EUROPEAN UNION RISK MANAGEMENT PLAN

Cinacalcet HCl

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	10.0
Date:	11 December 2020
Supersedes:	Version 9.1, dated 28 March 2019

Risk Management Plan (RMP) version to be assessed as part of this application

RMP version number:	10.0
Data lock point of this RMP:	28 February 2020
Date of final sign-off.	11 December 2020
Rationale for submitting an updated RMP:	• The following important identified risks have been removed: - Hypocalcemia in the adult population - Convulsions/seizures - QT prolongation and ventricular arrhythmias secondary to hypocalcemia • The important identified risk of hypocalcemia was retained for the pediatric population. This will now be described as the safety concern: - Hypocalcemia in the pediatric population. • Include the most recent post-marketing exposure data

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part II: Safety Specification		
SV: Postauthorization Experience	Updated postauthorization experience with the data lock-point 28 February 2020	Version 10.0; 11 December 2020
SVI: Additional EU Requirements for the Safety Specification		
SVII: Identified and Potential Risks	The following important identified risks have been removed: • Hypocalcemia in the adult population • Convulsions/ seizures • QT prolongation and ventricular arrhythmias secondary to hypocalcemia The important identified risk of hypocalcemia was retained for the pediatric population. This will now be described as the safety concern: • Hypocalcemia in the pediatric population	Version 10.0; 11 December 2020
SVIII: Summary of the Safety Concerns	Updated to reflect removal/modification of safety concerns as described above.	Version 10.0; 11 December 2020
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	Updated to reflect removal/modification of safety concerns as described above.	Version 10.0; 11 December 2020
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Updated to reflect removal/modification of safety concerns as described above.	Version 10.0; 11 December 2020
Part VI: Summary of the Risk Management Plan	Updated to reflect removal/modification of safety concerns as described above.	Version 10.0; 11 December 2020

Summary of significant changes in this RMP (continued)

Part/Module/Annex	Major Change(s)	Version Number and Date
Part VII: Annexes		
Annex 7: Other Supporting Data (Including Referenced Material)	Updated to include applicable references	Version 10.0; 11 December 2020
Annex 8: Summary of Changes to the Risk Management Plan Over Time	Updated to include v 10.0 updates	Version 10.0; 11 December 2020

Other RMP versions under evaluation:	
RMP version number:	None
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	9.1
Approved with procedure:	EMEA/H/C/00570/0062/G
Date of approval (opinion date):	16 May 2019
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm, and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder´s (MAH) QPPV. The electronic signature is available on file.

Table of Contents

PART I. PRODUCT(S) OVERVIEW 13

PART II. SAFETY SPECIFICATION 17

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s) 17

Part II: Module SII - Nonclinical Part of the Safety Specification 24

Part II: Module SIII - Clinical Trial Exposure 27

Part II: Module SIV - Populations Not Studied in Clinical Trials 35

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program 35

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs 40

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs 40

Part II: Module SV - Postauthorization Experience 43

SV.1 Postauthorization Exposure 43

SV.1.1 Method Used to Calculate Exposure 43

SV.1.2 Exposure 44

Part II: Module SVI - Additional EU Requirements for the Safety Specification 47

SVI.1 Potential for Misuse for Illegal Purposes 47

Part II: Module SVII - Identified and Potential Risks 48

SVII.1 Identification of Safety Concerns in the Initial RMP Submission 48

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP 48

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP 48

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP 48

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information 52

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks 52

SVII.3.2 Presentation of the Missing Information 56

Part II: Module SVIII - Summary of the Safety Concerns 57

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES) 58

III.1 Routine Pharmacovigilance Activities 58

III.2 Additional Pharmacovigilance Activities 58

III.3 Summary Table of Additional Pharmacovigilance Activities 60

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES 62

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES) 63

V.1 Routine Risk Minimization Measures 63

V.2 Additional Risk Minimization Measures 63

V.3 Summary of Risk Minimization Measures 63

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN 65

II.A. List of Important Risks and Missing Information 66

II.B. Summary of Important Risks 67

II.C. Postauthorization Development Plan 68

II.C.1. Studies Which Are Conditions of the Marketing Authorization 68

II.C.2. Other Studies in Postauthorization Development Plan 68

PART VII: ANNEXES 69

References 77

List of Tables

Table 1. Product(s) Overview 13

Table 2. Summary of Epidemiology of Secondary Hyperparathyroidism in Adult and Elderly Patients With Chronic Kidney Disease 17

Table 3. Summary of Epidemiology of Secondary Hyperparathyroidism in Pediatric Patients With End-stage Renal Disease on Maintenance Dialysis Therapy 19

Table 4. Summary of Epidemiology of Hypercalcemia in Patients With Parathyroid Carcinoma 20

Table 5. Summary of Epidemiology of Primary Hyperparathyroidism 22

Table 6. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage 24

Table 7. Example: Total Subject Exposure to Cinacalcet in Clinical Trials by Indication and Duration Safety Analysis Set 28

Table 8. Total Subject Exposure to Cinacalcet in Clinical Trials by Age Group and Gender Safety Analysis Set 30

Table 9. Total Subject Exposure to Cinacalcet in Clinical Trials by Product and Race/Ethnic Group Safety Analysis Set 34

Table 10. Important Exclusion Criteria in Pivotal Studies Across the Development Program 35

Table 11. Exposure of Special Populations Typically Under-represented in Clinical Trial Development Programs 41

Table 12. Estimated Number of Person-years of Exposure to Cinacalcet, by Region and Demographic Characteristics, in the Postmarketing Setting (Cumulative to 28 February 2020) 44

Table 13. Estimated Number of Patients Exposed to Cinacalcet, by Region and Demographic Characteristics, in the Postmarketing Setting. (Cumulative to 28 February 2020) 45

Table 14. New or Reclassification of Safety Concerns in the RMP 49

Table 15. Important Identified Risk: Hypocalcemia in the Pediatric Population 52

Table 16. Important Potential Risk: Medication Errors With Cinacalcet Granules in Capsules for Pediatric Use 55

Table 17. Missing Information: Pregnant or Breastfeeding Women 56

Table 18. Summary of Safety Concerns 57

Table 19. Specific Adverse Reaction Follow-up Questionnaires 58

Table 20. Category 1 to 3 Postauthorization Safety Studies 59

Table 21. Ongoing and Planned Additional Pharmacovigilance Activities 61

Table 22. Description of Routine Risk Minimization Measures by Safety Concern 63

Table 23. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern....64

Table 24. Annex 2: Planned and Ongoing Studies From the Pharmacovigilance Plan....71

Table 25. Summary of Changes to the Risk Management Plan Over Time....82

List of Annexes

Annex 1. EudraVigilance Interface....70
Annex 2. Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program....71
Annex 3. Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan....72
Annex 4. Specific Adverse Drug Reaction Follow-up Forms....73
Annex 5. Protocols for Proposed and Ongoing Studies in RMP Part IV....74
Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)....75
Annex 7. Other Supporting Data (Including Referenced Material)....76
Annex 8. Summary of Changes to the Risk Management Plan Over Time....82

List of Abbreviations

Term/Abbreviation	Explanation
ATC	Anatomical Therapeutic Chemical Classification System
CaR	calcium-sensing receptor
CKD	chronic kidney disease
CYP	cytochrome P450
DOPPS	Dialysis Outcomes and Practice Patterns Study
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERA-EDTA	European Renal Association European Dialysis and Transplant Association
ESRD	end-stage renal disease
ESPN	European Society for Paediatric Nephrology
EU	European Union
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GVP	Good Pharmacovigilance Practice
HCl	hydrochloride
HCV	Hepatitis C virus
HR	hazard ratio
HPT	hyperparathyroidism
IC_{50}	concentration of an inhibitor where response is reduced by half
INN	International Nonproprietary Name
IPDN	International Pediatric Dialysis Network
iPTH	intact PTH
IV	intravenous(ly)
KKC	Kyowa Kirin Co., Ltd.
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NKF-K/DOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
PBRER	periodic benefit-risk evaluation report
PD	peritoneal dialysis
primary HPT	primary hyperparathyroidism

Term/Abbreviation	Explanation
PI	prescribing information
PIL	Patient Information Leaflet
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
QPPV	Qualified Person for Pharmacovigilance
RenDER	USRDS Renal Data Extraction and Referencing system
RMP	risk management plan
RRT	renal replacement therapy
SEER	Surveillance, Epidemiology, and End Results
SHPT	secondary hyperparathyroidism
SmPC	Summary of Product Characteristics
SMR	standardized mortality ratio
SMQ	standardized MedDRA Query
UK	United Kingdom
US	United States
USRDS	United States Renal Data System

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Cinacalcet hydrochloride (HCl)
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	Calcimimetics ATC code H05BX01 (Anti-parathyroid agents)
Marketing authorization applicant or marketing authorization holder (MAH)	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	Mimpara®/Sensipar®
Invented name(s) in the European Economic Area (EEA)	Mimpara
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Cinacalcet HCl is a calcimimetic agent.
Summary of mode of action	The calcium-sensing receptor (CaR) 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 CaR to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.
Important information about its composition	Cinacalcet HCl is described chemically as N-[1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride. Its empirical formula is $C_{22}H_{22}F_3N$.HCl and has a molecular weight of 393.9 g/mol (hydrochloride salt) and 357.4 g/mol (free base). It has 1 chiral center having an R-absolute configuration. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity.
Hyperlink to the Product Information (PI)	The currently approved PI is provided in Module 1.3.1 (Sequence Number 0082).

Table 1. Product(s) Overview

Indication(s) in the European Economic Area (EEA)	
Current (if applicable):	Secondary hyperparathyroidism *Adults* Treatment of secondary hyperparathyroidism (SHPT) in adult patients with end-stage renal disease (ESRD) on maintenance dialysis therapy. *Pediatric Population* Treatment of SHPT in children aged 3 years and older with ESRD on maintenance dialysis therapy in whom SHPT is not adequately controlled with standard of care therapy. Parathyroid carcinoma and primary hyperparathyroidism in adults Reduction of hypercalcemia in adult patients with: • parathyroid carcinoma • primary hyperparathyroidism (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
Proposed (if applicable)	Not applicable
Dosage in the EEA	
Current (if applicable):	Secondary hyperparathyroidism *Adults and elderly > 65 years* The recommended starting dose for adults is 30 mg once per day. Mimpara should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target PTH in dialysis patients of between 150 to 300 pg/mL in the intact PTH (iPTH) assay. Parathyroid hormone levels should be assessed at least 12 hours after dosing with Mimpara. Reference should be made to current treatment guidelines.

