30 January 2020
EMA/92635/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cinacalcet Accordpharma

International non-proprietary name: cinacalcet

Procedure No. EMEA/H/C/005236/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

AAS:	Atomic Absorption Spectrometry
AE	Adverse event
ANIOVA	Analysis of variances
AP:	Applicant's Part (or Open Part) of a ASMF
API:	Active Pharmaceutical Ingredient
AR:	Assessment Report
AS:	Active substance
ASM:	Active Substance Manufacturer
ASMF:	Active Substance Master File
ATC	Anatomical therapeutic chemical (classification system)
AUC	Area under the plasma concentration versus time curve
BCS:	Biopharmaceutics classification system
BE:	Bioequivalence
BE Guideline:	Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 – January 2010)
BMD	Bone mineral density
BQL:	Below quantification limit
BSE:	Bovine spongiform encephalopathy
Ca	Calcium
Ca x P	Calcium-phosphorus product
CAC	Coronary artery calcification
CaR	Calcium-sensing receptor
CFU:	Colony-forming unit
CI	Confidence interval
CKD	Chronic kidney disease
CLcr	Creatinine clearance
Cmax	Maximal (peak) plasma concentration
CoA:	Certificate of analysis
CV	Coefficient of variation
CYP	Cytochrome P450
DPM:	Drug Product Manufacturer
DSC:	Differential scanning calorimetry
EC50	Effective concentration 50%
EMA	European Medicines Agency
ESRD	End-stage renal disease
EU	European Union
EU:	European Union
Fct:	Film coated tablet
FDA	Food and Drug Administration
FGF	Fibroblast growth factor

FHH	Familial hypocalciuric hypocalcaemia
GC	Gas chromatography
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GMP:	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HCL	Hydrochloride
HDPE:	High Density Polyethylene
HIV	Human immunodeficiency virus
HPLC:	High Performance Liquid Chromatography
HPT	Hyperparathyroidism
HR	hazard ratio
IC50	Inhibitory concentration 50%
ICH:	International Conference on Harmonisation
INN	International Nonproprietary Name
IPC:	In-process controls
iPTH	Intact parathyroid hormone
IR:	Infra-Red Spectroscopy
IV	intravenous(ly)
JECFA:	Joint Evaluation Committee on Food Additives
JP MO:	Japanese Ministerial Ordinance
JPE:	Japanese Pharmaceutical Excipients
KDOQI	Kidney Disease Outcome Quality Initiative
Kel	Elimination constant
LDPE:	Low Density Polyethylene
LOD:	Limit of Detection
LOQ:	Limit of Quantitation
LoQ:	List of Questions
LSmean	Least square mean
MAH	marketing authorization holder
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
ND:	Not detected
NLT:	Not Less Than
NMR:	Nuclear Magnetic Resonance
NMT	Not More Than
P	Phosphorus
PD	peritoneal dialysis
PE:	Polyethylene
Ph.Eur.	European Pharmacopoeia

PIL:	Patient Information Leaflet
PP:	Polypropylene
primary HPT	primary hyperparathyroidism
pmarp	per million of the age-related population
pmp	per million population
PRT	post-renal transplant
PSUR	periodic safety update report
PTH	parathyroid hormone
PY	patient years
PVC:	Poly vinyl chloride
QOS:	Quality Overall Summary
QP:	Qualified Person
QPPV	Qualified Person for Pharmacovigilance
R	Reference
RH:	Relative humidity
RMP	risk management plan
RP:	Restricted Part (or Closed Part) of an ASMF
RRF:	Relative Response Factors
RRT:	Relative retention time
SHPT	secondary hyperparathyroidism
RSSPM:	Rotation per minute
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA Query
T	Test
T1/2	Terminal-phase half-life
TGA:	Thermo-Gravimetric Analysis
Tmax	Time to maximal plasma concentration
TSE:	Transmissible spongiform encephalopathy
UK	United Kingdom
US	United States
USA	United States of America
USP:	United States Pharmacopoeia
USP-NF	United States Pharmacopoeia-National Formulary
UV:	Ultraviolet Spectroscopy
VDR	Vit D receptor
Vit D	1,25 dihydroxy vitamin D (calcitriol)
XRD:	X-Ray Diffraction
µ	Micro

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 10 January 2019 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cinacalcet Accordpharma, 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 15 November 2018.

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, as defined in Article 10 (2)(a) of Directive 2001/83/EC, 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:

> "Secondary hyperparathyroidism
>
> *Adults*
> Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.
>
> *Paediatric population*
> Treatment of secondary hyperparathyroidism (HPT) in children aged 3 years and older with end-stage
> renal disease (ESRD) on maintenance dialysis therapy in whom secondary HPT is not adequately controlled with standard of care therapy (see section 4.4).
>
> Cinacalcet Accordpharma may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate (see section 5.1).
>
> Parathyroid carcinoma and primary hyperparathyroidism in adults
>
> Reduction of hypercalcaemia in adult patients with:
> - parathyroid carcinoma.
> - primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated."

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 at least a bioequivalent study with the reference medicinal product Mimpara instead of non-clinical and clinical unless justified otherwise.

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 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:
  - Union

- 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:
  - Union
  - 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:
  - Union
  - Community Marketing authorisation number: EU/1/04/292/009-012
- Bioavailability study numbers: 0418/17

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Andrea Laslop Co-Rapporteur: N/A

The application was received by the EMA on	10 January 2019
The procedure started on	30 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 May 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	29 May 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	23 September 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	17 October 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	27 November 2019
The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	23 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	15 January 2020
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 Accordpharma on	30 January 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Abnormal parathyroid hormone (PTH) secretion, both as a primary or secondary condition, is one of the most common endocrine derangements.

Primary hyperparathyroidism (HPT) is an endocrinopathy characterised by overproduction of parathormone (PTH) due to a solitary adenoma (80%) or to multiple adenomas (5%), to hyperplasia (15%) and, rarely, (<1%) to carcinoma of the parathyroid glands. It is the third most common endocrine disorder, with a prevalence of 3 per 1,000 in the general population. The condition is characterised by hypercalcaemia and is variably associated with mineral bone loss and nephrolithiasis. Parathyroidectomy is the most commonly proposed therapy for primary HPT. There are currently only few nonsurgical treatment alternatives for patients for whom surgery failed or for whom surgery is precluded because of contraindications.

