stage I.

Results (Study No. 084-14)

Pharmacokinetic parameter	**Test**	**Reference**
	arithmetic mean ±SD	**arithmetic mean ±SD**
$AUC_{(0-72h)}$ (ng.h/mL)	390.881 ± 223.9957	431.562 ± 240.8547
C_{max} (ng/mL)	30.287 ± 16.3687	35.436 ± 17.6652
T_{max}* (hr)	6.00 (3.00-8.00)	5.250 (2.00-8.00)
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, range)	

Table 1: Pharmacokinetic parameters for cinacalcet (non-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%***
$lnAUC_{(0-72h)}$	91.1	83.99 - 98.92	18.8
lnC_{max}	85.8	78.66 - 93.65	20.1
* estimated from the Residual Mean Squares			

Table 2: Statistical analysis for cinacalcet (ln-transformed values)

Safety data (Study No. 084-14)

Eight (08) adverse events (AEs) were reported by eight (08) subjects during the conduct of the study. Three (03) AEs were reported in Period-I and five (05) AEs were reported in Period-II of the study.

Five (05) AEs were reported in subjects after administration of the Reference Product and three (03) AEs were reported in subjects after administration of Test Product.

All the AEs were mild in nature and the subjects were followed up for their AE until resolution.

The causality assessment was judged as possible for three (03) AEs, as unlikely for four (04) AEs and as unrelated for one (01) AE.

There were no deaths or serious AEs during the conduct of the study.

However, seven (07) significant AEs were reported during the conduct of the study – Vomiting and Excoriation. These subjects were withdrawn from the study on medical grounds.

They were treated accordingly and were followed up until resolution of their AE.

Study No: 712/14

Methods

Study design (Study No. 712/14)

This was an open label, balanced, randomized two-treatment, two-period, two-sequence single dose, crossover, two-stage oral bioequivalence study in healthy, adult subjects under fed conditions with a screening period of 28 days prior to enrolment.

In each period, Ondansetron Injection (Zofer) 4mg was administered intravenously before start of high fat and high calories breakfast as a preventive precaution for emesis.

Test and reference products (Study No. 712/14)

Treatment	Test (T)	Reference (R)
Name	Cinacalcet	Mimpara® (Cinacalcet)
Dosage Form	Film-coated Tablets	Film-coated Tablets
Strength	90 mg	90 mg
Manufactured by	Mylan Laboratories Limited, F-4 & F-12, MIDC, Malegaon, Sinnar, Nashik – 422 113, Maharashtra, INDIA	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, The Netherlands
Batch No	2002885	1039913
Mfg Date	March 2013	NA
Expiry Date	February 2015	May 2016

Treatment	Concomitant Medication
Name	Ondansetron (Zofer®)
Dosage Form	Injection
Strength	2mg/ml
Manufactured by	Unimed Technologies Limited
Batch No	HKN0658
Mfg Date	07/2014
Expiry Date	06/2017

Population(s) studied (Study No. 712/14)

As per the protocol, in stage 1, a total of 60 subjects were enrolled into the study and all 60 subjects were dosed in Period I. A total of 54 subjects turned-up for Period II and 52 Subjects were dosed in Period II. In total 52 subjects completed the clinical phase of the study. A total of 59 subjects were analysed in bioanalytical phase, 07 subjects were analysed for specific safety reasons and 52 subjects were considered

for pharmacokinetic and statistical analysis.

Subjects participated in the study were healthy male adults, aged between 18 and 45 years of age (both inclusive) weighing at least 50 kgs; having BMI between 18.5 and 29.90 kg/ height in m2 (both inclusive).

Analytical methods (Study No. 712/14)

Cinacalcet in study samples was determined by HPLC method using tandem mass spectrometry detection. Cinacalcet and internal standard (cinacalcet-d3) were extracted from K3EDTA plasma by liquid-liquid extraction.

Certificates of analysis for cinacalcet hydrochloride and the internal standard were enclosed in the Bioanalytical report.