Footnotes, including abbreviations, are defined on the last page of this table.

Table 1. Product Overview

Dosage in the EEA (continued)	
Current (if applicable) (continued)	*Pediatric 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 Mimpara, 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 (see table). The dose can be increased to achieve a desired target iPTH range. The dose should be increased sequentially through available dose levels (see table) 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. <u>Parathyroid carcinoma and primary hyperparathyroidism</u> *Adults and elderly (> 65 years)* The recommended starting dose of Mimpara for adults is 30 mg twice per day. The dose of Mimpara 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.
Proposed (if applicable):	Not applicable

Footnotes, including abbreviations, are defined on the last page of this table.

Table 1. Product Overview

Pharmaceutical form(s) and strength(s)	
Current (if applicable):	Mimpara is available as film coated tablets and as granules inside capsules for pediatric use. • Mimpara tablets are light green, film-coated, oval-shaped tablets at strengths of 30, 60, and 90 mg. • Mimpara granules inside capsules are available in 1 mg (dark green cap), 2.5 mg (rich yellow cap), and 5 mg (blue cap) strengths. The capsules should not be swallowed. The capsule must be opened and the entire contents of a capsule should be sprinkled in food or liquid and administered.
Proposed (if applicable):	Not applicable
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

Page 4 of 4

ATC = Anatomical Therapeutic Chemical Classification System Code; CKD = chronic kidney disease; EEA = European Economic Area; EU = European Union; HCl = hydrochloride; HPT = hyperparathyroidism; iPTH = intact parathyroid hormone; MAH = marketing authorization holder; PTH = parathyroid hormone; PI = prescribing information; RMP = risk management plan; SHPT = secondary hyperparathyroidism

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Secondary Hyperparathyroidism in Adult and Elderly Patients With Chronic Kidney Disease

Incidence	There is no report for SHPT incidence among chronic kidney disease (CKD) population around the world (Hedgeman et al, 2015).
Prevalence	Secondary hyperparathyroidism is a common and serious disease that develops early in CKD (glomerular filtration rate [GFR] ≤ 60 mL/min), before the initiation of dialysis and progresses as patients reach ESRD (Cunningham et al, 2011). Across Europe and Australia, the prevalence of SHPT in adults within dialysis populations (PTH > 300 pg/mL) was estimated to be between 30% to 49%. The prevalence within dialysis populations in North America (United States [US], Canada) was estimated to be 54%. Within Asia, prevalence estimates for SHPT (iPTH > 300 pg/mL) were only identified in India (28%) and Japan (11.5%) (Hedgeman et al, 2015). Within the population of patients with CKD, data are collected most consistently through renal replacement registries for patients who have progressed to CKD stage 5 (ie, ESRD with a GFR of ≤ 15 mL/min). At this advanced stage of kidney disease, the kidneys have lost nearly all their ability to function, and eventually dialysis or a kidney transplant is necessary for survival. At the end of 2014, there were 678 383 prevalent dialysis and transplant patients receiving treatment for ESRD — a 3.5% increase from 2013. In 2014, the unadjusted prevalence of treated ESRD pmp was 2076 per million in the US population (United States Renal Data System [USRDS], 2016).
Demographics of population in the authorized indication and risk factors for the disease	Across countries in the EU, prevalent SHPT patients are predominantly men and > 50 years of age (ERA-EDTA, 2010). Secondary hyperparathyroidism predominantly occurs among patients with CKD. Furthermore, there is evidence that vitamin D deficiency is a risk factor from both observational and interventional studies (Lee et al, 2008). Analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS) database indicates that approximately 30% of patients receiving dialysis have iPTH concentrations > 300 pg/mL (Tentori et al, 2008). Updated estimates reported US estimates were at 17% and the highest estimates were in Germany (26%) and Canada (33%) (Dialysis Outcomes and Practice Patterns Study, 2012).

Footnotes, including abbreviations, are defined on the last page of this table.

Table 2. Summary of Epidemiology of Secondary Hyperparathyroidism in Adult and Elderly Patients With Chronic Kidney Disease

Main existing treatment options	Current therapies for the biochemical abnormalities associated with SHPT include phosphate binders, which are used to reduce serum phosphorus levels, and vitamin D sterols, which are administered to reduce PTH. Cinacalcet is the first calcimimetic approved for the treatment of SHPT in adult patients receiving dialysis and is considered an important part of the treatment regimen for these patients. Etelcalcetide is the second calcimimetic drug that was recently approved in EU and the US, in 2016 and 2017 respectively, for the treatment of SHPT in patients undergoing hemodialysis.
Natural history of the indicated condition in the untreated population, including mortality and morbidity	SHPT is a clinical syndrome that results in adverse systemic effects associated with significant morbidity and mortality. Multiple factors are involved in the pathogenesis of the disease, including hypocalcemia, phosphate retention, reduced synthesis of 1,25-dihydroxy vitamin D (calcitriol), and skeletal resistance to the calcemic action of PTH (Slatopolsky et al, 2001). The resulting hypocalcemia and low circulating calcitriol concentrations stimulate PTH release and parathyroid cell hyperplasia (Goodman and Quarles, 2007). A primary consequence of SHPT is the development of renal osteodystrophy, which is present in > 70% of patients before the initiation of dialysis (Spasovski et al, 2003). Increased PTH results in augmented osteoclast activity, bone resorption, and high-turnover bone disease as documented by bone histology (Wang et al, 1995; Sherrard et al, 1993; Quarles et al, 1992; Andress et al, 1986; Chan et al, 1985; Cundy et al, 1985; Voigts et al, 1984; Shen et al, 1975). Other complications include muscle weakness, fatigue, pruritus, gastrointestinal complaints, bone and joint pain, vascular and soft tissue calcification, impaired cardiac function, spontaneous tendon rupture, pathological bone fracture, altered lipid metabolism, and, in rare instances, skeletal deformities and calciphylaxis (Atsumi et al, 1999; Rostand and Drueke, 1999; Gupta et al, 1997).
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Survival of patients starting renal replacement therapy (RRT) improved between 1997 to 2008 in the United Kingdom (UK) (Castledine et al, 2011). For example, the unadjusted 1-year survival increased from 85.9% in 1997 to 91.9% in 2008 among incident patients 18 to 64 years of age, and from 64.2% in 1997 to 75.8% in 2008 for incident patients ≥ 65 years of age. The age-adjusted 1-year survival of prevalent dialysis patients in the UK rose from 85% in 2000 to 89% in 2009 (Castledine et al, 2011). Based on the ERA-EDTA 2010, the 5-year survival probability was 46.2% (95% confidence interval [CI]: 46.0, 46.3) among SHPT patients in the EU (ERA-EDTA, 2013).
Important comorbidities	• Bone disease • Cardiovascular disease

CKD = chronic kidney disease; DOPPS = Dialysis Outcomes and Practice Patterns Study; ERA-EDTA = European Renal Association European Dialysis and Transplant Association; ESRD = end-stage renal disease; EU = European Union; GFR = glomerular filtration rate; iPTH = intact parathyroid hormone; pmp = per million population; RMP = risk management plan; RRT = renal replacement therapy; SHPT = secondary hyperparathyroidism

Table 3. Summary of Epidemiology of Secondary Hyperparathyroidism in Pediatric Patients With End-stage Renal Disease on Maintenance Dialysis Therapy

Incidence	Secondary hyperparathyroidism is common in adults and children with CKD, and it begins early in the course of renal decline (KDIGO, 2009; Levin et al, 2007). End-stage renal disease is a rare condition in childhood, with an estimated worldwide median reported incidence in 2008 of 9 (range: 4 - 18) per million of the age-related population (pmarp) (Harambat et al, 2012). The incidence of RRT in pediatric patients in Europe from 2009 to 2011 was estimated to be 5.5 cases pmarp in patients aged 0 to 14 years, and varied markedly between countries (interquartile range: 3.4 - 7.0 pmarp) (Chesnaye et al, 2014).
Prevalence	The prevalence of RRT was 27.9 pmarp and increased with age (Chesnaye et al, 2014). To understand the prevalence of SHPT in the pediatric dialysis population, a survey conducted among 18 sites belonging to the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS, unpublished data), included data from 320 pediatric hemodialysis and peritoneal dialysis (PD) patients, between the ages of 2 to less than 18. The results show that overall, 49% of the pediatric dialysis population has iPTH levels above 300 pg/mL (31.8 pmol/L), the upper limit recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI™) guidelines for all pediatric age groups. Based on data from an ERA-EDTA Registry, the prevalent dialysis population (hemodialysis and PD) in Europe is estimated to be 986 children (ERA-EDTA, 2015; European Society for Paediatric Nephrology [ESPN]/ERA-EDTA, 2015). Based on the percent of children expected to have SHPT (defined as iPTH > 300 pg/mL; USRDS Renal Data Extraction and Referencing system [RenDER], 2016), the European population with SHPT is estimated to be approximately 641 children.
Demographics of population in the authorized indication and risk factors for the disease	Demographic data is not available. Secondary hyperparathyroidism predominantly occurs among patients with CKD. Congenital causes account for almost 60% of cases of CKD in children (Wong et al, 2012; Ardissino et al, 2003).
Main existing treatment options	Currently, SHPT in children is treated with Vitamin D and phosphate binders, neither of which is specifically approved for SHPT in children. One calcimimetic drug, cinacalcet, is approved in the EU for SHPT in children aged 3 and older with ESRD on maintenance dialysis therapy. Pediatric information in product labelling for calcitriol products varies.
Natural history of the indicated condition in the population, including mortality and morbidity	The adjusted mortality rate for pediatric patients on dialysis (≤ 19 years) is 56.5 per 1000 patient year (PY)s at risk (Shroff and Ledermann, 2009).
Important comorbidities	• Bone disease • Cardiovascular disease

