EU/UK Risk Management Plan

for

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

Cinacalcet Accord 30 mg film-coated tablets
Cinacalcet Accord 60 mg film-coated tablets
Cinacalcet Accord 90 mg film-coated tablets
(Cinacalcet)

RMP version to be assessed as part of this application:

RMP Version number	2.0
Data lock point for this RMP	20-Oct-2023
Date of final sign off	12-Dec-2023

Rationale for submitting an updated RMP: This RMP has been updated as common RMP for two procedures (EMEA/H/C/0005236 and FI/H/0869/001-003/DC) and safety concerns have been updated to be in line with EPAR - Risk-management-plan summary of Mimpara (Cinacalcet) and in line with updated SmPC.

Summary of significant changes in this RMP: Significant changes have been done in following sections of RMP: Part I, Part II (Module SVII and Module SVIII), Part VI and Part VII (Annex 7 and Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

RMP Version	Procedure	Approval Date
2	FI/H/0869/001-003/R/001	20-Jan-2021
1.2	EMEA/H/C/005236/0000	30-Jan-2020

QPPV name: Ms. Agata Gesiewicz

[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Cinacalcet (as hydrochloride)
Pharmacotherapeutic group(s)(ATC Code)	Calcium homeostasis, anti-parathyroid agents **ATC code:** H05BX01
Marketing Authorisation Holder	Accord Healthcare S.L.U., Spain Accord Healthcare B. V., Netherlands
Medicinal products to which this RMP refers	6
Invented name(s) in the European Economic Area (EEA) and United Kingdom (UK)	Cinacalcet Accordpharma 30 mg film-coated tablets Cinacalcet Accordpharma 60 mg film-coated tablets Cinacalcet Accordpharma 90 mg film-coated tablets Cinacalcet Accord 30 mg film-coated tablets Cinacalcet Accord 60 mg film-coated tablets Cinacalcet Accord 90 mg film-coated tablets
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/0005236) Decentralised Procedure (FI/H/0869/001-003/DC and FI/H/0869/001-003/E/001)
Brief description of the product	**Chemical class:** Cinacalcet is a naphthalene derivative and calcimimetic agent that increases the sensitivity of parathyroid gland calcium-sensing receptors to serum calcium.
	Summary of mode of action: The calcium sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of parathyroid hormone (PTH) secretion. Cinacalcet is a calcimimetic agent which directly

	lowers PTH levels by increasing the sensitivity of the calcium sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels. Reductions in PTH levels correlate with cinacalcet concentration.
	Important information about its composition *Centralised Procedure (EMEA/H/C/0005236)* Each tablet contains 30 mg, 60 mg or 90 mg cinacalcet (as hydrochloride). *Decentralised Procedure (FI/H/0869/001-003/)* Each film-coated tablet contains 30 mg cinacalcet (as hydrochloride). Excipient with known effect: Each film coated tablet contains 67.2mg of lactose monohydrate. Each film-coated tablet contains 60 mg cinacalcet (as hydrochloride). Excipient with known effect: Each film coated tablet contains 134.3 mg of lactose monohydrate Each film-coated tablet contains 90 mg cinacalcet (as hydrochloride). Excipient with known effect: Each film coated tablet contains 202.0 mg of lactose monohydrate
Hyperlink to the Product Information	Refer Module 1.3.1 for Product Information.
Indication(s) in the EEA/UK	***Current*** 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. Cinacalcet may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate. <u>Parathyroid carcinoma and primary hyperparathyroidism in adults</u> 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.
Dosage in the EEA/UK	***Current:*** **Recommended Dosage:** <u>Secondary hyperparathyroidism</u> *Adults and elderly (> 65 years):* The recommended starting dose for adults is 30 mg once per day. Cinacalcet should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target parathyroid hormone (PTH) in dialysis patients of between 150-300 pg/mL (15.9-31.8 pmol/L) in the intact PTH (iPTH) assay. PTH levels should be assessed at

[redacted]

least 12 hours after dosing with Cinacalcet. Reference should be made to current treatment guidelines.

PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Cinacalcet. PTH should be monitored approximately every 1-3 months during maintenance. Either the intact PTH (iPTH) or bio-intact PTH (biPTH) may be used to measure PTH levels; treatment with Cinacalcet does not alter the relationship between iPTH and biPTH.

Paediatric population:

Corrected serum calcium should be in the upper range of, or above, the age-specified reference interval prior to administration of first dose of Cinacalcet, and closely monitored. The normal calcium range differs depending on the methods used by your local laboratory and the age of the child/patient.

The recommended starting dose for children aged ≥ 3 years to < 18 years is ≤ 0.20 mg/kg once daily based on the patient's dry weight.

The dose can be increased to achieve a desired target iPTH range. The dose should be increased sequentially through available dose levels no more frequently than every 4 weeks. The dose can be increased up to a maximum dose of 2.5 mg/kg/day, not to exceed a total daily dose of 180 mg.