Secondary HPT related to chronic renal failure (chronic kidney disease, CKD) is the most common secondary form of parathyroid gland dysfunction. Secondary HPT is characterised as a maladaptive process that develops in response to declining kidney and myocardial function, primary aldosteronism, impaired phosphate elimination, and failure to bioactivate vitamin D. The hallmarks of secondary HPT are a relative deficiency of extracellular calcium (Ca), elevated extracellular phosphate and reduced serum calcitriol. Secondary HPT is a common and serious disease that develops early in CKD when glomerular filtration rate (GFR) drops below 80 mL/min. Untreated, secondary HPT in CKD leads to significant skeletal toxicity including osteomalacia and osteodystrophy, as well as to extraskeletal damage including vascular calcification, peri-articular Ca deposits and an impaired cardiac function seriously increasing the risk of cardiovascular mortality. Conventional treatment options include dietary phosphate restriction, use of Ca and non-Ca based phosphate binders and vitamin D sterols, all of which targets a normalisation of the Ca/P/vitamin D axis and as a consequence, PTH levels. However, conventional treatments may lead to increases in Ca and/or phosphorus (P), which may preclude continuous, effective therapy.

2.1.2. About the product

The active substance in the medicinal product in question is cinacalcet hydrochloride. The pharmacotherapeutic group of cinacalcet is calcium homeostasis (ATC-code H05), anti-parathyroid agents (ATC-code H05B).

Cinacalcet is approved in the EU for

- Treatment of secondary hyperparathyroidism (HPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy and treatment of secondary hyperparathyroidism (HPT) in children aged 3 years and older with end-stage renal disease (ESRD) on maintenance dialysis therapy in whom secondary HPT is not adequately controlled with standard of care therapy
- Reduction of hypercalcaemia in adult patients with parathyroid carcinoma or with 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.

This is also the indication applied for by Accord Healthcare S.L.U..

Cinacalcet is taken orally and comes in tablet form in three strengths (30 mg, 60 mg, and 90 mg) or, for the Originator Mimpara, in granules in capsules (1 mg, 2.5 mg, and 5 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 secretion (PTH). Cinacalcet increases the sensitivity of calcium receptors on parathyroid cells to reduce parathyroid hormone (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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The applicable CHMP Guidelines were mostly followed.

The Applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are:

- Tablet core: microcrystalline cellulose, crospovidone, magnesium stearate
- Tablet coat: hypromellose (E464), titanium dioxide (E171), triacetin, FD&C blue/indigo carmine aluminum lake (E132), iron oxide yellow (E172)

The product is available in a clear PVC/Aluminium blister or in high density polyethylene (HDPE) bottle with a child-resistant polypropylene (PP) cap.

2.2.2. Active Substance

General Information

The INN of the active substance is cinacalcet. It is not described in the European Pharmacopoeia (Ph Eur). A draft monograph is however available in United States Pharmacopeia National Formulary (USP NF) 42(4).

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

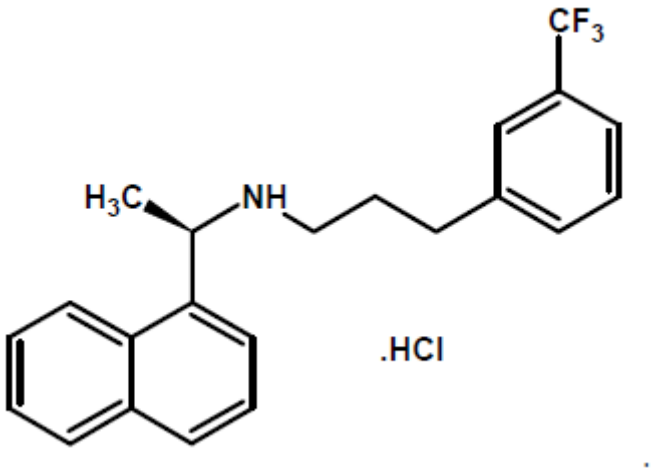

Figure 1: Structure of cinacalcet hydrochloride

Cinacalcet hydrochloride is a white to off-white, non-hygroscopic, crystalline powder, BCS class IV drug, soluble in methanol and ethanol, insoluble in water. The pH of a suspension of cinacalcet in water at a concentration of 1% w/v at about 25°C is 5.80 – 5.81.

The chemical structure has been adequately demonstrated by elemental analysis, ultraviolet (UV) spectroscopy, Fourier-transform infrared spectroscopy (FT-IR), ^{1}H- and ^{13}C- nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry, and thermal analysis by differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA).

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 the pharmacodynamic activity. The *S*-isomer is controlled in the active substance specification as an impurity by HPLC analysis.

Polymorphism has been observed for cinacalcet hydrochloride. Three different polymorphic forms of the active substance have been identified in literature. Of these polymorphs, only one form is stable at ambient temperature. Consistent manufacture of this desired polymorphic form has been confirmed by the manufacturer. It has also been shown that the polymorphic form remains stable during storage conditions and there is no conversion to other polymorphs.

Manufacture, process controls and characterisation

The information on the active substance has been 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.

The active substance is synthesized in 7 main steps using well defined starting materials with acceptable specifications. This includes two steps to obtain the intermediate and five steps to obtain the active substance.

Two starting materials were proposed. A major objection was raised in relation to one of the proposed starting materials as it is only introduced in the last chemical synthesis step and therefore not in line

with the principles outlined in ICH Q11. In response, the applicant redefined the starting material which was considered acceptable.

Characterization data, specifications, test methods, name and addresses of suppliers and a flow chart of the synthesis are provided for the defined starting materials. The potential impurities identified from the route of synthesis are discussed.

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

Potential and actual impurities were well discussed with regards to their origin and characterised. The discussion on impurities included organic and inorganic impurities, metal catalysts/elemental impurities and residual solvents. The proposed limits for related substances are in general in line with the USP NF Draft Monograph. However, a major objection was raised in relation to one impurity for which a higher limit as compared to the monograph was proposed**.** The manufacturer presented batch analysis data, stability data and a purging study to demonstrate the absence of the impurity in the final active substance. The method description, typical chromatograms and validation report were also provided upon request and the major objection was thereby considered resolved.