CKD = chronic kidney disease; ESRD = end-stage renal disease; pmarp = per million of the age-related population; PY = patient years; RRT = renal replacement therapy; SHPT = secondary hyperparathyroidism

Table 4. Summary of Epidemiology of Hypercalcemia in Patients With Parathyroid Carcinoma

Incidence	Parathyroid carcinomas are very rare tumors, with an estimated incidence of 0.015 per 100 000 population (Fraker, 2005; Hundahl et al, 1999). In Europe, the US, and Japan, parathyroid carcinoma has been estimated to cause HPT in 0.017% to 5.2% of cases; however, many series report parathyroid carcinoma to account for < 1% of patients with primary HPT (Fraker, 2005; Shane, 2001; Fraker, 2000; Favia et al, 1998).
Prevalence	The estimated prevalence of parathyroid carcinoma in the US of 0.005% (Wei and Harari, 2012).
Demographics of population in the authorized indication and risk factors for the disease	Parathyroid carcinoma cases identified from the Surveillance, Epidemiology, and End Results (SEER) cancer registry between 1988 and 2003 were equally distributed between men and women, with the majority (78%) in ≥ 45 years of age (Lee, 2007). Gender distribution among parathyroid carcinoma cases was equal in a study using data from the National Cancer Data Base from 1985 to 1995, with no disproportionate clustering by race, income level, or geographic region (Hundahl et al, 1999). The etiology of parathyroid carcinoma is largely unknown. Rarely, parathyroid carcinoma has been reported in patients with long-standing SHPT or with a history of head and neck irradiation (Fang and Lal, 2011). An increased risk of parathyroid cancer has been associated with multiple endocrine neoplasia and with autosomal dominant familial isolated HPT (Dionisi et al, 2002; Wassif et al, 1993; Mallette et al, 1974). Parathyroid cancer also has been associated with external radiation exposure; however, most reports describe an association between radiation and the more common parathyroid adenoma (Fraker, 2005; Shane, 2001).
Main existing treatment options	Cinacalcet is indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma. Surgery is the only effective therapy for parathyroid carcinoma (Rahbari and Kebebew, 2011; Lacobone et al, 2004; Shane, 2001).
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Parathyroid cancers are hyperfunctional, unlike other endocrine tumors that become less hormonally active when malignant (Fraker, 2005). The clinical features of parathyroid carcinoma are caused primarily by the effects of excessive secretion of PTH by the tumor, rather than by the infiltration of vital organs by tumor cells.

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of this table.

Table 4. Summary of Epidemiology of Hypercalcemia in Patients With Parathyroid Carcinoma

Natural history of the indicated condition in the untreated population, including mortality and morbidity (continued)	Serum PTH levels may be 3- to 10-times above the upper limit of normal for the assay employed; this marked elevation is uncommon in typical primary HPT, where serum PTH concentrations are generally < 2-times above the upper limit of normal (Shane, 2001). Accordingly, signs and symptoms of hypercalcemia typically dominate the clinical picture and may include typical hyperparathyroid bone disease and features of renal involvement, such as nephrolithiasis or nephrocalcinosis (Fraker, 2005). Renal colic is a frequent presenting complaint of patients with parathyroid carcinoma (Shane, 2001). A retrospective review of 37 patients with parathyroid carcinoma treated at a single university tertiary care center between 1966 to 2009 indicated that 5 factors were associated with increased mortality among patients with parathyroid carcinoma: lymph node metastasis (hazard ratio [HR] = 4.27, 95% CI: 1.19, 15.3), distant metastases (HR = 3.50, 95% CI: 1.60, 7.64), number of recurrences (HR = 1.18, 95% CI: 1.02, 1.36), higher calcium level at recurrence (HR = 1.35, 95% CI: 1.09, 1.68), and a high number of calcium-lowering medications (HR = 1.49, 95% CI: 1.18, 1.87) (Harari et al, 2011). Because of its low malignant potential, the morbidity and mortality associated with parathyroid cancer primarily result from the metabolic consequences of the disease and not directly from malignant growth (Busaidy et al, 2004; Sandelin et al, 1994). The 10-year survival of patients with parathyroid carcinoma was 49% in a study of 286 patients (Hundahl et al, 1999) and 77% in a study of 22 patients (which may be attributed to improvements in supportive medical care and in the prevention of fatal hypercalcemia) (Busaidy et al, 2004).
Important comorbidities	• Bone disease • Cardiovascular disease

HPT = hyperparathyroidism; HR = hazard ratio; PTH = parathyroid hormone; SEER = Surveillance, Epidemiology, and End Results; SHPT = secondary hyperparathyroidism

Table 5. Summary of Epidemiology of Primary Hyperparathyroidism

Incidence	Eighty-five percent of primary HPT cases are caused by solitary parathyroid adenomas with the majority of the rest resulting from hyperfunction in multiple parathyroid glands. Less than 1 percent of primary HPT cases are caused by parathyroid carcinoma (Marx, 2000). A population-based study in the US using data from the Rochester Epidemiology Project estimated an overall age- and sex-adjusted incidence of 21.6 cases per 100 000 PY during the period from 1993 to 2001 (Wermers et al, 2006). Eighty-five percent of primary HPT cases are caused by solitary parathyroid adenomas with the majority of the rest resulting from hyperfunction in multiple parathyroid glands. Less than 1 percent of primary HPT cases are caused by parathyroid carcinoma (Marx, 2000). Using serum PTH values along with the serum calcium concentration, Lundgren (1999) and Lundgren et al (1997) showed that 2.6% of postmenopausal women in Sweden had primary HPT (Lundgren, 1999; Lundgren et al, 1997). However, on follow-up testing, only two-thirds had confirmation of the diagnosis.
Prevalence	Published literature suggests that the prevalence of primary HPT in Europe is approximately 3 per 1000 population (Adami et al, 2002; Jorde et al, 2000), which translates to approximately 1.5 million people.
Demographics of population in the authorized indication and risk factors for the disease	Primary HPT generally occurs in middle-aged patients and disproportionately affects women (particularly those above the age of 50 years) compared with men in an approximately 3:1 ratio (Miller et al, 2008; Bilezikian and Silverberg, 2000). In primary HPT, excess PTH secretion occurs because the effect of extracellular calcium to inhibit PTH secretion through interaction with the CaR is altered (Silverberg and Bilezikian, 2006). In 80% of cases, this results from a single adenoma where the parathyroid cells lose their sensitivity to extracellular calcium and the set-point for serum calcium concentration is shifted to the right (Silverberg and Bilezikian, 2006; Bilezikian and Silverberg, 2004). The remaining cases of primary HPT are secondary to parathyroid carcinoma (Sosa and Udelsman, 2003). Vitamin D insufficiency also has been reported to affect the clinical expression of primary HPT and may modify the calcemic response to PTH in this disorder (Weaver et al, 2009; Silverberg et al, 1999).
Main existing treatment options	Surgical parathyroidectomy is considered the only definitive cure for primary HPT; however, a small percentage of patients have contraindications for surgery or are unable to receive surgery. Some patients who have had a parathyroidectomy have persistent primary HPT or a subsequent recurrence of primary HPT (Solorzano et al, 2008; Hedback and Oden, 2004; Hedback and Oden, 2003). Cinacalcet is indicated to treat severe hypercalcemia in patients with primary HPT (Cetani and Marcocci, 2012).

Footnotes, including abbreviations, are defined on the last page of this table.

Table 5. Summary of Epidemiology of Primary Hyperparathyroidism

Natural history of the indicated condition in the untreated population, including mortality and morbidity	Symptoms of primary HPT range from mild to severe and may have a number of adverse consequences, some of which can be life-threatening, including: kidney stones, muscle weakness, metabolic bone disease that causes bone pain and leads to bone loss and skeletal fractures, fibrous changes of the bone marrow, gastrointestinal disturbances, and neurobehavioral disorders (Silverberg et al, 2009; Silverberg and Bilezikian, 2006; Vestergaard and Mosekilde, 2003; Vestergaard et al, 2000). Persistent hypercalcemia also may result in soft tissue calcification and increase the risk of cardiovascular disease (Silverberg et al, 2009; Andersson et al, 2004; Lundgren et al, 2001; Stefenelli et al, 1997; Stefenelli et al, 1993; Bilezikian, 1992). In advanced cases of primary HPT, marked elevations in serum calcium can lead to alterations in mental status and ultimately to stupor, coma, and death (Ziegler, 2001; Bilezikian, 1992). A retrospective population-based observational study from Scotland reported increased mortality in symptomatic HPT between 1997 to 2006 (Yu et al, 2010). Patients had an increased risk of all-cause mortality and cardiovascular mortality (standardized mortality ratio [SMR]-all cause 2.62, 95% CI: 2.39, 2.86; SMR-cardiovascular 2.68, 95% CI: 2.34, 3.05) (Yu et al, 2010). Patients with mild primary HPT had a significantly increased risk of developing cardiovascular and cerebrovascular disease, renal dysfunction, and fractures compared with the age-and sex-adjusted general population. Therefore, when the disease presents in more symptomatic forms, mortality may be increased. However, there is also evidence that asymptomatic HPT does not lead to increased risk of mortality (Wermers et al, 1998). There does not appear to be any well-established predisposing factors for the development of primary HPT (Bilezikian and Silverberg, 2000). However, in a population-based study in the US using data from the Rochester Epidemiological Project (1965 to 1992), 2 factors were associated with increased all-cause mortality among patients with primary HPT: age (HR = 2.6, 95% confidence interval: 2.2, 3.1; per 10 year increase) and maximal serum calcium level (HR = 1.3, 95% CI: 1.1, 1.6); per mg/dL increase (Wermers et al, 2006).
Important comorbidities	• Bone disease • Cardiovascular disease

CaR = calcium-sensing receptor; HPT = hyperparathyroidism; HR = hazard ratio;
PTH = parathyroid hormone; SMR = standardized mortality ratio; US = United States

