Public Assessment Report

Decentralised Procedure

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

(Cinacalcet hydrochloride)

Procedure No: UK/H/6682/001-003/DC

UK Licence No: PL 33882/0059-0061

Glenmark Pharmaceuticals s.r.o.
LAY SUMMARY

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

(Cinacalcet hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Cinacalcet 30 mg, 60 mg and 90 mg film-coated tablets (PL 33882/0059-0061; UK/H/6682/001-003/DC). For ease of reading, Cinacalcet 30 mg, 60 mg and 90 mg film-coated tablets may be referred to as ‘Cinacalcet film-coated tablets’ in this lay summary. The lay summary explains how the applications for Cinacalcet film-coated tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Cinacalcet film-coated tablets.

For practical information about using Cinacalcet film-coated tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Cinacalcet film-coated tablets and what are they used for?
Cinacalcet film-coated tablets are ‘generic’ medicines. This means that Cinacalcet film-coated tablets are similar to ‘reference medicines’ called Mimpara 30 mg, 60 mg and 90 mg film-coated tablets (Amgen Europe B.V., The Netherlands), which were first authorised in the European Union (EU) on 22 October 2004. Mimpara 30 mg, 60 mg, and 90 mg film-coated tablets may be referred to as ‘Mimpara film-coated tablets’ in this lay summary.

Cinacalcet film-coated tablets are used in adults to:

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

Cinacalcet film-coated tablets are used in children aged 3 years to less than 18 years of age:

- to treat secondary hyperparathyroidism in patients with serious kidney disease who need dialysis to clear their blood of waste products, whose condition is not controlled with other treatments.

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

How do Cinacalcet film-coated tablets work?
The active substance, cinacalcet (as cinacalcet hydrochloride), works by controlling the levels of PTH, calcium and phosphorous in the body. It is used to treat problems with organs called parathyroid glands. The parathyroids are four small glands in the neck, near the thyroid gland, that produce PTH.
How are Cinacalcet film-coated tablets used?
These medicines should always be taken exactly as advised by the patient’s doctor or pharmacist. The patient should check with the doctor or pharmacist if not sure. The patient’s doctor will advise him/her as to how much medicine to take.

Cinacalcet film-coated tablets must be taken orally, with or shortly after food. The tablets must be taken whole and should not be chewed, crushed or divided.

Please read section 3 of the package leaflet (PL) for detailed information on dosing recommendations, the route of administration and the duration of treatment.

Cinacalcet film-coated tablets can only be obtained with a prescription.

What benefits of Cinacalcet film-coated tablets have been shown in studies?
As Cinacalcet film-coated tablets are generic medicines, studies in patients have been limited to tests to determine that Cinacalcet film-coated tablets are bioequivalent to their respective reference medicines, Mimpara film-coated tablets (Amgen Europe B.V., The Netherlands). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Cinacalcet film-coated tablets?
Because Cinacalcet film-coated tablets are generic medicines and are bioequivalent to the reference medicines Mimpara film-coated tablets (Amgen Europe B.V., The Netherlands), the possible side effects are taken as being the same as those of the reference medicines.

For the full list of all side effects reported with Cinacalcet film-coated tablets, see Section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Cinacalcet film-coated tablets approved?
It was concluded that, in accordance with EU requirements, Cinacalcet film-coated tablets have been shown to have comparable quality and to be bioequivalent to Mimpara film-coated tablets (Amgen Europe B.V., The Netherlands). Therefore, the view was that, as for Mimpara film-coated tablets (Amgen Europe B.V., The Netherlands), the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Cinacalcet film-coated tablets?
A Risk Management Plan has been developed to ensure that Cinacalcet film-coated tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflet for Cinacalcet film-coated tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Cinacalcet film-coated tablets
Germany, Denmark, Spain, the Netherlands, Sweden and the UK agreed to grant Marketing Authorisations for Cinacalcet film-coated tablets on 12 April 2018.

Marketing Authorisations were granted in the UK to Glenmark Pharmaceuticals s.r.o. on 09 May 2018.
The full PAR for Cinacalcet film-coated tablets follows this summary.

For more information about treatment with Cinacalcet film-coated tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in July 2018.
SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Cinacalcet 30 mg, 60 mg and 90 mg film-coated tablets (PL 33882/0059-0061; UK/H/6682/001-003/DC) could be approved. These are Prescription Only Medicines (POM). For ease of reading, the products may be collectively referred to as ‘Cinacalcet film-coated tablets’ in this scientific discussion.

Cinacalcet 30 mg, 60 mg and 90 mg film-coated tablets are indicated in the following:

- **Secondary hyperparathyroidism**
  
  **Adults**
  Treatment of secondary hyperparathyroidism (HPT) in 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. Cinacalcet may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate

- **Parathyroid carcinoma and primary hyperparathyroidism in adults**
  Reduction of hypercalcemia 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.

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Germany, Denmark, Spain, the Netherlands and Sweden as Concerned Member States.