In the context of the on-going review under Article 5(3) of Regulation (EC) No 726/2004 related to the potential presence of nitrosamine impurities in human medicinal products (https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-information-nitrosamines-marketing-authorisation-holders_en.pdf, https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation_en.pdf), MAHs of products containing chemically-synthesized active substances are being asked to review their products for potential presence of nitrosamine impurities and to conduct risk evaluations/risk assessments as appropriate.

No risk evaluation has been submitted for Cinacalcet Accordpharma within the current procedure. Therefore, it is recommended that a risk evaluation on the potential risk of presence of nitrosamine in Cinacalcet Accordpharma is conducted after the marketing authorisation, within six months of the publication of the call for review (19th September 2019). In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within 3 years of the publication of the call for review (19th September 2019), or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented. (See "Recommendations for future quality development")

Cinacalcet hydrochloride is packed in a clear low-density polyethylene (LDPE) bag and tied using thread or strip. This bag is placed in a black colour LDPE bag and tied using thread or strip. This double polyethylene bag is placed inside a triple laminated bag. The sealed triple laminated bag is placed inside a HDPE container. Specifications and appropriate certificates of analysis for the primary and secondary packaging have been provided.

The primary packing (LDPE bag) complies with Ph. Eur. Monograph 3.1.3 Polyolefines and with Commission regulation (EU) No 10/2011 as amended.

Specification, analytical procedures, reference standards, batch analysis, and container closure

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

(GC), triethylamine content (GC), acetic acid content (HPLC) and particle size (By Malvern mastersizer).

All tested parameters are considered relevant and adequate for control of the active substance. The proposed tests and acceptance criteria have been established based on relevant guidelines and batch analysis data.

Absence of tests identification by XRD and microbial contamination have been adequately justified. The proposed limits for related substances are in line with ICH Q3A (R2) (reporting threshold 0.05%, identification threshold 0.10%, qualification threshold 0.15%). Control of mesylated impurity was removed from the specification based on data demonstrating the absence of mesylated impurity in the active substance. Cinacalcet hydrochloride exhibits stereoisomerism, therefore a test for *S*-isomer content has been included in the specification.

The analytical methods have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

Cinacalcet hydrochloride working standard and impurity standards are routinely used in HPLC methods for identification, related substances, assay, and chiral purity. The standards have been well characterized and analysed.

Batch analysis data for validation batches have been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data in accordance with ICH guidelines from process validation batches stored under long term condition (25±2 °C/60±5% RH) and accelerated condition (40±2 °C/75±5% RH) in the intended commercial package were provided.

The following parameters were tested: description, identification (IR, HPLC), water content (KF), assay (HPLC), related substances (HPLC), and chiral purity (HPLC).

Forced degradation studies have been provided to prove the specificity of HPLC methods used for related substances, assay and chiral purity.

All available stability results were within the specification and no trends have been observed.

Based on the current available stability data a retest period of 48 months is proposed and accepted for the active substance.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is presented as follows:

- **Cinacalcet 30 mg film-coated tablets**

Light green coloured, oval shaped, biconvex, film-coated tablets debossed with "HB1" on one side and plain on other side. Dimension: approximately 9.65 x 6.00 mm.

- **Cinacalcet 60 mg film-coated tablets**

Light green coloured, oval shaped, biconvex, film-coated tablets debossed with "HB2" on one side and plain on other side. Dimension: approximately 12.20 x 7.60 mm.

- **Cinacalcet 90 mg film-coated tablets**

Light green coloured, oval shaped, biconvex, film-coated tablets debossed with "HB3" on one side and plain on other side. Dimension: approximately 14.00 x 8.70 mm.

Other ingredients are:

- Tablet core: microcrystalline cellulose, crospovidone, magnesium stearate
- Tablet coat: hypromellose (E464), titanium dioxide (E171), triacetin, FD&C blue/indigo carmine aluminum lake (E132), iron oxide yellow (E172)

The different strengths are fully dose proportional.

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.

The active substance was adequately characterized, taking into account its low solubility (class IV BCS). The particle size of cinacalcet hydrochloride is controlled by the finished product manufacturer as part of the active substance specification.

Cinacalcet exhibits polymorphism. The active substance manufacturer has proven the consistent manufacturing of crystalline form I. The applicant has confirmed that the polymorphic form of the active substance is maintained throughout the tablet manufacturing process and during stability.

The choice and function of the excipients has also been described, including information regarding the functionality related characteristics of the excipients. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph Eur, except the coating agent which is a premixture, but its components comply with Ph. Eur, where available. Iron oxide yellow (E172) and FD&C Blue #2/indigo carmine aluminum lake (E132) are not described in Ph. Eur. but they comply with Commission Regulation (EU) No. 231/2012. There are no novel excipients used in the finished product formulation.

The results of compatibility studies of the active substance with the excipients are provided showing that the active substance is compatible with the selected excipients.

Formulation development was done by a conventional approach based on the literature search and the characterization of reference product i.e. Mimpara 30 mg, 60mg and 90 mg film-coated tablets. The formulation of Cinacalcet Accord is different from the formulation of the reference product. Povidone and colloidal anhydrous silica are used for Mimpara but not for Cinacalcet Accordpharma. In addition there are differences in the composition of the film-coating and in diluents used: whereas microcrystalline cellulose is used as a diluent in Cinacalcet Accord, 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.

The proposed dissolution method was adequately justified. The demonstration of the discriminative power of the dissolution method is considered sufficient.

A bioequivalence study has been carried out for the highest strength 90 mg. The reference product is Mimpara 90 mg film-coated tablets (EU/1/04/292) marketed by Amgen Europe B.V. The reference product is sourced from the EU market. The test product used in the bioequivalence study has the same quantitative composition and is manufactured by the same process as proposed for commercialisation. The comparative *in-vitro* dissolution profile between the test and the reference

product used in bioequivalence studies has been generated in 0.1 N HCl, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer performed using a paddle stirring speed of 50 rpm and, in 0.05 N HCl performed using a paddle stirring speed of 75 rpm. This is in accordance with the Guideline on the investigation of bioequivalence.