Part II: Module SII - Nonclinical Part of the Safety Specification

Table 6. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity	Toxicology studies of cinacalcet demonstrated that most observed toxicities were related to hypocalcemia. This was consistent with the pharmacologic action of cinacalcet, which reduces PTH, concomitantly lowering serum calcium concentrations.	Cinacalcet should not be initiated in patients with corrected serum calcium values below the lower limit of normal and patients should be monitored carefully during treatment with cinacalcet for the occurrence of hypocalcemia.
Reproductive Toxicity	In pregnant rats, there were slight decreases in body weight and food consumption at the highest dose. Decreased fetal weights were seen in rats at doses where dams had severe hypocalcemia. Cinacalcet has been shown to cross the placental barrier in rabbits. Cinacalcet is excreted in the milk of lactating rats with a high milk-to-plasma ratio. It is not known whether cinacalcet is excreted in human milk.	Cinacalcet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A decision on whether to abstain from breastfeeding or to abstain from therapy with cinacalcet should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of cinacalcet therapy to the woman.
Juvenile Toxicity	In a 6-month toxicity study in 10-week old juvenile dogs that evaluated dose levels of 10, 30, and 100 mg/kg/day, tremors, emesis, decreased activity, black feces, decreased food consumption, minimal femoral growth plate thickening, lymphoid hyperplasia in the thoracic cavity, and mononuclear cell infiltration in the esophagus occurred at all dose levels. Decreased body weight, decreased red cell mass, increased platelet count, and slight decreases in bone densitometry and geometry parameters occurred at ≥ 30 mg/kg/day.	These changes can be monitored for in the clinic. Cinacalcet is indicated for the use in pediatric patients aged ≥ 3 years to < 18 years for the treatment of SHPT in patients with ESRD on maintenance dialysis therapy in whom SHPT is not adequately controlled with standard of care therapy.

Footnotes, including abbreviations, are defined on the last page of this table.

Table 6. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Juvenile Toxicity (continued)	All of the changes observed in the study were fully to partially reversible over a 3-month recovery period at ≥ 30 mg/kg/day, except for decreased red cell mass in both sexes and decreases in body weight and bone geometry parameters in females. Due to the minor degree of the changes that occurred at the low dose level, the no observed adverse effect level for this study was 10 mg/kg/day.	
General Safety Pharmacology Cardiovascular (including potential for QT interval prolongation)	A slight prolongation of the QT interval, which was correlated with reduction in serum calcium levels, was observed in monkeys that had received repeated doses of cinacalcet for 3 months. In a 12 month, repeat-dose study in monkeys, no electrocardiogram abnormalities were detected that could be attributed to cinacalcet administration.	Cinacalcet should not be initiated in patients with corrected serum calcium values below the lower limit of normal and patients should be monitored carefully during treatment with cinacalcet for the occurrence of hypocalcemia.
Mechanisms for Drug Interactions	In human liver microsomes, clearance of cinacalcet was associated predominantly with cytochrome P450 (CYP) enzymes, CYP1A2 and CYP3A activities, and correlated only weakly with CYP2D6 activity. The inhibitory potency of cinacalcet against CYP1A2, CYP3A, CYP2C8, CYP2C9, and CYP2C19 was low (IC_{50} > 10 µM).	Concomitant use of cinacalcet with strong inhibitors or inducers of CYP3A4 and/or CYP1A2, as well as to smoking during cinacalcet treatment may require dose adjustment, dose adjustments of concomitant medicinal products may be required when cinacalcet is administered with individually titrated, narrow therapeutic index substances that are predominantly metabolized by CYP2D6.

Footnotes, including abbreviations, are defined on the last page of this table.

Table 6. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Mechanisms for Drug Interactions (continued)	Although cinacalcet was not extensively metabolized by CYP2D6, it bound CYP2D6 with high affinity (IC_{50} < 0.1 µM). These data suggest that a clinically significant inhibition of CYP2D6 by cinacalcet may occur, which may elevate plasma concentrations of CYP2D6 substrates, such as tricyclic antidepressants.	

Page 3 of 3

CYP = cytochrome P450; ESRD = end-stage renal disease; IC_{50} = concentration of an inhibitor where response is reduced by half; PTH = parathyroid hormone; SHPT = secondary hyperparathyroidism

Part II: Module SIII - Clinical Trial Exposure

Table 7. Example: Total Subject Exposure to Cinacalcet in Clinical Trials by Indication and Duration
Safety Analysis Set

	Exposure to Cinacalcet by Duration								
Cinacalcet	<1 year n (subj-yrs)	≥1 year n (subj-yrs)	≥2 years n (subj-yrs)	≥3 years n (subj-yrs)	≥4 years n (subj-yrs)	≥5 years n (subj-yrs)	≥6 years n (subj-yrs)	≥7 years n (subj-yrs)	Total n (subj-yrs)
All Phase 1 studies	766 (8.81)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	766 (8.81)
Pediatric	24 (0.07)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	24 (0.07)
All Phase 2, 3 and 4 studies	4433 (2069.83)	2364 (6269.34)	1401 (4942.97)	864 (3608.90)	556 (2540.42)	66 (345.46)	1 (6.24)	0 (0.00)	6797 (8339.16)
SHPT	4271 (1988.25)	2267 (6021.47)	1358 (4757.50)	829 (3444.36)	523 (2382.73)	53 (275.07)	1 (6.24)	0 (0.00)	6538 (8009.72)
Pediatric	81 (33.73)	2 (2.28)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	83 (36.02)
CRI	276 (126.42)	139 (190.83)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	415 (317.26)
ESRD	3914 (1828.10)	2126 (5828.35)	1358 (4757.50)	829 (3444.36)	523 (2382.73)	53 (275.07)	1 (6.24)	0 (0.00)	6040 (7656.45)
Primary HPT and Parathyroid Carcinoma	129 (52.67)	73 (223.46)	43 (185.47)	35 (164.54)	33 (157.69)	13 (70.40)	0 (0.00)	0 (0.00)	202 (276.12)
PRT	33 (28.91)	24 (24.41)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	57 (53.32)

n = number of subjects exposed to cinacalcet; subj-yrs = total subject-years of follow-up.
Note: All data is from completed studies. A study is considered 'completed' if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes all subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/calci/safety/RMP/analysis/2018/tables/program/t-exp-cum-dur-all.sas
Output: t-05-exp-cum-dur-all.rtf (Date Generated: 14MAR2018:00:48) Source Data: jpsur_country

Table 7. Example: Total Subject Exposure to Cinacalcet in Clinical Trials by Indication and Duration
Safety Analysis Set

	Exposure to Cinacalcet by Duration								
Cinacalcet	<1 year n (subj-yrs)	≥1 year n (subj-yrs)	≥2 years n (subj-yrs)	≥3 years n (subj-yrs)	≥4 years n (subj-yrs)	≥5 years n (subj-yrs)	≥6 years n (subj-yrs)	≥7 years n (subj-yrs)	Total n (subj-yrs)
Total	5199 (2078.63)	2364 (6269.34)	1401 (4942.97)	864 (3608.90)	556 (2540.42)	66 (345.46)	1 (6.24)	0 (0.00)	7563 (8347.97)

n = number of subjects exposed to cinacalcet; subj-yrs = total subject-years of follow-up.
Note: All data is from completed studies. A study is considered 'completed' if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes all subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/calci/safety/RMP/analysis/2018/tables/program/t-exp-cum-dur-all.sas
Output: t-05-exp-cum-dur-all.rtf (Date Generated: 14MAR2018:00:48) Source Data: jpsur_country

Table 8. Total Subject Exposure to Cinacalcet in Clinical Trials by Age Group and Gender
Safety Analysis Set

Cinacalcet	New Born Infants (0 to 27 days) n (subj-yrs)	Infants and Toddlers (28 days to 23 months) n (subj-yrs)	Children (2 to 11 years) n (subj-yrs)	Adolescents (12 to 17 years) n (subj-yrs)	Adults (18 to 64 years) n (subj-yrs)	Elderly People (65 to 74 years) n (subj-yrs)	Elderly People (75 to 84 years) n (subj-yrs)	Elderly People (≥85 years) n (subj-yrs)	Total n (subj-yrs)
Male									
All Phase 1 studies	1 (0.00)	1 (0.00)	8 (0.02)	1 (0.00)	526 (6.50)	9 (0.24)	0 (0.00)	0 (0.00)	546 (6.77)
Pediatric	1 (0.00)	1 (0.00)	8 (0.02)	1 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	11 (0.03)
All Phase 2, 3 and 4 studies	0 (0.00)	0 (0.00)	19 (6.03)	25 (11.75)	2830 (3713.20)	738 (822.60)	357 (354.49)	29 (25.90)	3998 (4933.98)
SHPT	0 (0.00)	0 (0.00)	19 (6.03)	25 (11.75)	2768 (3639.74)	714 (770.47)	351 (352.50)	25 (23.27)	3902 (4803.77)
Pediatric	0 (0.00)	0 (0.00)	19 (6.03)	25 (11.75)	1 (0.21)	0 (0.00)	0 (0.00)	0 (0.00)	45 (17.99)
CRI	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	97 (75.56)	87 (65.47)	54 (41.46)	8 (6.08)	246 (188.57)

n = number of subjects exposed to cinacalcet; subj-yrs = total subject-years of follow-up.
Note: All data is from completed studies. A study is considered 'completed' if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes all subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/calci/safety/RMP/analysis/2018/tables/program/t-exp-cum-by-age-sex.sas
Output: t-06-exp-cum-by-age-sex.rtf (Date Generated: 05APR2018:01:59) Source Data: jpsur_country

Table 8. Total Subject Exposure to Cinacalcet in Clinical Trials by Age Group and Gender
Safety Analysis Set