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of originator medicinal products Mímpara 30 mg, 60 mg, and 90 mg film-coated tablets (Amgen Europe B.V., The Netherlands), which were first authorised in the European Union via the Centralised procedure (EMEA/H/C/000570) on 22 October 2004.

The active substance, cinacalcet (as cinacalcet hydrochloride), is a type II calcimimetic, an allosteric activator of calcium-sensing receptor. These type II calcimimetics interact with the membrane-spanning segments of the calcium-sensing receptor and enhance signal transduction, reducing the threshold for calcium-sensor receptor activation, thereby reducing PTH secretion in the absence of a change in concentration of extracellular calcium. Activation of the calcium-sensing receptor not only reduces hormone secretion but also decreases parathyroid cell proliferation.

No new non-clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

A bioequivalence study was submitted to support these applications comparing the applicant’s test product Cinacalcet 90 mg tablets (Genepharm S.A Greece) with the reference product Mímpara 90 mg film-coated tablets (Amgen Europe B.V., The Netherlands) under fed conditions. The applicant has stated that the bioequivalence study was conducted in compliance with the ethical requirements of Directive 2001/83/EC. International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirements and the Declaration of Helsinki.
With the exception of the bioequivalence study, no new clinical data were submitted, which is acceptable given that these applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

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

The Member States considered that the applications could be approved at the end of procedure (Day 206) on 12 April 2018. After a subsequent national phase, licences were granted in the UK to Glenmark Pharmaceuticals s.r.o. on 09 May 2018.

II QUALITY ASPECTS

II.1 INTRODUCTION

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The 30 mg strength tablet is green, oblong, biconvex, film-coated, engraved with ‘30’ on one side and plain on the other side, with a length of 9.8 mm (± 0.2 mm) and a width of 6.2 mm (± 0.2 mm).

The 60 mg strength tablet is green, oblong, biconvex, film-coated, engraved with ‘60’ on one side and plain on the other side with a length of 12.4 mm (± 0.2 mm) and a width of 7.8 (± 0.2 mm).

The 90 mg strength tablet is green, oblong, biconvex, film-coated, engraved with ‘90’ on one side and plain on the other side, with a length of 14.2 mm (± 0.2 mm) and a width of 8.9 mm (± 0.2 mm).

The products also contain pharmaceutical excipients in the tablet cores, namely pregelatinised maize starch, microcrystalline cellulose, croscarmellose sodium, anhydrous colloidal silica (E551) and magnesium stearate (E470b). In addition, the tablet coatings contain hypromellose (E464), lactose monohydrate, titanium dioxide (E171), triacetin, indigo carmine aluminium lake (E132) and iron oxide yellow (E172). Appropriate justification for the inclusion of each excipient has been provided.

The products are packaged in transparent polyvinylchloride/polyvinylidene chloride/aluminium blisters or polyvinylchloride/polychlorotrifluoroethylene (Aclar)/aluminium blisters, in pack sizes of 14, 28 and 84 film-coated tablets.

Not all pack sizes may be marketed.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2  DRUG SUBSTANCE

Cinacalcet hydrochloride

INN: Cinacalcet hydrochloride

Chemical name: (N-[1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride)

Molecular formula: C_{22}H_{22}F_{3}N.HCl

Structure:

\[
\begin{align*}
\text{M}_r & : \quad 393.91 \\
\text{Appearance} & : \quad \text{A white to off white crystalline powder} \\
\text{Solubility} & : \quad \text{Freely soluble in dichloromethane and practically insoluble in diisopropyl ether at temperature 25°C± 2} \\
\text{Stereoisomerism} & : \quad \text{Cinacalcet hydrochloride has a one chiral centre. Hence it shows optical isomerism; there are two isomers possible.} \\
\text{Polymorphism} & : \quad \text{Cinacalcet exhibits polymorphism.}
\end{align*}
\]

Cinacalcet hydrochloride is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.
II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable film-coated tablets, which were bioequivalent to Mimpara 30 mg, 60 mg, and 90 mg film-coated tablets (Amgen Europe B.V.). Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution profiles have been provided for the proposed and reference products. The in-vitro dissolution profiles were satisfactory.

With the exception of yellow iron oxide (E172) and indigo carmine aluminium lake (E132), all excipients comply with their respective European Pharmacopoeia monographs. Yellow iron oxide (E172) and indigo carmine aluminium lake (E132) are in compliance with the current EU Directive concerning the use of colouring agents.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Based on full-scale production and pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder (MAH) has committed to performing process validation studies on first full-scale production batches.

Control of Finished Product
The finished product specifications are acceptable. Test methods have been described and have been validated adequately. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 5 years has been accepted. These medicinal products do not require any special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted, from a quality point of view.
III. NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of cinacalcet are well-known, no new non-clinical data are required and none have been provided.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new data have been submitted and none are required for applications of this type. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for applications of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for applications of this type. Refer to Section III.1, Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). Since Cinacalcet film-coated tablets are intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion of the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of an originator product that has been licensed for over 10 years.