For the additional 30 mg and 60 mg strengths a bio-waiver is claimed. All three strengths are qualitatively similar, quantitatively proportional and manufactured out of the same bulk granule. Furthermore, all three strengths are manufactured according to the same manufacturing process. Comparative *in vitro* dissolution studies between the 90 mg bio-batch versus the additional 60 mg and 30 mg strengths were performed in 0.1N HCl, pH 4.5 and pH 6.8 media using the paddle apparatus, showing comparable dissolutions throughout the tested pH range. For the 30 mg strength however, the f2 value was just near the 50 limit in one of the buffers and the lower dose level did not reach a plateau. To address the issue of dissolution dissimilarity for the lowest strength, which triggered a major objection, a comparison study with the reference medicinal product, Mimpara 30 mg vs test product, Cinacalcet Accordpharma 30 mg film coated tablets was conducted. Similarity between reference and test product was demonstrated. Additionally, the applicant showed similar profiles at the same dose (three tablets of 30 mg versus one tablet of 90 mg). Based on the data provided the bio-waiver for the 30 mg and 60 mg strengths is considered justified.

Manufacturing process development

As the flow property of the active substance is very poor, a wet granulation technique was adopted to start the development trials. The manufacturing process comprised of granulation, lubrication, compression and coating. All these process variables might have a direct impact on quality attributes of the finished product so the following process parameters have been optimised during process development: granulation parameters, lubrication time, compression parameters and coating.

Container closure system

The primary packaging consists of a clear PVC/Aluminium blister (pack sizes of 14, 28 or 84 tablets) or a high density polyethylene (HDPE) bottle with a child-resistant polypropylene cap (pack size of 30 tablets). The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The materials comply with Ph.Eur. and EC requirements.

The bulk pack for transportation and further re-packaging into final container closure system consists of a clear, transparent LDPE bag in a high molecular weight high density polyethylene (HMHDPE) container. Stability data and appropriate information regarding the bulk pack for transportation have been provided.

Manufacture of the product and process controls

The manufacturing process is considered a standard process and it consists of the following main steps:

- wet granulation
- pre-compression blending
- compression
- coating

The manufacturing steps have been described in detail.

The applicant has confirmed that the shelf-life of the finished product will be set in accordance with the NfG on start of the shelf-life of the finished dosage form (CPMP/QWP/072/96).

Process validation has been carried out on three consecutive commercial scale batches of Cinacalcet 30 mg, 60 mg and 90 mg film-coated tablets. The batches were manufactured by using common granulation. The common granules were further divided into three parts for the compression of the individual strengths. The process validation report shows that the proposed process is capable of consistently produce finished product that meets the specifications.

Product specification, analytical procedures, batch analysis

The release and shelf life specifications include appropriate tests for this dosage form: description, tablet weight, identification (UV, HPLC), loss on drying (in-house), dissolution (UV), uniformity of dosage units (content uniformity, HPLC), related substances (HPLC), assay (HPLC) and microbial examination (Ph Eur).

The applicant provided a discussion regarding the impurities of the finished product focusing on degradation products arising from the manufacturing process and those expected during storage.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

The reference standards (cinacalcet hydrochloride standards and impurity standards) used by the finished product manufacturer are adequately characterised.

Batch analysis results for three validation batches of each strength of the finished product are presented. The batch analysis data are acceptable and indicate that all tested parameters are within set specifications, showing low variations and indicating the reliability of the production process.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

Stability of the product

Stability data from 3 commercial scale batches for each of the tablet strength of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (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 both primary packaging systems (PVC-Alu blister and HDPE bottle) proposed for marketing.

Samples were tested for appearance (visual inspection), dissolution (UV), assay (HPLC), related substances (HPLC), water content (loss of drying), and microbiological test (Ph. Eur.). The analytical procedures used were the same as for release. The methods for related substances and assay were shown to be stability indicating.

Photostability study has been performed on one batch of cinacalcet hydrochloride 90 mg film-coated tablet (direct exposure) by exposure to 1.2 million lux hours and then to near UV energy of 200 watt hours/square meter. No out of specification results were observed. Cinacalcet hydrochloride film coated tablets are therefore not considered to be photosensitive.

An in-use stability study was performed for one batch of each tablet strength stored in the HDPE bottle. The results showed that the finished product was stable and no trends were observed.

Based on the data provided, the shelf life claim of 36 months without special storage conditions can be accepted for both PVC-Alu blister and HDPE bottle.

Based on stability data provided for the bulk shipment pack (6 months at accelerated conditions (40°C ± 2°C/75% ± 5 %RH) and 12 months at long term conditions (25°C ± 2°C/60% ± 5 %RH)), the shelf life claim of 12 months without special storage conditions can be accepted.

Adventitious agents

None of the materials used in this formulation are of human or animal origin. Magnesium stearate is of vegetable origin. TSE-BSE free statements were provided for following excipients: microcrystalline cellulose, crospovidone, magnesium stearate (vegetable origin) and opadry 03K510007 green.

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.

Three major objections relating to quality aspects were raised during the procedure.

One major objection was raised in relation to one of the proposed starting materials. Following a redefinition of the starting material the major objection was considered resolved.

Another major objection was raised in relation to the proposed limit for an impurity. The manufacturer presented batch analysis data, stability data and a purging study to demonstrate the absence of the impurity in the final active substance. The method description, typical chromatograms and validation report were also provided upon request and the major objection was thereby considered resolved.

A third major objection was raised in relation to the data provided to support the biowaiver for the 30 mg strength. To address the issue of dissolution dissimilarity for between the bio-batch and the 30 mg strength, a comparison study with the reference medicinal product, Mimpara 30 mg vs test product, Cinacalcet Accordpharma 30 mg film coated tablets was conducted. Additionally, the applicant showed similar profiles at the same dose (three tablets of test product of 30 mg versus one tablet of 90 mg). Based on the data provided the bio-waiver for the 30 mg and 60 mg strengths is considered justified.

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

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended points for investigation, including a risk evaluation on the potential presence of nitrosamine impurities.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of Cinacalcet Hydrochloride are well known. As Cinacalcet Hydrochloride is a widely used, well-known active substance, the Applicant has not provided additional studies and further studies are not required. This application is based on a literature overview, which is considered appropriate.