Cinacalcet	New Born Infants (0 to 27 days) n (subj-yrs)	Infants and Toddlers (28 days to 23 months) n (subj-yrs)	Children (2 to 11 years) n (subj-yrs)	Adolescents (12 to 17 years) n (subj-yrs)	Adults (18 to 64 years) n (subj-yrs)	Elderly People (65 to 74 years) n (subj-yrs)	Elderly People (75 to 84 years) n (subj-yrs)	Elderly People (≥85 years) n (subj-yrs)	Total n (subj-yrs)
ESRD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2670 (3563.98)	627 (705.00)	297 (311.04)	17 (17.19)	3611 (4597.20)
Primary HPT and Parathyroid Carcinoma	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	36 (47.61)	19 (47.15)	6 (1.99)	4 (2.63)	65 (99.38)
PRT	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	26 (25.85)	5 (4.98)	0 (0.00)	0 (0.00)	31 (30.83)
Total	1 (0.00)	1 (0.00)	27 (6.05)	26 (11.75)	3356 (3719.70)	747 (822.84)	357 (354.49)	29 (25.90)	4544 (4940.75)

n = number of subjects exposed to cinacalcet; subj-yrs = total subject-years of follow-up.
Note: All data is from completed studies. A study is considered 'completed' if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes all subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/calci/safety/RMP/analysis/2018/tables/program/t-exp-cum-by-age-sex.sas
Output: t-06-exp-cum-by-age-sex.rtf (Date Generated: 05APR2018:01:59) Source Data: jpsur_country

Table 8. Total Subject Exposure to Cinacalcet in Clinical Trials by Age Group and Gender
Safety Analysis Set

Cinacalcet	New Born Infants (0 to 27 days) n (subj-yrs)	Infants and Toddlers (28 days to 23 months) n (subj-yrs)	Children (2 to 11 years) n (subj-yrs)	Adolescents (12 to 17 years) n (subj-yrs)	Adults (18 to 64 years) n (subj-yrs)	Elderly People (65 to 74 years) n (subj-yrs)	Elderly People (75 to 84 years) n (subj-yrs)	Elderly People (≥85 years) n (subj-yrs)	Total n (subj-yrs)
Female									
All Phase 1 studies	1 (0.00)	0 (0.00)	7 (0.02)	5 (0.01)	199 (1.79)	8 (0.21)	0 (0.00)	0 (0.00)	220 (2.04)
Pediatric	1 (0.00)	0 (0.00)	7 (0.02)	5 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	13 (0.04)
All Phase 2, 3 and 4 studies	0 (0.00)	2 (0.62)	16 (9.07)	19 (8.06)	1768 (2351.54)	641 (706.61)	316 (297.54)	37 (31.73)	2799 (3405.18)
SHPT	0 (0.00)	2 (0.62)	16 (9.07)	19 (8.06)	1679 (2230.58)	602 (659.61)	287 (269.11)	31 (28.90)	2636 (3205.95)
Pediatric	0 (0.00)	2 (0.62)	16 (9.07)	19 (8.06)	1 (0.28)	0 (0.00)	0 (0.00)	0 (0.00)	38 (18.03)
CRI	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	75 (58.11)	55 (42.95)	33 (23.48)	6 (4.13)	169 (128.68)

n = number of subjects exposed to cinacalcet; subj-yrs = total subject-years of follow-up.
Note: All data is from completed studies. A study is considered 'completed' if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes all subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/calci/safety/RMP/analysis/2018/tables/program/t-exp-cum-by-age-sex.sas
Output: t-06-exp-cum-by-age-sex.rtf (Date Generated: 05APR2018:01:59) Source Data: jpsur_country

Table 8. Total Subject Exposure to Cinacalcet in Clinical Trials by Age Group and Gender
Safety Analysis Set

Cinacalcet	New Born Infants (0 to 27 days) n (subj-yrs)	Infants and Toddlers (28 days to 23 months) n (subj-yrs)	Children (2 to 11 years) n (subj-yrs)	Adolescents (12 to 17 years) n (subj-yrs)	Adults (18 to 64 years) n (subj-yrs)	Elderly People (65 to 74 years) n (subj-yrs)	Elderly People (75 to 84 years) n (subj-yrs)	Elderly People (≥85 years) n (subj-yrs)	Total n (subj-yrs)
ESRD	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1603 (2172.19)	547 (616.66)	254 (245.63)	25 (24.77)	2429 (3059.24)
Primary HPT and Parathyroid Carcinoma	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	67 (100.82)	36 (44.74)	28 (28.34)	6 (2.84)	137 (176.74)
PRT	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	22 (20.14)	3 (2.26)	1 (0.08)	0 (0.00)	26 (22.49)
Total	1 (0.00)	2 (0.62)	23 (9.09)	24 (8.08)	1967 (2353.33)	649 (706.83)	316 (297.54)	37 (31.73)	3019 (3407.22)

Page 4 of 4

n = number of subjects exposed to cinacalcet; subj-yrs = total subject-years of follow-up.
Note: All data is from completed studies. A study is considered 'completed' if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes all subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/calci/safety/RMP/analysis/2018/tables/program/t-exp-cum-by-age-sex.sas
Output: t-06-exp-cum-by-age-sex.rtf (Date Generated: 05APR2018:01:59) Source Data: jpsur_country

Table 9. Total Subject Exposure to Cinacalcet in Clinical Trials by Product and Race/Ethnic Group
Safety Analysis Set

Cinacalcet	White n (subj-yrs)	Black or African American n (subj-yrs)	Hispanic or Latino n (subj-yrs)	Asian n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
All Phase 1 studies	532 (3.98)	150 (3.88)	62 (0.74)	8 (0.07)	10 (0.13)	4 (0.01)	766 (8.81)
Pediatric	8 (0.02)	3 (0.01)	8 (0.02)	1 (0.00)	0 (0.00)	4 (0.01)	24 (0.07)
All Phase 2, 3 and 4 studies	4252 (5045.22)	1685 (2067.97)	560 (859.82)	160 (177.79)	135 (185.63)	5 (2.73)	6797 (8339.16)
SHPT	4029 (4735.60)	1670 (2058.10)	548 (855.01)	154 (174.77)	132 (183.50)	5 (2.73)	6538 (8009.72)
Pediatric	64 (26.07)	15 (8.08)	0 (0.00)	0 (0.00)	4 (1.87)	0 (0.00)	83 (36.02)
CRI	310 (245.46)	69 (47.54)	21 (13.98)	9 (6.15)	6 (4.12)	0 (0.00)	415 (317.26)
ESRD	3655 (4464.07)	1586 (2002.48)	527 (841.03)	145 (168.62)	122 (177.51)	5 (2.73)	6040 (7656.45)
Primary HPT and Parathyroid Carcinoma	176 (265.85)	10 (4.84)	10 (3.25)	4 (1.04)	2 (1.15)	0 (0.00)	202 (276.12)
PRT	47 (43.77)	5 (5.03)	2 (1.56)	2 (1.98)	1 (0.98)	0 (0.00)	57 (53.32)
Total	4784 (5049.20)	1835 (2071.85)	622 (860.56)	168 (177.86)	145 (185.76)	9 (2.74)	7563 (8347.97)

n = number of subjects exposed to cinacalcet; subj-yrs = total subject-years of follow-up.
Note: All data is from completed studies. A study is considered 'completed' if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes all subjects who received at least 1 dose of investigational product
Program: /userdata/stat/calci/safety/RMP/analysis/2018/tables/program/t-exp-cum-cmpl-by-ind-ethnic.sas
Output: t-07-exp-cum-cmpl-by-ind-ethnic.rtf (Date Generated: 05APR2018:01:58) Source Data: jpsur_country

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 10. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Hypersensitivity to the active substance or to any of the excipients	Hypersensitivity to cinacalcet or any of the excipients should not receive cinacalcet.	No	Hypersensitivity to cinacalcet and any of its excipients is an identified risk and is a contraindication in the Summary of Product Characteristics (SmPC).
Conditions That Could Interfere With Assessment of the Primary Endpoint			
Parathyroidectomy within 3 months (adult subjects) or 6 months (pediatric subjects) of study entry	Allowance of this condition would interfere with an appropriate assessment of cinacalcet efficacy.	No	In primary HPT, cinacalcet is indicated only for patients in whom parathyroidectomy is not a treatment option.
Anticipated parathyroidectomy within 6 months after randomization	Allowance of this condition would interfere with an appropriate assessment of cinacalcet efficacy.	No	An anticipated parathyroidectomy represents a reason not to enroll a patient into a study since a parathyroidectomy will interfere with the subject eligibility and the assessment of the efficacy endpoint, but it does not represent a contraindication for the use of cinacalcet since it does not present a risk to patients.
Prior systemic glucocorticoid, fluoride, or thyroid replacement therapy (primary HPT or parathyroid carcinoma only)	Use of these medications concomitantly would confound the assessment of efficacy and safety.	No	These medications do not interact with the metabolism of cinacalcet but may alter serum calcium levels and bone metabolism.

Page 1 of 6

Footnotes, including abbreviations, are defined on the last page of this table.

Table 10. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Conditions That Could Interfere With Assessment of the Primary Endpoint (continued)			
Sarcoidosis, tuberculosis, or other diseases known to cause hypercalcemia	Conditions known to cause elevations in serum calcium would interfere with the assessment of efficacy in the trial.	No	Cinacalcet is not indicated for use in these patient populations.
Drugs that affect renal tubular calcium handling, and drugs that affect bone metabolism (primary HPT or parathyroid carcinoma only)	Drugs known to alter in serum calcium or bone metabolism would interfere with the assessment of efficacy in the clinical trial.	No	These medications do not interact with the metabolism of cinacalcet but may alter serum calcium levels. The SmPC informs prescribers that during dose titration, serum calcium levels should be monitored frequently, and within 1 week of initiation or dose adjustment of cinacalcet and approximately monthly thereafter.
Prior bisphosphonate use (primary HPT or parathyroid carcinoma only)	Because bisphosphonates reduce serum calcium and because they incorporate into bone and long-term use of bisphosphonates is associated with continued effects of the drug after treatment is stopped, it was deemed most appropriate to exclude previous bisphosphonate treatment.	No	These medications do not interact with the metabolism of cinacalcet but may alter serum calcium levels. Within Section 4.4 of the SmPC, prescribers are informed that cinacalcet treatment should not be initiated in patients with CKD receiving dialysis if serum calcium is < 8.4 mg/dL (2.1 mmol/L). Hypocalcemia that develops during treatment may be managed by appropriate dose adjustment or withholding, and concomitant adjunctive therapy.