Incurred sample reanalysis were performed on 10% for first 1000 samples and 5% on rest of the samples. Total number of 176 samples were reanalysed and 100% met the acceptance criteria specified in the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/1922177/2009 Rev1).

Bioanalytical method validation

The validation results of a high performance liquid chromatographic method using tandem mass spectrometry detection for determination of Cinacalcet in human plasma are presented. The method was validated. The long term stability data of cinacalcet in human plasma were submitted. Haemolysis effect and IS normalized matrix effect were assessed during partial method validation and reported in the bioanalytical report.

Pharmacokinetic Variables (Study No. 712/14)

Primary pharmacokinetic parameters: Cmax and AUC(0-72)

Secondary pharmacokinetic parameters: Tmax, λz and t1/2

These pharmacokinetic parameters were calculated for Cinacalcet by using non-compartmental model of WinNonlin Professional Software Version 5.3 (Pharsight Corporation, USA).

The pharmacokinetic variables are adequate and in line with the EMA Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr **.

Statistical methods (Study No. 712/14)

Statistical analysis was performed using the SAS Version 9.1.3 for Windows, (SAS Institute Inc. USA). The pharmacokinetic and statistical analysis was performed on subjects who completed both the periods of the study and who had been analysed in the bioanalytical laboratory for Cinacalcet.

The descriptive statistics (such as mean, median, minimum, maximum, standard deviation and coefficient of variation) for the relevant pharmacokinetic parameters (Cmax and AUC(0-72)) estimated for both Test and Reference formulations.

The geometric mean and coefficient of variation were estimated for Cmax and AUC(0-72).

The log-transformed pharmacokinetic parameters (Cmax and AUC(0-72)) of Cinacalcet were analysed using an analysis of variance (ANOVA) model at 5% significance level. The ANOVA model included predictor variables Sequence, Period, Subject (Sequence) and Treatment. The significance level for the sequence effect was chosen 10 % and sequence effect was tested using the subjects nested within the sequence as the error term.

Consistent with the two one-sided tests for Bioequivalence, 90% confidence intervals for the difference between treatments least-square means were calculated for ln-transformed AUC(0-72) and Cmax. The confidence interval was to express as percentages relative to the LSM of the reference treatments.

Probability (p) values were derived from TYPE III sums of squares. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05. Based on pair wise comparisons of the untransformed of AUC(0-72) and Cmax data, the ratios of the least-squares means, calculated according to the formula "e(X-Y) x 100", as well as the 90% confidence intervals for ln-transformed AUC(0-72) and Cmax were determined. Finally, the intra-subject CV % was also determined.

Originally (according to the protocol), the study was planned to have two-staged approach for the assessment of bioequivalence in adherence to procedure C of Potvin et al. As the statistical power after the first stage was found to be sufficient, i.e. at least 80%, the study has not been extended to stage two.

Results (Study No. 712/14)

Pharmacokinetic parameter	**Test (N=52)**		**Reference (N=52)**	
	Mean±SD	**CV%**	**Mean±SD**	**CV%**
$AUC_{(0-72)}$ (ng*h/ml)	574.003±218.628	38.088	592.201±210.899	35.613
C_{max} (ng/ml)	63.645±25.674	40.340	69.461±25.191	36.266
T_{max}*(hr)	4.5 (2.00-6.50)	20.45	4.5 (2.00-7.00)	30.99

*Tmax is represented in median value (Range)

Table 3: Pharmacokinetic parameters for cinacalcet (non-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference (%)**	**Confidence Intervals**	**CV%***
$lnAUC_{(0-72h)}$	95.79	90.68 - 101.20	27
lnC_{max}	89.66	82.14 - 97.86	16.8
* estimated from the Residual Mean Squares			

Table 4: Statistical analysis for cinacalcet (ln-transformed values)

Safety data (Study No. 712/14)

Six (06) subjects reported six (06) adverse events during period I who have received test product (T). Ten (10) subjects reported ten (10) adverse events during period I who have received reference product (R). One (01) subject reported two (02) adverse events during washout period who has received reference product (R) in period I.