The impurity profile has not been discussed in the non-clinical overview. For the relevance of impurities the reader should refer to the quality sections of this report.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the Applicant as follows:

This product is already available as a generic product on the market. Hence, marketing authorization of the proposed product will not lead to any increased environmental risk. The risk assessment is based on the following assumptions:

- The proposed marketing authorization will not lead to increase the use of this product. This would rather replace some of the product already available on the market.
- There are no additional precautionary or safety measures required for generic form, if the product is available on the market for more than 10 years.
- There is no specific requirement to be included in the SmPC and PIL in line with the reference product.
- Generic products are not exempted from providing an ERA according to the current guideline.

The Applicant's justification for not submitting ERA data (see EMA document (EMA/CHMP/SWP/44609/2010 Rev.1) was substantiated by suitable information. It is noted that according to the AR of the latest Cinacalcet PSUSA, the market exposure (in patient years) did not increase significantly. An additional impact of Cinacalcet Accordpharma on the environment is considered unlikely.

2.3.3. Discussion on non-clinical aspects

The non-clinical sections of the SmPC of Cinacalcet Accordpharma are identical to the non-clinical sections of the SmPC of the reference product (Mimpara) and hence acceptable. Additionally, the grounds for not providing new data is justified adequately.

2.3.4. Conclusion on non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

The applicant provided an overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of cinacalcet based on published literature, which is considered acceptable. The SmPC is in line with the SmPC of the reference product. The indications, posology and method of

administration in the proposed SmPC are in line with the SmPC of the reference product Mimpara, including the paediatric indication.

As there is no paediatric formulation available for Cinacalcet Accordpharma and exact dosing/titration is not possible below 30 mg, the inclusion of a respective statement in the SmPC was implemented:

'Note: Cinacalcet Accordpharma is only available as film-coated tablet. Thus, it is not possible to administer Cinacalcet Accordpharma to paediatric patients that require less than a full 30 mg dose. If an alternate dose is required, other cinacalcet products offering such an option should be used.'

The Applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation. Relevant for the assessment are the Guideline on the Investigation of Bioequivalence ((CPMP/EWP/QWP/1401/98 Rev 01 – January 2010; = BE Guideline) and Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009).

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

The Applicant conducted a single bioequivalence study in which only the highest strength (90 mg tablets Cinacalcet Accordpharma) was evaluated. The Applicant applies for a biowaiver for the 30 mg and 60 mg strengths.

Pharmacokinetics of cinacalcet has been shown to be dose-proportional between 30 and 180 mg (see EPAR of reference product Mimpara and literature on the matter). According to the BE guideline the following criteria have to be met in addition to qualify for a biowaiver:

a) The pharmaceutical products have to be manufactured by the same manufacturing process, this requirement is met according to documentation provided by the Applicant.

b) The qualitative composition of different strengths of the test product is the same and thus adequate to qualify for a biowaiver.

c) the composition of the strengths is quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths.

d) appropriate **in vitro dissolution data** should confirm the adequacy of waiving additional in vivo bioequivalence testing:

Similarity of in vitro dissolution should be demonstrated at all conditions within the applied product series, i.e. between additional strengths and the strength(s) (i.e. batch(es)) used for bioequivalence testing.

In-vitro dissolution tests have been provided with Cinacalcet Tablets 30/60/90 mg in 0.1 N HCl, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer. This is in line with what is proposed in the applicable guideline.

As for no strength (30/60 or 90mg) > 85% of drug is dissolved within 15 minutes (irrespective of pH), further mathematical evaluation has been conducted to justify qualification for a biowaiver:

The f_2-values calculated at pH 1.2, 4.5 & 6.8 are in the range of 50 to 100 and thus in accordance with the respective limits of acceptability according to the BE Guideline. For the 30 mg strength at pH 6.8

however, the f2 value is just near the 50 limit (50.4). The Applicant provided results of a comparison analysis with the reference medicinal product (Mimpara 30 mg) vs. the test product (Cinacalcet 30 mg film coated tablets) conducted at 50 rpm at pH 4.5 and pH 6.8 (see assessment in the quality part).

RSD values were calculated and all values were less than 20% for the first point and less than 10% from second to last time point which is in accordance with the respective guideline.

It is noted that the excipients for Cinacalcet Accordpharma enlisted by the Applicant are not listed in the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) (EMA/CHMP/302620/2017) and hence considered to not be an issue.

Clinical studies

To support the application, the applicant has submitted a single bioequivalence study.

Table 1: Tabular overview of clinical studies

Type of study	Study Identifier	Location of study report	Study title	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
Pivotal	Project No. 0418-17	Module 5, Section 5.3.1.2	An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of two products of Cinacalcet Tablets 90 mg in normal, healthy, adult, human subjects under fed condition	Test Product: Cinacalcet Tablets 90 mg Ref product: Mimpara® (Cinacalcet) film-coated tablets 90 mg Single dose (90 mg) Oral administration	Total subjects included in pharmacokinetic and statistical analysis, N = 60	Healthy subjects	Single dose	Completed, Full

2.4.2. Pharmacokinetics

To support the application, the applicant submitted one bioequivalence study (Study/Project No. 0418-17) which is discussed in the following sections of this report.

Methods

Study design

The study was an open label, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study of two products of Cinacalcet Tablets 90 mg in normal, healthy, adult, male human subjects under fed condition, with a screening period of 28 days prior to the dosing in Period-I. In each study period, 33 blood samples including one pre-dose blood sample were collected from each subject (except for the discontinued/withdrawn subjects and missing samples) to analyse the pharmacokinetic profile of the test as well as the reference products.

The design of the study is in line with the Guideline on the Investigation of Bio-equivalence (CPMP/EWP/QWP/1401/98 Rev 01 – January 2010) and thus considered appropriate to investigate bioequivalence between immediate release formulations of the test and reference products.

After an overnight fast of at least 10 hours, the subjects were served a standardized high fat and high calorie vegetarian breakfast, which they consumed within 30 minutes. A single oral dose (90 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast. Since the SmPC of the reference product Mimpara recommends administration with food, it is appropriate that the study was conducted under fed conditions.

Considering the decline of the cinacalcet concentration in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours, the washout period was more than 5 half-lifes of the active substances', and thus enough to avoid potential carry-over effects and in line with the guideline.