Page 2 of 6

Footnotes, including abbreviations, are defined on the last page of this table.

Table 10. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Conditions That Could Interfere With Assessment of the Primary Endpoint (continued)			
Prior bisphosphonate use (primary HPT or parathyroid carcinoma only) (continued)			Also, cinacalcet HCl treatment should not be initiated in pediatric patients with CKD receiving dialysis if the corrected serum calcium level is < 9.4 mg/dL in patients less than 2 years of age and < 8.8 mg/dL in patients from 2 years to less than 18 years of age.
Scheduled date for kidney transplant from a known living donor that makes completion of the study unlikely	Allowance of this condition would interfere with an appropriate assessment of cinacalcet efficacy.	No	A scheduled date for transplant does not necessarily ensure the transplant occurs or that it is successful. Cinacalcet has a short half-life and can be discontinued in time for the transplant procedure. If the transplant is unsuccessful and the patient needs to go back on dialysis, SHPT may not resolve and cinacalcet may still be required.
Drug Interactions			
Medications predominantly metabolized by CYP2D6	Cinacalcet is a strong inhibitor of CYP2D6. Concomitant use of medications metabolized by this enzyme would not allow for adherence to the protocol defined dosing algorithm.	No	Guidance is provided in Section 4.5, Interaction with other medicaments and other forms of interaction of the SmPC that states dose adjustments of concomitant medications may be required when cinacalcet HCl is administered with medications that are predominantly metabolized by this enzyme (eg, metoprolol) and particularly those with a narrow therapeutic index (eg, flecainide, vinblastine, thioridazine and most tricyclic antidepressants).

Page 3 of 6

Footnotes, including abbreviations, are defined on the last page of this table.

Table 10. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Special Populations			
Pregnancy	In animal studies, there were slight decreases in body weight and food consumption in pregnant rats at the highest dose. Decreased fetal weights were seen in rats at doses where dams had severe hypocalcemia. Cinacalcet has been shown to cross the placental barrier in rabbits.	Yes	Not applicable
Lactation	It is not known whether cinacalcet is excreted in human milk. Cinacalcet is excreted in the milk of lactating rats with high milk to plasma ratio. The potential for absorption and harm to the infant after ingestion is unknown.	Yes	Not applicable
Safety			
Seizures within 12 months of study entry	The risk of seizure is increased in those patients who have a history of seizures, and by decreases in serum calcium levels.	No	The risk of seizure may be mitigated by anticonvulsant treatment and maintenance of serum calcium levels in the normal range. The SmPC Section 4.4 (Special warnings and precautions) informs the prescriber that that the threshold for seizure is lowered by significant reduction in serum calcium levels.

Page 4 of 6

Footnotes, including abbreviations, are defined on the last page of this table.

Table 10. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Safety (continued)			
Seizures within 12 months of study entry (continued)			Therefore, serum calcium levels should be closely monitored in patients receiving Mimpara, particularly in patients with a history of a seizure disorder.
Hypocalcemia	The mechanism of action of cinacalcet involves lowering PTH, with an associated lowering of serum calcium levels.	No	Within Section 4.4 of the SmPC, prescribers are informed that cinacalcet treatment should not be initiated in patients with CKD receiving dialysis if serum calcium is < 8.4 mg/dL (2.1 mmol/L). Hypocalcemia that develops during treatment may be managed by appropriate dose adjustment or withholding, and concomitant adjunctive therapy. Cinacalcet HCl treatment should not be initiated in pediatric patients with CKD receiving dialysis if the corrected serum calcium level is < 9.4 mg/dL in patients less than 2 years of age and < 8.8 mg/dL in patients from 2 years to less than 18 years of age.

Page 5 of 6

Footnotes, including abbreviations, are defined on the last page of this table.

Table 10. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Safety (continued)			
Prior myocardial infarction	A condition of prior myocardial infarction would confound the assessment of safety in the clinical trial.	No	Based on clinical data to date, cinacalcet has not been associated with an increased incidence of myocardial ischemia.
Ventricular rhythm disturbance requiring treatment	A condition of ventricular rhythm disturbance that requires treatment would confound the assessment of safety in the trial. Hypocalcemia may increase the risk of ventricular arrhythmias.	No	Prevention and management of hypocalcemia in association with cinacalcet use should be effective in preventing or reducing the risk of QT prolongation and ventricular arrhythmias. Within Section 4.4 of the SmPC, the risk of QT prolongation and ventricular arrhythmia secondary to hypocalcemia is described, as are provisions for avoidance and management of hypocalcemia.

Page 6 of 6

CYP = cytochrome P450; CKD = chronic kidney disease; HCl = hydrochloride; HPT = hyperparathyroidism; SmPC = summary of product characteristics

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 11. Exposure of Special Populations Typically Under-represented in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	No cinacalcet exposure to pregnant women was planned in the clinical program. A total of 9 pregnancies have been reported in clinical studies.
Breastfeeding women	Not included in the clinical development program. No cases of lactation have been reported in clinical trials.
Patients with relevant comorbidities	
Patients with hepatic impairment	Study 990162 with 24 subjects investigated the pharmacokinetics of cinacalcet (50 mg) in subjects with various degrees of hepatic impairment (mild, moderate, or severe according to the Child Pugh Classification [Food and Drug Administration (FDA), 2003]).
Patients with renal impairment	In the cinacalcet clinical program, the pharmacokinetic profile of cinacalcet in 46 subjects with mild, moderate, and severe renal insufficiency was investigated. In the post-renal transplant (PRT) setting, 57 subjects received cinacalcet during Phase 3.
Patients with cardiovascular impairment	The clinical development program included 1938 subjects with baseline cardiovascular history.
Immunocompromised patients	End-stage renal disease patients are generally considered immunocompromised.
Patients with relevant comorbidities (continued)	
Patients with a disease severity different from inclusion criteria in clinical trials	Patients with a broad severity of disease were enrolled in cinacalcet clinical studies.
Population with relevant different ethnic origin	In SHPT studies, 61% of the 6040 subjects with SHPT and CKD receiving dialysis were white, 26% of subjects were black, and 13% were of other ethnic origin. Seventy-five percent of the 415 subjects not receiving dialysis were white, 17% of subjects were black, and 9% of subjects were of other ethnic origin. Of the 140 subjects with primary HPT or parathyroid carcinoma who received cinacalcet during the clinical development program, most subjects were white (85%); 4% of subjects were black, and 11% were of other ethnic origin.

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of this table.

Table 11. Exposure of Special Populations Typically Under-represented in Clinical Trial Development Programs

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other Elderly	Geriatric patients were not underrepresented in cinacalcet clinical studies. In the phase 3 registrational SHPT clinical program, significant proportion of geriatric subjects were enrolled, with approximately one-fourth of subjects over 65 years of age and 9% of subjects over 75 years of age. Of the 29% (1767/6040) of subjects with SHPT and CKD receiving dialysis and 59% (243/415) of subjects with SHPT and CKD not receiving dialysis who have received cinacalcet in clinical studies were ≥ 65 years of age. Of the subjects with primary HPT or parathyroid carcinoma who received cinacalcet during the clinical development program, 38% (53/140) were ≥ 65 years of age.

Page 2 of 2

CKD = chronic kidney disease; ESRD = end-stage renal disease; FDA = Food and Drug Administration; HCl = hydrochloride; HPT = hyperparathyroidism; PRT = post-renal transplant; SHPT = secondary hyperparathyroidism

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data, and in part on observed drug utilization parameters. Worldwide unit sales are recorded monthly by country, and are converted to a monthly estimate of person count (when feasible) or person-time using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

SV.1.2 Exposure

Table 12. Estimated Number of Person-years of Exposure to Cinacalcet, by Region and Demographic Characteristics, in the Postmarketing Setting (Cumulative to 28 February 2020)

Demographic Characteristic	Cumulative Patient-years of Exposure					
	AU	CA	EUR	US	Other	Total
Overall	23 817	22 434	1 260 069	1 679 402	179 025	3 164 747
Sex						
Female	11 423	10 759	604 320	805 429	85 859	1 517 790
Male	12 395	11 675	655 749	873 973	93 166	1 646 957
Age						
< 18	27	25	1432	1908	203	3596
18 - 34	570	537	30 175	40 216	4287	75 786
35 - 49	3115	2934	164 804	219 649	23 415	413 918
50 - 64	9805	9236	518 751	691 385	73 702	1 302 879
65 - 74	5222	4918	276 253	368 186	39 249	693 827
≥ 75	5078	4783	268 654	358 058	38 169	674 742
Sex/age						
Female						
< 18	5	5	275	367	39	691
18 - 34	231	218	12 224	16 292	1737	30 702
35 - 49	1260	1187	66 682	88 872	9474	167 475
50 - 64	4471	4211	236 552	315 273	33 608	594 116
65 - 74	2517	2370	133 143	177 451	18 916	334 398
≥ 75	2938	2767	155 444	207 173	22 085	390 407
Male						
< 18	22	21	1156	1541	164	2904
18 - 34	339	320	17 951	23 924	2550	45 084
35 - 49	1855	1747	98 123	130 777	13 941	246 442
50 - 64	5334	5024	282 199	376 112	40 094	708 763
65 - 74	2705	2548	143 110	190 734	20 332	359 429
≥ 75	2140	2016	113 210	150 885	16 084	284 335

AU = Australia and New Zealand; CA = Canada; EUR = European Union, European Economic Area, and Switzerland; Other = emerging markets in Asia, Africa, Middle East, and Latin America where Amgen is the market authorization holder; US = United States

Note: Numbers may not add to the total due to rounding.

[a] Age and sex breakdowns are based on patient characteristics in MarketScan, a US health insurance claims database. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.