Cinacalcet daily dose in paediatric patients:

Patient dry weight (kg)	**Starting dose (mg)**	**Available sequential dose levels (mg)**
10 to < 12.5	1	1, 2.5, 5, 7.5, 10 and 15
≥ 12.5 to < 25	2.5	2.5, 5, 7.5, 10, 15, and 30
≥ 25 to < 36	5	5, 10, 15, 30, and 60
≥ 36 to < 50		5, 10, 15, 30, 60, and 90

[redacted]

≥ 50 to < 75	10	10, 15, 30, 60, 90, and 120
≥ 75	15	15, 30, 60, 90, 120, and 180

Cinacalcet 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.

Parathyroid carcinoma and primary hyperparathyroidism

Adults and elderly (> 65 years):

The recommended starting dose of Cinacalcet for adults is 30 mg twice per day. The dose of Cinacalcet should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to reduce serum calcium concentration to or below the upper limit of normal. The maximum dose used in clinical trials was 90 mg four times daily.

Serum calcium should be measured within 1 week after initiation or dose adjustment of Cinacalcet. Once maintenance dose levels have been established, serum calcium should be measured every 2 to 3 months. After titration to the maximum dose of Cinacalcet, serum calcium should be periodically monitored; if clinically relevant reductions in serum calcium are not maintained, discontinuation of Cinacalcet therapy should be considered.

Paediatric population

The safety and efficacy of Cinacalcet in children for the treatment of parathyroid carcinoma and primary hyperparathyroidism have not been established. No data are available.

[redacted]

	Method of administration: For oral use.
Pharmaceutical form(s) and strengths	***Current:*** Film-coated tablet 30 mg, 60 mg or 90 mg
Is the product subject to additional monitoring in the EU/UK?	No

Part II: Safety specification

Module SI – Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII – Non-clinical part of the safety specification

Not applicable

Module SIII – Clinical trial exposure

Not applicable

Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Not applicable

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Not applicable

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Not applicable

Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable

Module SVII – Identified and potential risks

The safety concerns of this RMP have been updated as per European Public Assessment Report (EPAR) Risk Management Plan (RMP) of Mimpara (Cinacalcet) published by EMA.

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable

SVII.3.2. Presentation of the missing information

Not applicable

Module SVIII – Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Hypocalcemia in the pediatric population
Important potential risks	• None
Missing information	• Pregnant or breastfeeding women

[redacted]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concerns mentioned in "Module SVIII - Summary of the safety concerns".

III.2 Additional pharmacovigilance activities

None proposed, this is endorsed by agency as per rapporteur day 150 joint response assessment report of Cinacalcet (EMEA/H/C/005236), dated 23-Sep-2019.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

None proposed

V.3 Summary of risk minimisation measures

Not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets (Cinacalcet hydrochloride)

This is a summary of the risk management plan (RMP) for Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets. The RMP details important risks of Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets' risks and uncertainties (missing information).

Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets should be used.

This summary of the RMP for Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets' RMP.

I. The medicine and what it is used for

Cinacalcet Accordpharma is authorised for:

Secondary hyperparathyroidism

Adults

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

Paediatric population

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

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 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.

It contains cinacalcet hydrochloride as the active substance and it is given by oral route.

Further information about the evaluation of Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets' benefits can be found in Cinacalcet's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/documents/rmp-summary/cinacalcet-accordpharma-epar-risk-management-plan-summary_en.pdf

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets together with measures to minimise such risks and the proposed studies for learning more about Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Important identified risks	• Hypocalcemia in the pediatric population
Important potential risks	• None
Missing information	• Pregnant or breastfeeding women

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

[redacted]

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Cinacalcet Accordpharma 30 mg, 60 mg and 90 mg film-coated tablets.

Part VI: Summary of the risk management plan

Summary of risk management plan for Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets (Cinacalcet hydrochloride)

This is a summary of the risk management plan (RMP) for Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets. The RMP details important risks of Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets' risks and uncertainties (missing information).

Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets should be used.

Important new concerns or changes to the current ones will be included in updates of Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets' RMP.

I. The medicine and what it is used for

Cinacalcet Accord is authorised for:

Secondary hyperparathyroidism

Adults

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

Paediatric population

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

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 hypercalcaemia in adult patients with:

- Parathyroid carcinoma

[redacted]

- 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.

It contains cinacalcet hydrochloride as the active substance and it is given by oral route.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets together with measures to minimise such risks and the proposed studies for learning more about Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential.

[redacted]

Identified risks are concerns for which there is sufficient proof of a link with the use of Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Important identified risks	• Hypocalcemia in the pediatric population
Important potential risks	• None
Missing information	• Pregnant or breastfeeding women

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Cinacalcet Accord 30 mg, 60 mg and 90 mg film-coated tablets.