The sampling period and sampling scheme seems adequate to estimate the primary PK parameters of cinacalcet. The sampling is frequent enough around the expected T_{max} (mean ~6 hours) to sufficiently approximate C_{max}. Considering the rather long terminal half-life of cinacalcet, it is considered acceptable to collect blood samples until 192 hours post-dose to calculate the AUC. The majority of the subject's samples at 192 hours post-dose were below the Limit of Quantification Quality Control (LOQ QC, 0.261 ng/mL). The $AUC_{(0-t)}$ seems to easily cover over 80% of the $AUC_{(0-\infty)}$.

According to the Applicant, the major circulating metabolites are inactive and thus considered not an issue. They have not been evaluated separately in the experiment. The SmPC of the Originator Mimpara does not mention relevant metabolites.

A block-randomization scheme was used (block size of two).

Test and reference products

The choice of reference product is appropriate.

The batch size of the test product applied in the bioequivalence study is in accordance with the BE Guideline where a production scale above 100,000 is recommended. Certificates of analysis have not been provided, however since only one batch was used for either test or reference product this seems acceptable.

In contrast to the reference product Mimpara, the test product Cinacalcet Accordpharma does not include Lactose. Therefore, the excipient warning as outlines in the Excipients guideline (EMA/CHMP/302620/2017) does not apply here and has been deleted from the product information.

According to the Applicant the formulation of the test product batch used in the BE study is identical to the formulation of the batches for the market.

Population(s) studied

Subjects participated in the study were non-smokers, normal, healthy, adult, male human volunteers between 18 to 45 years of age (both inclusive), having a Body Mass Index (BMI) between 18.5 to 30.0 kg/m^2 (both inclusive), were able to understand and comply with the study procedures and given their written informed consent were checked in for the study. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray (posterior-anterior view) recordings. Subjects had clinically acceptable values for tests of serum calcium, serum phosphorus and iPTH at the time of screening. The inclusion and exclusion criteria have been adequately described and seem acceptable.

Table 2: Demographics

Parameter (Units)	Mean ± SD	
	N = 69 (Dosed Subjects)	N=60 (Subjects included in BE evaluation)
Age (years)	31.9 ± 5.92	31.9 ± 6.04
Height (cm)	167.09 ± 5.750	167.56 ± 5.798
Weight (kg)	62.874 ± 8.5757	63.017 ± 8.7280
BMI (kg / m^2)	22.506 ± 2.7278	22.428 ± 2.7307

No female volunteers were enrolled in the study. According to the BE guideline, the subjects could belong to either sex; however, the risk to women of childbearing potential should be considered. A subgroup analysis by age, sex, race and geographic region showed no differences in the magnitude of the treatment effect of cinacalcet across subgroups (see EMA EPAR Mimpara 2005). Hence, the inclusion of only male subjects is acceptable.

The criteria for restrictions, concomitant medication, subject screening and examination, investigations and post study procedures seem to be adequately defined.

As per the protocol, the subjects were instructed not to take any medicine [prescribed and over the counter (OTC) medication including herbal remedies, CYP3A4 inhibitor (e.g., ketoconazole, itraconazole)] at any time within 14 days prior to the drug administration in Period-I until completion of the study (i.e. until the last pharmacokinetic sample of Period-II). Any such subjects could have been removed from the study.

Patient disposition

A total of 73 subjects including three additional subjects were checked in for the study. They were checked in for the study in order to compensate for any dropout prior to dosing in Period-I. According to the Applicant, one of these additional subjects was checked out of the facility prior to dosing in Period-I as no more subject discontinued/was withdrawn from the study and he was not needed. As this subject has not been dosed within the study, this approach seems acceptable.

Table 3: Number of Subjects (planned and analysed)

Number of Subjects (planned and analysed):

Planned for inclusion			70
Pre-dose discontinued subjects			03
Dosed	Group-I	Period-I	34
		Period-II	31
	Group-II	Period-I	35
		Period-II	32
Post-dose discontinued / withdrawn subjects			09
Analyzed			69 (In which, withdrawn Subject Nos. 1005, 1029, 1032, 1034, 1042, 1050, 1063, 1066 & 1070 were also analysed as per protocol requirement)
Considered for statistical analysis			60

Determination of sample size

Based on the applicant's in-house study data, the maximum intra-subject variability observed for primary pharmacokinetic parameter was found to be approximately 25%; the sample size computation was determined using SAS by considering the following assumptions: T/R ratio = 90.0-110.0%, intra-subject coefficient of variation (%) approximately 25%, significance level 5%, power ≥ 80% and bioequivalence limits 80.00-125.00%.

Based on the above estimates, a sample size of 56 subjects was required to establish bioequivalence between formulations with adequate power. Considering approximately 20% drop-outs and/or withdrawals, a sample size of 70 subjects was sufficient to establish bioequivalence between formulations with adequate power for this pivotal study.

Determination of sample size is rather conservative and acceptable.

Analytical methods

The plasma concentrations of the analyte Cinacalcet in the subject samples were determined by a validated LC-MS/MS method. The analyte and internal standard were extracted from a 0.250 mL aliquot of K_2EDTA (Dipotassium Ethylene Diamine Tetra Acetate) human plasma using liquid-liquid extraction method. The extracted samples were injected into a liquid chromatograph.

The detection method used was tandem mass spectrometry detector. Quantitation is determined by peak area ratio method. A weighted ($1/c^2$) linear regression is performed to determine the concentration of the analytes.

The validation of the analytical methods was adequately explained and is acceptable

The analytical method for the determination of Cinacalcet in K_2EDTA human plasma as well as respective validations (including partial validations) are described adequately; the validation including two annexes was performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). Acceptance criteria are in a plausible range and are fulfilled.

The bioanalytical method demonstrates acceptable performance and is suitable for the determination of Cinacalcet in K_2EDTA human plasma over the calibration range.

All chromatograms of all subjects have been provided.

Pharmacokinetic Variables

The primary pharmacokinetic parameters were C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

The secondary pharmacokinetic parameters were T_{max}, λ_z, $t_{½}$ and AUC_%Extrap_obs. These pharmacokinetic parameters were calculated for Cinacalcet by using non-compartmental model of Phoenix® WinNonlin® Version 6.4 software (Certara L.P.).

The chosen (primary and secondary) parameters and the software used seem adequate.