Table 13. Estimated Number of Patients Exposed to Cinacalcet, by Region and Demographic Characteristics, in the Postmarketing Setting. (Cumulative to 28 February 2020)

	Cumulative Patients Exposed					
Demographic Characteristic	AU	CA	EUR	US	Other	Total
Overall	34 815	30 382	1 778 531	1 638 192	691 608	4 173 527
Sex						
Female	16 697	14 571	852 971	785 665	331 690	2 001 593
Male	18 118	15 811	925 561	852 527	359 918	2 171 934
Age						
< 18	40	35	2021	1861	786	4742
18 - 34	834	728	42 590	39 230	16 562	99 943
35 - 49	4553	3974	232 614	214 259	90 455	545 856
50 - 64	14 333	12 508	732 195	674 419	284 725	1 718 179
65 - 74	7633	6661	389 918	359 151	151 625	914 988
≥ 75	7423	6478	379 193	349 272	147 455	889 820
Sex/age						
Female						
< 18	8	7	389	358	151	912
18 - 34	338	295	17 254	15 892	6709	40 488
35 - 49	1842	1608	94 118	86 692	36 599	220 859
50 - 64	6536	5704	333 883	307 537	129 835	783 494
65 - 74	3679	3210	187 926	173 097	73 078	440 989
≥ 75	4295	3748	219 402	202 089	85 318	514 852
Male						
< 18	32	28	1632	1503	635	3830
18 - 34	496	433	25 337	23 337	9852	59 455
35 - 49	2711	2366	138 496	127 568	53 856	324 997
50 - 64	7797	6804	398 312	366 882	154 889	934 685
65 - 74	3954	3451	201 993	186 054	78 548	473 999
≥ 75	3128	2730	159 791	147 182	62 137	374 968

AU = Australia and New Zealand; CA = Canada; EUR = European Union, European Economic Area, and Switzerland; Other = emerging markets in Asia, Africa, Middle East, and Latin America where Amgen is the market authorization holder; US = United States

Note: Numbers may not add to the total due to rounding.

[a] Age and sex breakdowns are based on patient characteristics in MarketScan, a US health insurance claims database. Applying these distributions to regions outside the United States requires strong assumptions that are not easily testable.

Postauthorization Use From Business Partners

Cumulatively through 28 February 2020, an estimated 759 431 patients have been treated with cinacalcet in Kyowa Kirin Co., Ltd (KKC) territories.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and Potential Risks

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, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 14. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns From the RMP		
Important Identified Risks		
Hypocalcemia	Hypocalcemia, previously classified as an important identified risk, is being revised to Hypocalcemia in the pediatric population in the list of safety concerns.	Cumulatively through the DLP (28 February 2020) of PSUR # 21, there were 3156 cases in the Amgen Global Safety Database (AGSD) with events of hypocalcemia of which 350 cases were from clinical trials (388 events/323 events serious) and 2806 cases were from postmarketing (3251 events/922 events serious). The majority of the hypocalcemia cases were reported in adults. Three of the 350 cases from clinical trials and 35 of the 2806 cases from postmarketing were reported in pediatric population. A cumulative review of these events of hypocalcemia did not identify either a new safety finding or a change in the characteristics of the risk. The important identified risk of Hypocalcemia in the adult population is being removed from the safety specification as the risk is well characterized, adequately managed through product labelling, and no additional risk characterization is planned. The risk is reclassified as not important and will continue to be monitored through routine pharmacovigilance activities. Additional pharmacovigilance activities are ongoing to further characterize hypocalcemia in pediatric population.

Page 1 of 3

Footnotes, including abbreviations, are defined on the last page of this table.

Table 14. New or Reclassification of Safety Concerns in the RMP

Removal of Safety Concerns From the RMP		
Important Identified Risks (continued)		
Convulsions/ seizures	Convulsions/seizures, previously classified as an important identified risk, is removed from the list of safety concerns.	Cumulatively through the DLP (28 February 2020) of PSUR # 21, there were 424 cases in the AGSD with events of Convulsions/Seizures of which 93 cases were from clinical trials (93 events/all events serious) and 331 cases were from postmarketing (334 events/322 events serious). A cumulative review of these events of Convulsions/Seizures did not identify either a new safety finding or a change in the characteristics of the risk. The important identified risk of convulsions/seizures is being removed from the safety specification as the risk is well characterized, adequately managed through product labelling, and no additional risk characterization is planned. The risk will continue to be monitored through routine pharmacovigilance activities.

Footnotes, including abbreviations, are defined on the last page of this table.

Table 14. New or Reclassification of Safety Concerns in the RMP

Removal of Safety Concerns From the RMP		
Important Identified Risks		
QT prolongation and ventricular arrythmias secondary to hypocalcemia	QT prolongation and ventricular arrythmias secondary to hypocalcemia, previously classified as an important identified risk, has been removed from the list of safety concerns.	Cumulatively through the DLP (28 February 2020) of PSUR #21, there were 585 cases in the AGSD with events of QT Prolongation and Ventricular Arrhythmias Secondary to Hypocalcemia of which 313 cases were from clinical trials (325 events/322 events serious) and 272 cases were from postmarketing (296 events/270 events serious). A cumulative review of these events of QT Prolongation and Ventricular Arrhythmias Secondary to Hypocalcemia did not identify either a new safety finding or a change in the characteristics of the risk. The important identified risk of QT prolongation and ventricular arrythmias secondary to hypocalcemia is being removed from the safety specification as the risk is well characterized, adequately managed through product labelling, and no additional risk characterization is planned. The risk will continue to be monitored through routine pharmacovigilance activities.
Modification of Safety Concerns in the RMP		
Important Identified Risks		
Hypocalcemia in the pediatric population	Hypocalcemia in the pediatric population, which was previously included under the safety concern hypocalcemia, is retained as important identified risk.	Hypocalcemia was previously included as an important identified risk for all age groups and indications. Hypocalcemia in adults has been well-characterized and is to be removed from the list of safety concerns. Hypocalcemia in the pediatric population is being retained as important identified risk as there are additional pharmacovigilance activities ongoing to further characterize this risk in this population.

PBRER = periodic benefit-risk evaluation report; RMP = risk management plan

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

Table 15. Important Identified Risk: Hypocalcemia in the Pediatric Population

Potential mechanisms	Normally, PTH helps to maintain ionised calcium levels by 3 distinct mechanisms, which include activation of bone resorption, stimulation of renal hydroxylation of vitamin D3, and increased renal reabsorption of calcium. The pharmacologic action of cinacalcet reduces PTH secretion by the parathyroid gland, with concomitant lowering of serum calcium concentrations.
Evidence source(s) and strength of evidence	Hypocalcemia in the pediatric population was identified as an important risk based on the pharmacologic action of cinacalcet in lowering serum calcium. This risk was identified in the 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.
Characterization of the risk	
Frequency	*Pediatric SHPT Population (Study 20070208)* The subject incidence of hypocalcemia during the double-blind phase was 22.73% in cinacalcet-treated subjects and 19.05% in placebo-treated subjects; the relative risk ratio was 1.19 (95% CI: 0.31, 4.42). The subject incidence of hypocalcemia during both the double-blind and open-label phases was 32.14% in cinacalcet-treated subjects. *Pediatric SHPT Population (Study 20130356)* The subject incidence of hypocalcemia in Study 20130356 was 28.00% in cinacalcet-treated subjects and 10.00% in standard of care-treated subjects; the relative risk ratio was 2.80 (95% CI: 0.81, 17.62).

Page 1 of 3

Footnotes, including abbreviations, are defined on the last page of this table.

Table 15. Important Identified Risk: Hypocalcemia in the Pediatric Population

Characterization of the risk (continued)	
Severity	In pediatric studies, the adverse events of hypocalcemia were mild to severe. Some life-threatening events were reported however there were no fatal events.
Reversibility	The management of hypocalcemia depends upon the severity of symptoms. In patients with acute symptomatic hypocalcemia, intravenous (IV) calcium gluconate is the preferred therapy, whereas milder degrees of hypocalcemia can be treated with oral calcium and vitamin D supplements. Generally, patients recover when their hypocalcemia is treated.
Long-term outcomes	Patients may be hospitalized for treatment and disability may occur. Improved outcomes are anticipated in patients who undergo consistent serum calcium monitoring.
Impact on quality of life	For severe symptomatic hypocalcemia, patients may be hospitalized for treatment. Potential manifestations of hypocalcemia may include paresthesias, myalgias, muscle cramping, and in severe cases, tetany, also convulsion, QT prolongation and ventricular arrhythmia.
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.
Preventability	The cinacalcet SmPC states that cinacalcet should only be initiated in pediatric patients with ESRD receiving dialysis if the corrected serum calcium level is in the upper range of, or above, the age-specified reference interval. It also states that since cinacalcet lowers serum calcium, patients should be monitored carefully during treatment for the occurrence of hypocalcemia. The SmPC notes that in the event of hypocalcemia in children, treatment with cinacalcet should be stopped and calcium supplements, calcium-containing phosphate binders and/or vitamin D sterols should be administered, as clinically indicated, in the event of hypocalcemia. Potential manifestations of hypocalcemia, including paresthesias, myalgias, cramping, tetany, convulsion, and QT prolongation and ventricular arrhythmia are described. The SmPC also contains information about the apparent increased risk of hypocalcemia in cinacalcet-treated patients with CKD not receiving dialysis as compared with cinacalcet-treated patients receiving dialysis, and specifies that cinacalcet is not indicated for patients with CKD not receiving dialysis.

Page 2 of 3

Footnotes, including abbreviations, are defined on the last page of this table.

Table 15. Important Identified Risk: Hypocalcemia in the Pediatric Population

Preventability (continued)	The SmPC instructs that the half-life of etelcalcetide should be taken into account when switching patients from etelcalcetide to cinacalcet. Caution should be given to ensure serum calcium levels are within the normal range before cinacalcet is initiated. The SmPC advises that patients receiving cinacalcet should not be given etelcalcetide and that cinacalcet should be administered with caution in patients receiving any other medicinal products known to lower serum calcium.
Impact on the risk-benefit balance of the product	The risk of hypocalcemia has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. Routine risk minimization measures for hypocalcemia and adverse events secondary to hypocalcemia is considered appropriate.
Public health impact	Cinacalcet is indicated only in a specific and limited population. In addition, there are guidelines in the SmPC for monitoring and treating hypocalcemia. As a result the overall impact on public health is considered to be low.