It is recommended that Marketing Authorisations are granted, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, safety and efficacy of cinacalcet are well-known.

The clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacokinetics, pharmacodynamics, efficacy and safety.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted a bioequivalence study under fed conditions to support the applications. With the exception of data from the bioequivalence study detailed in Section IV.2, Pharmacokinetics below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for applications of this type.

IV.2 Pharmacokinetics
In support of the applications, the applicant submitted the following bioequivalence study:
Study 1

An open-label, randomised, two-treatment, two-period, two-sequence two-way single dose, crossover bioequivalence study comparing the pharmacokinetics of the applicant’s test product Cinacalcet 90 mg film-coated tablets (Genepharm S.A Greece) versus the reference product Mimpara 90 mg film-coated tablets (Amgen Europe B.V., The Netherlands) in healthy adult subjects, under fed conditions.

The subjects were administered a single dose (1 x 90 mg tablet) of either treatment with 240 ml of water after a high fat, high calorie breakfast, after at least a 10 hour overnight fast. Breakfast was started by each subject exactly 30 min prior to drug administration. Blood samples were collected before, up to and including 72 hours after each administration. The washout period between the treatment phases was 17 days. The geometric means and 90% confidence intervals based on least squares means. The geometric means and 90% confidence intervals based on least squares means obtained for the In-transferred pharmacokinetic parameters $C_{\text{max}}$ and $AUC_{0-t}$ for R-Cinacalcet are summarized in the following table:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>*Geometric mean</th>
<th>% Ratio</th>
<th>90% Confidence Interval for ln-transformed data</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-t}$</td>
<td>320.265</td>
<td>100.371</td>
<td>92.7513 to 114.6182</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>31.611</td>
<td>100.00</td>
<td>85.4120 to 114.6182</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$ = Maximum plasma concentration

$AUC_{0-t}$ = Area under the plasma concentration curve from administration to last observed concentration at time t.

Ratios and 90% CI calculated from ln-transformed data

Conclusion

The 90% confidence intervals of the test/reference ratio for $AUC_{0-t}$, and $C_{\text{max}}$ lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr***)’. Thus, these data support the claim that the applicant’s 90 mg strength test product is bioequivalent to the reference product Mimpara 90 mg film-coated tablets (Amgen Europe B.V., The Netherlands) under fed conditions.

The results with the applicant’s 90 mg strength product can be extrapolated to the 30 mg and 60 mg strength products, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacodynamics

The clinical pharmacodynamic profile of a cinacalcet is well-known. No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical Efficacy

The clinical efficacy of cinacalcet is well-known. No new efficacy data are presented for these applications and none are required. Efficacy is adequately reviewed in the clinical overview.

IV.5 Clinical Safety

No new safety data are presented for these applications and none are required. The safety profile of cinacalcet is well-known and has been adequately summarised by the Applicant in the clinical overview. No new or unexpected safety concerns arose from these applications.
IV.6 Risk Management Plan
The MAH has submitted a Risk Management Plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cinacalcet film-coated tablets.

A summary of safety concerns in listed in the table below:

<table>
<thead>
<tr>
<th>Table 2: Summary of Safety Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
</tr>
<tr>
<td>1. Hypocalcaemia</td>
</tr>
<tr>
<td>2. Seizures</td>
</tr>
<tr>
<td>3. Hypotension and/or worsening heart failure</td>
</tr>
<tr>
<td>4. Hypersensitivity reactions including urticana and angioedema</td>
</tr>
<tr>
<td>5. QT prolongation and ventricular arrhythmias secondary to hypocalcaemia</td>
</tr>
<tr>
<td><strong>Important potential risks</strong></td>
</tr>
<tr>
<td>1. Use in patients with moderate and severe hepatic impairment</td>
</tr>
<tr>
<td><strong>Missing information</strong></td>
</tr>
<tr>
<td>1. Use in pregnancy and lactation</td>
</tr>
<tr>
<td>2. Use in paediatric population (age &lt; 18 years)</td>
</tr>
</tbody>
</table>

Routine pharmacovigilance and risk minimisation activities are proposed for all safety concerns.

IV.7 Conclusion
It is recommended that Marketing Authorisations are granted, from a clinical point of view.

V. USER CONSULTATION
A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence between the test and reference product has been demonstrated in accordance with the current CHMP guidelines. Extensive clinical experience with cinacalcet is considered to have demonstrated the therapeutic value of the compound.

The benefit/risk balance is therefore considered to be positive.

The grant of Marketing Authorisations is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPCs and PIL are available on the MHRA website.

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

Cinacalcet 60 mg film-coated tablets

Cinacalcet 90 mg film-coated tablets

Each film-coated tablet contains 90 mg of cinacalcet hydrochloride equivalent to 90 mg cinacalcet.

For oral use.

Read the package leaflet before use.

Keep out of the sight and reach of children.

For further information, please see the package leaflet.
Annex 1

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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</thead>
</table>