In addition, the $AUC_{(0-t)}$ and the sampling time (last sample taken 192 hours after dosing) is considered adequate as 80% of the $AUC_{0-\infty}$ are apparently covered.

Statistical methods

The following parameters were pre-specified:

• T/R ratio = 90.0-110.0%

• Intra-Subject C.V (%) ~ 25%

• Significance Level = 5%

· Power ≥ 80%

• Bioequivalence Limits = 80.00 - 125.00%

Descriptive statistics were computed and reported for the pharmacokinetic parameters for Cinacalcet.

As the study was conducted in groups, ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ from all the groups were to be subjected to Analysis of Variance (ANOVA) for Cinacalcet. The ANOVA model included Group, Sequence, Sequence*Group, Subject (Sequence*Group), Period (Group) and Formulation effects. Each analysis of variance included the calculation of least-squares mean values, the difference between the adjusted formulation mean values and the standard error associated with the differences. If the number of subjects for BE-evaluation was <5 subjects in any group, then that group was combined to another group.

According to the BE Guideline, the ANOVA model is acceptable for analysis of logarithmically transformed pharmacokinetic parameters C_{max} and AUC. In addition, the pre-specified parameter are in line with the Guideline.

An 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 power of the single BE-study was computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Cinacalcet.

Ratio of geometric least squares mean values of the test and reference formulations was computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Cinacalcet.

Intra-subject variability was computed and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Cinacalcet.

Using two one-sided tests for bioequivalence, 90% confidence intervals for the ratio of geometric least squares mean values between drug formulations were computed for ln-transformed data of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Cinacalcet.

There were no Bioanalytical Protocol deviations during subject sample analysis.

According to the Guideline on the Investigation of Bioequivalence, "subjects in a crossover trial who do not provide evaluable data for both of the test and reference products (or who fail to provide evaluable data for the single period in a parallel group trial) should not be included". However, in the study report, the Applicant used and included data from subjects who failed to provide such data. The Applicant provided re-calculated data without the results from these subjects as requested and only these data are presented below. Aberrations to the results initially provided are marginal and do not change the outcome of the BE exercise.

Results

Table 4: Pharmacokinetic parameters for Cinacalcet (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ (ng.h/ml)	499.299	245.6576	503.935	254.9161
$AUC_{(0-\infty)}$	520.880	253.5037	525.529	263.9335
C_{max}	43.416	24.7532	43.518	21.7443
T_{max}*	5.032	1.667 - 12.000	5.106	1.667 - 10.000
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 5: Statistical analysis for Cinacalcet (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	100.2	95.52 - 105.15	14.9
$AUC_{(0-\infty)}$	100.4	95.86 - 105.18	14.4
C_{max}	98.6	92.55 - 105.15	21.0
* estimated from the Residual Mean Squares			

Table 6: Pharmacokinetic parameters of Cinacalcet for Test-Product (T) and Reference-Product (R)

	T_{max} (h)		C_{max} (ng/mL)		AUC_{0-t} (ng.h/mL)		AUC_{inf} (ng.h/mL)	
	T	R	T	R	T	R	T	R
Min	1.667	1.667	11.929	9.277	140.468	128.845	152.069	135.602
Max	12.000	10.000	127.377	116.726	1166.063	1226.943	1199.998	1246.331

Table 7: ANOVA p-values for Cinacalcet

Measures		Tmax (h)	Cmax (ng/mL)	AUC0-t (ng.h/mL)	AUC0-inf (ng.h/mL)
ANOVA p-value					
ln-transformed	Group	-	0.3146	0.1480	0.1862
	Sequence	-	0.0027	0.1722	0.2483
	Group*Sequence	-	0.3990	0.1818	0.1128
	Subject(Group*Se	-	<0.0001	<0.0001	<0.0001
	Formulation	-	0.7227	0.9393	0.8818
	Period(Group)	-	0.7826	0.6805	0.6694

The pharmacokinetic parameter data including confidence intervals and point estimates presented by the Applicant in table 4-6 are well in line with the acceptance criteria set in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr – revised 2010) and support the notion of bioequivalence between the reference and test product. This is supported by the p-values calculated in table 7.

The 90% confidence interval for the ln-transformed values for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max} were within the 80.00-125% limit and are thus considered acceptable.

The SD seems rather high (and the CV% rather low) which likely reflects a high inter-individual - and a low intra-individual variability. This is seen for both, the test- and the reference product. It is unknown whether SD could also be influenced by the observed sequence effect in ln C_{max}:

Statistical analysis was performed with the samples of totally 60 subjects.

C_{max} was not observed in any subject in the first sample time point (=pre-dose), which is reassuring.

Safety data

According to the Applicant, safety was assessed from the screening period to the end of the study. It was assessed through clinical examination, vital signs assessment, 12-lead electrocardiogram (ECG), chest X-ray (posterior-anterior view) recording, clinical laboratory parameters [e.g. biochemistry (including serum calcium and serum phosphorus), haematology, immunology (including iPTH) and urine analysis], subjective symptomatology and monitoring of adverse events. Monitoring practices seem adequate.

Table 8

Test Product-T									
Adverse event (Preferred Term)	Mild		Moderate		Severe		Total		Total
	R	NR	R	NR	R	NR	R	NR	R+NR
Gastrointestinal disorders									
Vomiting	4 (5.97%)	1 (1.49%)	0	0	0	0	4 (5.97%)	1 (1.49%)	5
Subject Nos.	1032, 1042, 1050 and 1066	1070							
General disorders and administration site conditions									
Pyrexia	0	1 (1.49%)	0	0	0	0	0	1 (1.49%)	1
Subject No.		1034							
Investigations									
Blood creatinine increased	0	1 (1.49%)	0	0	0	0	0	1 (1.49%)	1
Subject No.		1068							
Reference Product-R									
Adverse event (Preferred Term)	Mild		Moderate		Severe		Total		Total
	R	NR	R	NR	R	NR	R	NR	R+NR
Gastrointestinal disorders									
Vomiting	2 (3.08%)	0	0	0	0	0	2 (3.08%)	0	2
Subject Nos.	1005 and 1029								

R=Related; NR=Not Related

Nine (9) adverse events (AEs) were reported by nine (9) subjects during the conduct of the study. The Applicant states that four (4) AEs were reported in Period-I, four (4) AEs were reported in Period-II and one (1) AE was reported during post-study safety assessment.

According to the Applicant, all the AEs were mild in nature and all the subjects were followed up until resolution of their AEs.

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

Out of the total reported nine (9) AEs, one (1) AE was significant. Subject (No. 1070) had a single episode of vomiting during a high fat high calorie vegetarian breakfast prior to dosing in Period-II and was thus withdrawn from the study on medical grounds. He was treated appropriately and followed up until resolution of his AE. The causality assessment was judged as unlikely related for this AE.

According to the Applicant, seven (7) AEs were reported after administration of test-product and two (2) AEs were reported after administration of reference-product, indicating a slight imbalance between the arms. Of the 7 AEs in the test-product group, 5 were 'vomiting' (4 of them possibly related), one was 'pyrexia' and one was 'blood creatinine increase' (both unrelated), whereas the 2 AEs in the reference-product group were 'vomiting' (both considered possibly related).

Due to the small sample sizes of the two compared groups and the overall small number of events, the impact of the factor 'product' on the frequency of AEs cannot be definitively assessed. Taking into account the causality assessment of the AEs and the similarity of the products in terms of qualitative and quantitative composition, a clinically relevant difference seems unlikely, however.

2.4.3. Pharmacokinetic Conclusion

The bioequivalence study appears to have been well conducted. Based on the presented bioequivalence study Cinacalcet Accordpharma is considered bioequivalent with Cinacalcet Mimpara. The results of the study can be extrapolated to other strengths, according to conditions in the Guidelines.

2.4.4. Pharmacodynamics

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

2.4.5. Post-marketing experience

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

The originator has been licensed in 2004 and several generic products are on the marked.

In general, adverse reactions observed in clinical practice are concordant with the safety profile of the drug in the clinical studies. In addition to nausea and vomiting, the following adverse reactions have been identified during post-marketing use of cinacalcet, the frequencies of which cannot be estimated from available data; There have been reports of isolated, idiosyncratic cases of hypotension and/or worsening heart failure in cinacalcet-treated patients with impaired cardiac function in postmarketing safety surveillance, cases of allergic reactions, including angioedema and urticaria as well as QT prolongation and ventricular arrhythmia secondary to hypocalcaemia.

2.4.6. Discussion on clinical aspects

To support this application, the Applicant submitted the data of one open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study (Study No. 0418-17) of two products of Cinacalcet Tablets 90 mg (Test product: Cinacalcet Accordpharma 90mg tablets and Reference product: Mimpara 90 mg film-coated tablets) in normal, healthy, adult, human subjects under fed conditions. 73 subjects were checked in for the study and the data of 60 subjects were analysed. The parameters for evaluation of bioequivalence are considered adequate. The results of this study, namely $AUC_{(0-t)}$ (point estimate: 100.2, CI: 95.52 - 105.15), $AUC_{(0-\infty)}$ (point estimate: 100.4, CI: 95.86 - 105.18) and C_{max} (point estimate: 98.6, CI: 92.55 - 105.15), well support the notion of bioequivalence between the test and the reference product.

Overall, the study seems to be well conducted and straight forward. The design of the single bioequivalence study is in line with the regulatory guidance and considered appropriate. The grounds to justify the biowaiver for the 30 mg and 60 mg seem to be in accordance with the Guideline.

2.4.7. Conclusions on clinical aspects

The bioequivalence study appears to have been well conducted and the results of the single bioequivalence study support bioequivalence between the reference product Mimpara and the test product Cinacalcet Accordpharma.

2.5. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Hypocalcaemia • QT prolongation and ventricular arrhythmias secondary to hypocalcaemia • Convulsions/ seizures
Important potential risks	• None
Missing information	• Pregnant or breastfeeding women

Pharmacovigilance plan

There are no planned or ongoing additional pharmacovigilance activities. Routine pharmacovigilance is considered sufficient to identify and characterise the safety specification of the product.

Risk minimisation measures

Important identified risks: hypoglycaemia

Risk minimisation measures	Routine risk minimisation measures: Sections 4.2, 4.3, 4.4, 4.5, 4.8, 4.9, 5.1 and 5.3 of Cinacalcet SmPC have information on this safety concern and corresponding sections of PIL has information on this safety concern. Other routine risk minimisation measure includes the prescription only status of the product. Additional risk minimisation measures: None

Important Identified Risks: QT prolongation and ventricular arrhythmias secondary to hypocalcaemia

Risk minimisation measures	Routine risk minimisation measures: Sections 4.4 and 4.8 of Cinacalcet SmPC have information on this safety concern and corresponding sections of PIL has information on this safety concern. Other routine risk minimisation measure includes the prescription only status of the product. Additional risk minimisation measures: None

Important Identified Risks: Convulsions/ seizures

Risk minimisation measures	Routine risk minimisation measures: Sections 4.4, 4.7 and 4.8 of Cinacalcet SmPC have information on this safety concern and corresponding sections of PIL has information on this safety concern. Other routine risk minimisation measure includes the prescription only status of the product. Additional risk minimisation measures: None

Missing Information: Pregnant or breastfeeding women

Risk minimisation measures	Routine risk minimisation measures: Sections 4.6 and 5.3 of Cinacalcet SmPC have information on this safety concern and corresponding sections of PIL has information on this safety concern.

Missing Information: Pregnant or breastfeeding women

	Other routine risk minimisation measure includes the prescription only status of the product. Additional risk minimisation measures: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

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.

Periodic Safety Update Reports submission requirements

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.

2.7. Product information

2.7.1. User consultation

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

3. Benefit-Risk Balance

The application contains adequate quality, non-clinical and clinical data and the bioequivalence has been shown. A benefit/risk ratio comparable to the reference product can therefore be concluded.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Cinacalcet Accordpharma is favourable in the following indication:

"Secondary hyperparathyroidism

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

Paediatric population
Treatment of secondary hyperparathyroidism (HPT) in children aged 3 years and older with end-stage
renal disease (ESRD) on maintenance dialysis therapy in whom secondary HPT is not adequately controlled with standard of care therapy (see section 4.4).

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

Parathyroid carcinoma and primary hyperparathyroidism in adults

Reduction of hypercalcaemia in adult patients with:
- parathyroid carcinoma.
- primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated."

The CHMP 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.

Other 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