One (01) subject reported one (01) adverse event before dosing in period II who had received reference product (R) in period I.

Five (05) adverse events of vomiting, three (03) adverse events each of elevated SGPT levels, dyspepsia and nausea, two (02) adverse events each of decreased PTH and headache, one (01) adverse event each of back ache, diarrhoea, dizziness, elevated SGOT levels and rashes were possibly related to the study drug; one (01) adverse event each of vomiting and fever with chills were unlikely related to the study drug.

Three (03) adverse events of nausea, two (02) adverse events of headache, one (01) adverse event each of back ache, diarrhoea, fever with chills and rashes were moderate in nature; six (06) adverse events of vomiting, three (03) adverse events each of elevated SGPT levels and dyspepsia, two (02) adverse events of decreased PTH, one (01) adverse event each of dizziness and elevated SGOT levels were mild in nature.

All these adverse events were resolved with the exception of three (03) adverse events of elevated SGPT levels, one (01) adverse event of elevated SGOT levels and two (02) adverse events of decreased PTH, which were under follow-up.

One (01) adverse event each of fever with chills and diarrhoea reported by subject S33 during washout period was finally reported as acute gastroenteritis by the referral hospital which was reported as SAE, which was unlikely related to the study drug and moderate in nature. This adverse event was resolved.

Conclusions

The company has submitted two bioequivalence studies (No. 084-14 and No. 712/14). Results of study No. 084-14 do not support bioequivalence between Cinacalcet Mylan and Mimpara; the applicant states that this study has been submitted as part of fulfilling the sponsor obligations to submit all the studies (including inconclusive studies) associated with the formulation seeking approval, but not as pursuit to get the approval of the application based on this study (084-14) results and data.

The bioequivalence between the test and reference products has been demonstrated with respect to the rate and extent of absorption in the other bioequivalence study (No. 712/14).

Based on the results in the two conducted bioequivalence studies the Applicant has been requested to explain on which grounds the results of 712/14 should be preferred to those of the first BE study (084-14) and discuss the totality of evidence. Adequate justification has been provided as described in the discussion section below and all issues are considered to be resolved.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The company has submitted two bioequivalence studies (study No. 084-14 and study No. 712/14). Both studies had an identical study protocol; however conduct of these studies has been done in different CROs. Both studies have two stage design based on the Procedure C of Potvin et al. As this approach does not strictly control the type I error and hence the uncertainty of the overall alpha-level, the applicant was

requested to provide the 94.12% confidence interval (AUC and Cmax) for both studies, as a reference, in addition to the 90% confidence interval already provided. In his response to CHMP Day 120 Questions the applicant has submitted 94.12% CI of ln-transformed pharmacokinetic parameters Cmax and AUC from study # 084-14 and study # 712/14. These are presented individually in summary tables:

94.12% confidence interval (AUC and C_{max}) for study # 084-14:

Dependent	Ratio [%Ref]	CI_94.12_ Lower	CI_94.12_ Upper	Power	Bioequivalence
Ln(AUC 0-72)	91.1	82.91	100.20	99.4	Conclusive
Ln(Cmax)	85.8	77.58	94.95	98.8	Inconclusive

94.12% confidence interval (AUC and C_{max}) for study # 712/14:

Dependent	Ratio [%Ref]	CI_94.12 _Lower	CI_94.12_ Upper	Power	Bioequivalence
Ln(AUC 0-72)	95.79%	89.91%	102.06%	100.0%	Conclusive
Ln(Cmax)	89.66%	81.04%	99.18%	99.4%	Conclusive

Bioequivalence of study 712/14 was also established using 94.12% confidence interval for target PK parameters. Results of study No. 084-14 do not support bioequivalence between Cinacalcet Mylan and Mimpara and the applicant states that this study has been submitted as part of fulfilling the sponsor obligations to submit all the studies (including inconclusive studies) associated with the formulation seeking approval, but not as pursuit to get the approval of the application based on this study (084-14) results and data. In the submitted clinical overview the applicant concludes that the reason for not showing BE might be because of smaller sample size than initially planned (30 vs. 38 planned); although this claim is not fully supported by the CHMP as the retrospective statistical power has been shown to be almost 100% (99.3% for lnCmax and 99.7% for lnAUC0-72) (see tables on pp. 24 of the clinical report). This would suggest that the number of subjects would have been sufficient had the actual results mirrored those assumed in the sample size calculation.

Although the bioequivalence between the test and reference products has been demonstrated in study No. 712/14 with respect to the rate and extent of absorption, unusually high plasma levels of cinacalcet have been reached. Based on the results from the previous study (084-14), the mean Cmax observed was 30.287 ± 16.3687 ng/mL (T) and 35.436 ± 17.6652 ng/mL(R). As in both studies the same batches of cinacalcet tablets 90 mg have been used and no significant food effect is expected as the breakfasts administered to the subjects seem comparable, no rational explanation for two times higher Cmax (63.645±25.674 /T/ and 69.461±25.191/R/) observed in this Study No. 712/14 seems applicable. The applicant has been requested to duly clarify this issue and applicant´s reasoning for these differences due to genetic differences in PK response to cinacalcet can be followed. No analytical reasons which might lead to these differences are envisaged. As bioequivalence study No. 712/14 conducted in GPC QPS Bioserve confirmed the bioequivalence between the tested and reference product and the results of the routine GCP inspection done in April 2015 have not revealed any findings this issue was not further considered of major concern.

Overall, the applicant was asked to thoroughly discuss the totality of evidence. Two bioequivalence studies have been submitted, one demonstrating bioequivalence (study 712/14), and one that does not (study 084-14). In order to assess the totality of evidence a pooled analysis of both studies, using both 90% and 94.12% confidence intervals was requested. In their responses the applicant has submitted these analyses:

Pooled analysis: Relative Bioavailability Results for Cinacalcet from both studies i.e., 084-14 and 712/14 (N = 82)

Dependent	Ratio [%Ref]	CI_90 _Lower	CI_90 _Upper	CI_94.12 _Lower	CI_94.12_ Upper	Power
Ln(AUC Inf)	93.88	89.66	98.28	89.05	98.97	1.00
Ln(AUC last)	93.84	89.59	98.30	88.97	98.99	1.00
Ln(Cmax)	88.11	82.72	93.85	81.94	94.74	1.00
Note: N=52 subjects from the study No.712/14 and N=30 subjects study No. 084-14 were included for the combined analysis. Total number of subjects from both the studies considered for the combined statistical analysis N=82.						

Although the Applicant has not provided the analysis model, which has been used for the pooled analysis of the two trials and it is not known whether a factor for study has been included or not, the inclusion or otherwise was not considered pivotal to the interpretation by CHMP. There was no discussion on heterogeneity of the trials, although with only two studies it would have been difficult to interpret any estimates of heterogeneity. It should be noted that the individual trial results did not give rise to suspicion of a treatment-by-study interaction, despite the marked differences in the level of C_{max} attained. While none of the justifications for the failure of trial 084-14 is agreed (the power had been large, continuation of the trial was not allowed anymore, projection of trial results to a larger sample size not acceptable, a treatment difference other than assumed does not justify failure to show equivalence), the overall trend regarding the treatment comparison was broadly in line with that of study 712/14. This is also supported by the comparable results from analyses of the single trials as well as the pooled trial analysis. Although the justifications of the Applicant were not fully convincing, results were close to the lower acceptance limit and a clear tendency for lower exposure of the test treatment was found, bioequivalence was still shown (fulfilling the 80%-125% equivalence acceptance range) in the view of the CHMP.

No unexpected safety signals have been reported from both submitted studies. Although of note is that high incidence of vomiting has been observed despite the preventive administration of ondansetron.

2.4.6. Conclusions on clinical aspects

Two bioequivalence studies have been submitted, one demonstrating bioequivalence (study 712/14), whereas the other did not (study 084-14). However, after further analyses of the data, the CHMP concluded on the totality of evidence that bioequivalence (with respect to the 80%-125% equivalence acceptance range) with the reference product can be accepted. As all criteria for a biowaiver were met, the CHMP also agreed that the results with the Cinacalcet Mylan 90 mg tablet formulations can be extrapolated to Cinacalcet Mylan 30 and 60 mg film-coated tablets.

2.5. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 3 with the following content:

Safety concerns

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

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Hypocalcaemia	• Sections 4.4, 4.8 and 4.9 of SPC address this safety concern to the prescriber adequately in detail. • Sections 2 and 4 of PIL contain warning on this risk.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Product is POM only.	
Important identified risks: Convulsions/seizures	• Sections 4.4 and 4.8 of SPC address this safety concern to the prescriber adequately in detail. • Sections 2 and 4 of PIL contain warning on this risk. • Product is POM only.	None
Important identified risks: Hypotension and/or worsening heart failure	• Sections 4.4 and 4.8 of SPC address this safety concern to the prescriber adequately in detail. • Section 4 of PIL contains warning on this risk. • Product is POM only.	None
Important identified risks: Hypersensitivity reactions (including rash, urticaria, and angioedema)	• Sections 4.3 and 4.8 of SPC address this safety concern to the prescriber adequately in detail.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Sections 2 and 4 of PIL contain warning on this risk. • Product is POM only.	
Important identified risks: QT prolongation and ventricular arrhythmias secondary to hypocalcaemia	• Sections 4.4 and 4.8 of SPC address this safety concern to the prescriber adequately in detail. • Sections 2 and 4 of PIL contain warning on this risk. • Product is POM only.	None
Important potential risks: Fractures	• The MAH will close monitor this reaction and provide summary in PSURs. • Product is POM only.	None
Important potential risks: Acute pancreatitis	• The MAH will close monitor this reaction and provide summary in PSURs. • Product is POM only.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risks: Possible drug-related hepatic disorders	• The MAH will close monitor this reaction and provide summary in PSURs. • Product is POM only.	None
Important potential risks: Nervous system disorders (excluding seizure)	• Section 4.8 of SPC addresses this safety concern to the prescriber adequately in detail. • Section 4 of PIL contains warning on this risk. • Product is POM only.	None
Important potential risks: Neoplastic events	• The MAH will close monitor this reaction and provide summary in PSURs. • Product is POM only.	None
Important potential risks: Myocardial infarction	• Sections 4.4, 4.8 and 5.1 of SPC address this safety concern to the prescriber adequately in detail.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Sections 2 and 4 of PIL contain information on this risk. • Product is POM only.	
Missing information: Pregnant or lactating women	• Sections 4.6 and 5.3 of SPC address this safety concern to the prescriber adequately in detail. • Section 2 of PIL contains warning on this risk. • Product is POM only.	None
Missing information: Paediatric patients	• Sections 4.2, 4.8 and 5.2 of SPC address this safety concern to the prescriber adequately in detail. • Sections 2 and 4 of PIL contain warning on this risk. • Product is POM only.	None

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to reference product Mimpara. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of cinacalcet hydrochloride film-coated tablets. The reference product Mimpara is indicated for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy, and for the treatment of hypercalcaemia in patients with parathyroid carcinoma or with primary hyperparathyroidism who are unable to undergo parathyroidectomy. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence studies form the pivotal basis. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The analytical methods were validated. Pharmacokinetic and methods applied were adequate and statistical methods applied were found to be sufficient.

With regard to the two bioequivalence studies submitted, the CHMP concluded on the totality of evidence that bioequivalence (with respect to the 80%-125% equivalence acceptance range) with the reference product can be accepted.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Cinacalcet Mylan in the:

Treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy. Cinacalcet Mylan may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section 5.1).

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 favourable and therefore recommends the granting of the marketing authorisation subject to the following

conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.