PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Mimpara® (cinacalcet)

This is a summary of the risk management plan (RMP) for Mimpara. The RMP details important risks of Mimpara, how these risks can be minimized, and how more information will be obtained about Mimpara's risks and uncertainties (missing information).

Mimpara's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Mimpara should be used.

This summary of the RMP for Mimpara should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Mimpara's RMP.

I. The medicine and what it is used for

Mimpara is authorized to:

- treat secondary hyperparathyroidism in adults with serious kidney disease who need dialysis to clear their blood of waste products
- treat secondary hyperparathyroidism in children with serious kidney disease who need dialysis to clear their blood of waste products whose disease is not well-controlled by other therapies
- reduce high levels of calcium in the blood (hypercalcemia) in patients with parathyroid cancer
- reduce high levels of calcium in the blood (hypercalcemia) in patients with primary hyperparathyroidism who still have high calcium levels after removal of the parathyroid gland or when removal of the gland is not possible

It contains cinacalcet as the active substance and it is given by orally in tablet or capsule form.

Further information about the evaluation of Mimpara's benefits can be found in Mimpara's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/Mimpara

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Mimpara together with measures to minimize such risks and the proposed studies for learning more about Mimpara's risks, are outlined below.

Measures to minimize 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 authorized 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 public (eg, with or without prescription) can help to minimize its risks.

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

In addition to these measures, information about adverse events is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment 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 Mimpara is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Mimpara are risks that need special risk management activities to further investigate or minimize 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 Mimpara. 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 (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important Identified Risk	Hypocalcemia Convulsion/seizures QT prolongation and ventricular arrhythmias secondary to hypocalcemia
Important Potential Risk	Medication errors with granules in capsules for pediatric use
Missing Information	Pregnant or breastfeeding women

II.B. Summary of Important Risks

Important identified risk: Hypocalcemia	
Evidence for linking the risk to the medicine	Hypocalcemia is the main risk of cinacalcet and is related to the pharmacologic action of cinacalcet in lowering serum calcium. This risk was identified in the nonclinical and clinical study setting; both asymptomatic and symptomatic events of low calcium (hypocalcemia) were reported more frequently in cinacalcet-treated subjects compared with placebo-treated subjects in the phase 3 placebo-controlled studies. Additionally, other products in the same pharmacological class have shown an increased incidence of hypocalcemia.
Risk factors and risk groups	Reductions in serum calcium to the low-normal or overt hypocalcemic range are consistent with the pathophysiology of SHPT and consequently are not uncommon in patients with SHPT and CKD receiving dialysis. To date, no additional risk factors or risk groups for the development of hypocalcemia have been identified in dialysis patients.
Risk minimization measures	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.3, Contraindications • Section 4.4, Special warnings and precautions • Section 4.5, Interaction with other medicinal products and other forms of interaction • Section 4.8, Undesirable effects • Section 4.9, Overdose • Section 5.1, Pharmacodynamic properties • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the PIL: • What you need to know before you take Mimpara • Possible side effects
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Registry study 20180204: Cinacalcet use among pediatric patients with secondary hyperparathyroidism receiving maintenance dialysis and the incidence, risk factors, and management of hypocalcemia – International Pediatric Dialysis Network registry (IPDN). See Section II.C of this summary for an overview of the postauthorization development plan.

Ca = calcium; CKD = chronic kidney disease; IPDN = International Pediatric Dialysis Network; P = phosphorus; PTH = parathyroid hormone; SHPT = secondary hyperparathyroidism

Important identified risk: Convulsions/seizures	
Evidence for linking the risk to the medicine	Data to evaluate the risk for convulsions with cinacalcet derive from clinical studies, postmarketing adverse event reporting, pharmacoepidemiological assessment of background prevalence rates, and postauthorization usage in the targeted patient populations. The threshold for convulsions/seizures is lowered by significant reductions in serum calcium levels. Since the pharmacologic action of cinacalcet reduces PTH with concomitant lowering of serum calcium concentrations, this could possibly increase the risk of convulsions/seizures.
Risk factors and risk groups	Convulsions in adult SHPT Patients with CKD undergoing dialysis are at increased risk for convulsions (Burn and Bates, 1998; Bergen et al, 1994; Schwartz, 1993; Glenn et al, 1992). These conditions are thought to result from accumulating metabolites, blood pressure alterations, and electrolyte abnormalities (including hypocalcemia). In cinacalcet clinical trials, more convulsions were observed in patients receiving cinacalcet compared with placebo, and were most often reported in patients with an underlying history of seizure disorder. Convulsions in primary HPT Published literature regarding the risk of seizures in the primary HPT population is very limited. Convulsions associated with hypocalcemia are generally not likely to be a concern in patients with primary HPT, which characteristically is associated with hypercalcemia. However, situations that may lead to hypocalcemia, such as vitamin D deficiency and/or therapy-induced hypoparathyroidism, could lead to hypocalcemic convulsions in these patients. One literature report has associated convulsions in a first trimester primigravid patient with primary HPT and hypercalcemia (Cherry et al, 2002).
Risk minimization measures	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • What you need to know before you take Mimpara • Possible side effects • How to take Mimpara

HPT = hyperparathyroidism; PTH = parathyroid hormone; PIL = patient information leaflet;
SmPC = summary of product characteristics

Important identified risk: QT prolongation and ventricular arrhythmias secondary to hypocalcemia	
Evidence for linking the risk to the medicine	Data to evaluate the risk for QT prolongation and ventricular arrhythmias with cinacalcet derive from clinical studies, postmarketing adverse event reporting, pharmacoepidemiological assessment of background prevalence rates, and postauthorization usage in the targeted patient populations. The combination of QT prolongation and ventricular arrhythmias was identified as an important identified risk based on the pharmacologic action of cinacalcet in lowering serum calcium.
Risk factors and risk groups	There is a potential for drug-drug interaction between cinacalcet and metoprolol, as cinacalcet is an inhibitor of CYP2D6, and substrates of CYP2D6. Information on the effect of cinacalcet on other medications has been provided in the SmPC, this includes metoprolol. Additional risk factors include reduced calcium, magnesium or potassium blood levels; family history of QT prolongation; known history of QT prolongation.
Risk minimization measures	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions • Section 4.8, Undesirable effects Relevant text is provided in the following sections of the PIL: • What you need to know before you take Mimpara • Possible side effects

PIL = patient information leaflet; SmPC = summary of product characteristics

Important potential risk: Medication errors with cinacalcet granules in capsules for pediatric use	
Evidence for linking the risk to the medicine	Data to evaluate the risk for medication error with cinacalcet granules in capsules for pediatric use will be derived from clinical studies, postmarketing adverse event reporting, pharmacoepidemiological assessment of background prevalence rates, and postauthorization usage in the targeted patient populations. This potential risk has been identified in the pre-approval setting.
Risk factors and risk groups	Pediatric patients who require doses lower than 30 mg, or who are unable to swallow tablets.
Risk minimization measures	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.9, Overdose Relevant text is provided in the following sections of the PIL: • How to take Mimpara

PIL = patient information leaflet; SmPC = summary of product characteristics

Missing information: Pregnant or breastfeeding women	
Risk minimization measures	Relevant text is provided in the following sections of the SmPC: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data Relevant text is provided in the following sections of the PIL: • What you need to know before you take Mimpara

PIL = patient information leaflet; SmPC = summary of product characteristics

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of cinacalcet.

II.C.2. Other Studies in Postauthorization Development Plan

Study Short Name	Purpose of the Study
Registry to Describe Cinacalcet Use and Risk of Hypocalcemia in Pediatric Patients Receiving Dialysis	To evaluate the risk of hypocalcemia (eg, clinical characteristics, laboratory variables [PTH, Ca, and P], hospitalization due to hypocalcemia, co-medication, cinacalcet doses) in pediatric patients treated with cinacalcet

Ca = calcium; P = phosphorus; PTH = parathyroid hormone