Page 3 of 3

CKD = chronic kidney disease; ESRD = end-stage renal disease; HR = hazard ratio; HPT = hyperparathyroidism; IV = intravenous(ly); MedDRA = Medical Dictionary for Regulatory Activities; n = number of patients; PASS = post-authorization safety study; PTH = parathyroid hormone; SHPT = secondary hyperparathyroidism; SmPC = summary of product characteristics

Table 16. Important Potential Risk: Medication Errors With Cinacalcet Granules in Capsules for Pediatric Use

Potential mechanisms	Accidental mix-ups between different granules in capsule strengths and preparation and administration errors may occur.
Evidence source(s) and strength of evidence	Data to evaluate the risk for medication error with cinacalcet 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.
Characterization of the risk	
Frequency	Pediatric SHPT Population (Study 20070208): The subject incidence of medication errors during the double-blind phase was 4.55% in cinacalcet-treated subjects and 0.0% in placebo-treated subjects. The subject incidence of medication errors during both the double-blind and open-label phases was 3.57% in cinacalcet-treated subjects. Pediatric SHPT Population (Study 20130356): The subject incidence of medication errors during the double-blind phase was 4.00% in cinacalcet-treated subjects and 0.0% in standard of care-treated subjects.
Severity	Two medication errors (one mild, one moderate in severity) were reported in a pediatric clinical trial (Study 20070208).
Reversibility	A consequence of the potential medication error of overdose would be hypocalcemia which would generally be reversible if identified and treated. In the event of hypocalcemia, adequate calcium supplementation and treatment of hypocalcemia complications are required.
Long-term outcomes	Long term outcomes would depend on the clinical consequences or the actual error. In case of underdose, cinacalcet may not be effective. In case of overdose, hypocalcemia may occur. For severe symptomatic hypocalcemia, patients may be hospitalized for treatment of hypocalcemia and disability may occur. Improved outcomes are anticipated in patients who undergo consistent serum calcium monitoring.
Impact on quality of life	In the event of a medication error leading to overdose, potential manifestations of hypocalcemia may include paresthesias, myalgias, muscle cramping, and in severe cases, tetany, also convulsion, QT prolongation and ventricular arrhythmia.

Page 1 of 2

Footnotes, including abbreviations, are defined on the last page of this table.

Table 16. Important Potential Risk: Medication Errors With Cinacalcet Granules in Capsules for Pediatric Use

Risk groups or risk factors	Pediatric patients who require doses lower than 30 mg, or who are unable to swallow tablets.
Preventability	To prevent this potential risk the capsules are color-coded and detailed instruction for use is described in the SmPC.
Impact on the risk-benefit balance of the product	The risk of medication errors with cinacalcet granules in capsules for pediatric use has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive.
Public health impact	Cinacalcet is indicated only in a specific and limited population. Different capsule strengths have different colors and this is described in the SmPC. In addition, the SmPC has guidelines for monitoring serum calcium. As a result the overall impact on public health is considered to be low.

Page 2 of 2

n = number of patients; SHPT = secondary hyperparathyroidism;
SmPC = summary of product characteristics

SVII.3.2 Presentation of the Missing Information

Table 17. Missing Information: Pregnant or Breastfeeding Women

Evidence source	In pregnant rats, there were slight decreases in body weight and food consumption at the highest dose. Decreased fetal weights were seen in rats at doses where dams had severe hypocalcemia. Cinacalcet has been shown to cross the placental barrier in rabbits. Cinacalcet is excreted in the milk of lactating rats with a high milk-to-plasma ratio. It is not known whether cinacalcet is excreted in human milk.
Population in need of further characterization	No cinacalcet exposure for pregnant women was planned in the clinical program. A small number of pregnancies have been reported in clinical trials and from postmarketing sources. These limited data are insufficient to draw conclusions about safety in pregnancy for cinacalcet. No cases of lactation have been reported in clinical trials and only limited data is available from postmarketing sources. These limited datasets are insufficient to draw conclusions about safety in breastfeeding women.

Part II: Module SVIII - Summary of the Safety Concerns

Table 18. Summary of Safety Concerns

Important identified risks	Hypocalcemia in the Pediatric Population
Important potential risks	Medication errors with cinacalcet granules in capsules for pediatric use
Missing information	Pregnant or breastfeeding women

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 19.

Table 19. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Hypocalcemia	Hypocalcemia in the Pediatric Population	To further characterize the incidence, severity, seriousness, possible risk factors, and outcome of this risk.

III.2 Additional Pharmacovigilance Activities

Table 20. Category 1 to 3 Postauthorization Safety Studies

Study Title and Category Number	Rationale and Study Objectives	Study Design	Study Population	Milestones
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) Category 3	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	Registry study	Pediatric patients	Start of data collection Q4 2018 Final study results Q4 2024

Ca = calcium; IPDN = International Pediatric Dialysis Network; P = phosphorus; PTH = parathyroid hormone; Q4 = 4th quarter

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned cinacalcet category 1 and category 2 studies.

Table 21. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
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) Category 3	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	Hypocalcemia in the pediatric population	Protocol Final report	18 July 2018 Q4 2024

Ca = calcium; IPDN = International Pediatric Dialysis Network; P = phosphorus; PTH = parathyroid hormone

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 22. Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Hypocalcemia in the Pediatric Population	*Routine risk communication:* 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
Safety Concern	**Routine Risk Minimization Activities**
Medication Errors With Cinacalcet Granules in Capsules For Pediatric Use	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
Pregnant or Breastfeeding Women	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

V.2 Additional Risk Minimization Measures

Routine risk minimization measures as described in Part V.1 are sufficient to manage the safety concerns of cinacalcet.

V.3 Summary of Risk Minimization Measures

Table 23. Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hypocalcemia in the Pediatric Population	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	Hypocalcemia event questionnaire for postmarketing reports Registry study in pediatric patients
Medication Errors With Cinacalcet Granules in Capsules For Pediatric Use	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	None
Pregnant or Breastfeeding Women	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	None

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 in the Pediatric Population
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 in the Pediatric Population	
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 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
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

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

Follow-up Form Title	Version Number	Date of Follow-up Version
Hypocalcemia Event Questionnaire	1.0	September 2012

DATE:_____ HYPOCALCEMIA EVENT- CINACALCET AMGEN AER#_____

INSTRUCTIONS:
Complete this form with information specific to Hypocalcemia.
Postmarket Adverse Event (PMAE) Form – complete Sections 1-4.
ONLY if additional adverse events are being reported, PMAE Form - complete Sections 5-11.

CINACALCET INFORMATION (including dosing changes/titration)				**INDICATION (check all that apply)**
Dose	Route	Frequency	Start Date	Stop Date	☐ SHPT on dialysis ☐ PHPT ☐ Other (please specify):

HYPOCALCEMIA ADVERSE EVENT INFORMATION

ONSET DATE	**RESOLVED DATE**	**HOSPITALIZATION**		**ACTION TAKEN** 1=None 2=Dose Reduced 3=Dose Increased 4=Drug Withdrawn 5=Drug Rechallenge	**OUTCOME** 1=Resolved 2=Resolved w/ sequelae 3=Resolving 4=Event ongoing 5=Died of event	**RELATIONSHIP TO PRODUCT** *Is there a reasonable possibility that this event may have been caused by cinacalcet?*	
		ADMIT DATE	**DISCHARGE DATE**			**YES**	**NO**
DD|MM|YYYY	**DD|MM|YYYY**	**DD|MM|YYYY**	**DD|MM|YYYY**				

HYPOCALCEMIA SIGNS AND SYMPTOMS (CHECK ALL THAT APPLY)

☐ Arrhythmia
Date (DD|MM|YYYY): Specify type: QTc interval (msec):

Baseline EKG findings prior to hypocalcemia related arrhythmia (including DD|MM|YYYY):

If abnormal, please specify / include QTc values:

☐ Convulsion (include type):	☐ Hypotension (include BP):	☐ Paraesthesia (specify locations):	☐ Other:

☐ Heart Failure	☐ Laryngospasm	☐ Syncope	☐ Muscle cramping	☐ Muscle twitching	☐ Tetany

CHEMISTRY VALUES

At Time of Hypocalcemia Event:

Lab	**Value**	**Units**	**Date**	**Unknown**
Serum Calcium (*circle:* Corrected | Ionized | Total)				
Phosphorous				
Magnesium				
Potassium				
Serum Creatinine				
Albumin				
Serum Bicarbonate				
pH				

Most Recent Serum Calcium and Albumin Prior to Hypocalcemia Event:

Lab	**Value**	**Units**	**Date**	**Unknown**
Serum Calcium (*circle:* Corrected | Ionized | Total)				
Albumin				

Risk factors (check all that apply):

☐ History of Hypoparathyroidism	☐ Hyperphosphatemia	☐ Magnesium deficiency/ hypomagnesemia	Other:
☐ History of Chronic renal failure	☐ Vitamin D deficiency	☐ Sepsis	Recent surgery (specify):
☐ History of Malignancy	☐ Hypoproteinemia	☐ Acute Pancreatitis	

DATE:_____ HYPOCALCEMIA EVENT- CINACALCET AMGEN AER#_____

Was patient on any of these medications at time of hypocalcemia event?			Start Date	Stop Date	Is this a Suspect Drug?	
Type	Brand / Generic Name	Dose/Units	DD|MM|YYYY	DD|MM|YYYY	Yes	No
Nutritional Vitamin D supplement						
Active Vitamin D supplement						
Calcium supplement						
Calcium containing phosphate binder						
Citrate containing anticoagulation						
Blood transfusions						

Did patient receive any other drugs or treatments which are known to cause hypocalcemia? Yes / No			Start Date	Stop Date	Is this a Suspect Drug?	
Brand / Generic Name	Dose/Units	Route	DD|MM|YYYY	DD|MM|YYYY	Yes	No

TREATMENT FOR HYPOCALCEMIA (ie: ICU admission, dialysis)

TREATMENT MEDICATION FOR HYPOCALCEMIA (ie: calcium, dialysate calcium, anti-arrhythmic medications, anticonvulsants)				Start Date	Stop Date
Brand / Generic Name	Dose / Units	Route	Frequency	DD|MM|YYYY	DD|MM|YYYY

OTHER SYMPTOMATIC TREATMENT

ADDITIONAL INFORMATION:

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable