European Medicines Agency

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ASSESSMENT REPORT
FOR
MIMPARA

International Nonproprietary Name:
Cinacalcet

Procedure No. EMEA/H/C/000570/II/0010

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

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1. Introduction

Parathyroid hormone (PTH) maintains normal serum calcium levels by mobilising calcium from bone, by reabsorption of calcium from the renal tubular fluid and by increased gastrointestinal absorption of calcium through stimulation of renal production of 1,25-dihydroxy vitamin D.

Cinacalcet (Mimpara) is a calcimimetic, i. e. it belongs to a class of small organic synthetic molecules that act as allosteric modulators of the calcium receptor (CaR) on the cell surface of the parathyroid gland cells. Calcimimetics can regulate PTH secretion by amplifying the receptor sensitivity to extracellular calcium and thereby reducing PTH, resulting in a decrease in serum calcium levels.

The CaR is activated by elevated calcium concentrations and this activation signals inhibition of PTH secretion. Decreased serum calcium inhibits CaR, thereby stimulating PTH secretion.

Worldwide, cinacalcet is approved in 36 countries, including the US and the EU, for the treatment of secondary hyperparathyroidism (HPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis and for the treatment of hypercalcaemia in patients with parathyroid carcinoma.

When cinacalcet was approved within the EU in 2004, the CHMP considered the indication for use in patients with parathyroid carcinoma to be approvable while the proposed indication "patients with intractable primary HPT for whom parathyroidectomy is not a treatment option" was not considered to be sufficiently well defined to support approval based on the limited data submitted in support of this indication. At the time of the initial application for cinacalcet, study 20000204 included results from 10 subjects with parathyroid carcinoma and 5 subjects with intractable primary HPT.

In 2005 the MAH submitted the interim results from study 20000204 and in May 2006 the final results from this study. The CHMP concluded that the assessment of these data showed that: "*The treatment is clearly of benefit for patients with parathyroid carcinoma even though the interindividual variability seems to be rather large. Also patients with intractable primary HPT have a benefit of cinacalcet treatment. The patients are still rather few, but the results are clearly positive*."

The MAH now therefore submits final data from the 20000204 study plus additional supportive data from the four other completed clinical studies in patients with mild to moderate primary HPT.

The aim of the variation is to introduce a new indication, "*primary HPT in patients with 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*". Some subsequent changes of sections 4.2, 4.8 and 5.1 are also suggested, plus a major revision of the PL.

The MAH has submitted an updated Pharmacovigilance System and a new Risk Management Plan (version 1.0).

2. Clinical aspects

Rationale for the proposed change

Parathyroidectomy is the only curative treatment for primary HPT and is very successful in experienced hands. Serum PTH as well as serum and urinary calcium are normalised after successful parathyroidectomy, bone mineral density (BMD) is normalised, the risk of fracture and of kidney stone formation is reduced as is the risk of cardiovascular disease; in addition the quality of life (QoL) as well as survival is improved.

Parathyroidectomy is recommended for patients with symptomatic HPT. In the US, the NIH in 2002 published a workshop on symptomatic primary HPT, with guidelines for criteria for surgery in these

asymptomatic patients. According to these guidelines, patients who have symptoms of primary HPT (history of kidney stones) or meet one or more of the following criteria should undergo surgery:

- serum calcium > 1 mg/dl above the upper limit of normal (ULN)
- 24-hour urine calcium excretion > 400 mg
- 30 % reduction in creatinine clearance compared with age-matched controls
- BMD T-score < -2.5 at the lumbar spine, hip or distal 1/3 radius
- age < 50 years

No approved medical therapy for primary HPT exists in the EU.

Clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

3. Clinical efficacy

Main studies

Three randomised double-blind placebo-controlled studies were performed on patients with primary HPT plus one open label extension study for these studies plus one open-label pivotal study in patients with parathyroid cancer or intractable primary HPT (see table 1).

Table 1. Overview of cinacalcet studies for the treatment of primary HPT

Study Number/ Type	Key Entry Criteria	No. of Subjects Enrolled/Treatment	Geographic Region	Duration of Cinacalcet Exposure
980125 Randomized, double-blind, placebo-controlled, dose-ranging	Primary HPT: iPTH ≥ 45 pg/mL, serum calcium > 10.3 mg/dL and ≤ 12.5 mg/dL	48 total[a] 39/cinacalcet (50, 75, 100 mg QD; 30, 40, 50 mg BID) 9/placebo	US	QD phase, 6 weeks BID phase, 15 days
990160 Randomized, double-blind, placebo-controlled, fixed-dose	Primary HPT: iPTH > 45 pg/mL, serum calcium ≥ 11.0 mg/dL	10 total 6/cinacalcet (65 mg BID) 4/placebo	US	4 weeks (treatment) 1 week (follow up)
990120 Randomized, double-blind, placebo-controlled, dose titration	Primary HPT: iPTH > 45 pg/mL, serum calcium > 10.3 mg/dL and ≤ 12.5 mg/dL	78 total[b] 40/cinacalcet (30 mg BID with dose titration to 40 and 50 mg BID) 38/placebo	US	12 weeks (titration) 12 weeks (maintenance) 28 weeks (follow up)
20000159 Open-label, single-arm, dose-titration extension	Patients with primary HPT who completed protocol-specified treatment and end-of-study assessments from Study 990120	45[c]/cinacalcet (30 mg BID with dose titration to 50 or 60 mg BID; could dose reduce to 30 mg QD[d])	US	12 weeks (titration) 4.5 years (maintenance)
20000204 Open-label, single-arm, dose-titration	Parathyroid carcinoma or intractable primary HPT with serum calcium > 12.5 mg/dL	46[e]/cinacalcet (30 mg BID to 90 mg QID)	US/Canada/ Europe	2 to 16 weeks (titration) 3 years (maintenance)

QD: once daily; BID: twice daily; iPTH: intact parathyroid hormone

[a] Forty subjects (32 cinacalcet, 8 placebo) were enrolled in the QD phase of this study. Twenty-two subjects (16 cinacalcet, 6 placebo) were enrolled in the BID phase of this study. Eight subjects (7 cinacalcet, 1 placebo) in the BID phase had not participated in the QD phase.

[b] Twenty-two subjects who enrolled in Study 990120 had previously participated in Study 980125.

[c] All subjects had participated in Study 990120 before enrolling in Study 20000159.

[d] Before July 2004, subjects titrated from 30 mg BID to 50 mg BID. After July 2004, because of a change in dose strengths, subjects instead titrated from 30 mg BID to 60 mg BID. Ongoing subjects receiving 50 mg BID were switched at that time to 60 mg BID. Subjects receiving 30 mg BID had the option to reduce to 30 mg QD, if necessary.

[e] Twenty-nine subjects with parathyroid carcinoma and 17 subjects with intractable primary HPT participated in Study 20000204.

Studies 980125, 990120 and 990160 included patients with primary HPT defined on the basis of both PTH and calcium concentrations. Studies 990120 and 990160 requested patients to have an iPTH concentration > 45 pg/ml and study 98 0125 had iPTH ≥ 45 pg/ml as an inclusion criterion. For studies 990120 and 980125, serum calcium concentration had to be > 10.3 and ≤ 12.5 mg/dl while in study 990160 it was to be ≥ 11 mg/dL. Study 20000159 enrolled patients who had completed the protocol-specific treatment for the parent cinacalcet study 990120. Study 20000204 included subjects with more severe disease, parathyroid carcinoma or intractable primary HPT, with serum calcium concentration > 12.5 mg/dL. This study was an open study as placebo was not considered ethical for this group of severely ill patients; the study had no inclusion criteria related to iPTH.

Methods

Table 2. International System of Units/Traditional Units Conversion Table for Serum Calcium and Serum Phosphorus

iPTH		Serum Calcium		Serum Phosphorus	
pg/mL	pmol/L	mg/dL	mmol/L	mg/dL	mmol/L
100	10.6	7	1.75	2.4	0.77
150	15.9	7.2	1.8	2.6	0.84
200	21.2	7.4	1.85	2.8	0.90
250	26.5	7.6	1.9	3	0.97
300	31.8	7.8	1.95	3.2	1.03
350	37.1	8	2	3.4	1.10
400	42.4	8.2	2.05	3.6	1.16
450	47.7	8.4	2.1	3.8	1.23
500	53	8.6	2.15	4	1.29
550	58.3	8.8	2.2	4.2	1.36
600	63.6	9	2.25	4.4	1.42
650	68.9	9.2	2.3	4.6	1.49
700	74.2	9.4	2.35	4.8	1.55
750	79.5	9.6	2.4	5	1.61
800	84.8	9.8	2.45	5.2	1.68
850	90.1	10	2.5	5.4	1.74
900	95.4	10.2	2.55	5.6	1.81
950	100.7	10.4	2.6	5.8	1.87
1000	106	10.6	2.65	6	1.94
1050	111.3	10.8	2.7	6.2	2.00
1100	116.6	11	2.75	6.4	2.07

Endpoints of the main studies

All five studies on primary HPT assessed the absolute values and percentage changes in calcium and iPTH concentrations over time. The primary endpoint of study 990120 was the proportion of subjects with a mean serum calcium concentration ≤ 10.3 mg/dl and a mean decrease in serum calcium of at least 0.5 mg/dl during the maintenance phase. In study 20000204, the primary endpoint was the proportion of subjects with a ≥ 1 mg/dl reduction in serum calcium from baseline to the end of titration phase.

Study 20000204

This study enrolled the first patient in April 2001 and the last patient was discontinued in September 2005. The study was a multicentre, open-label, single-arm, dose-titration study consisting of three parts: a 30-day screening period, a variable-length titration phase of two to sixteen seeks and a maintenance phase. During the titration phase, assessments of serum calcium took place at weekly visits. The initial cinacalcet dose was 30 mg twice daily (BID) and then titration was done every 2 weeks to a maximum dose of 90 mg four times daily (QID). Dose escalation was halted when the subject reached a serum calcium concentration of 10 mg/dl or the subject reached the maximum study dose or an adverse event (AE) precluded further dose escalation. Dose adjustments were permitted during the maintenance phase according to the same procedures as during the titration phase. For key inclusion criteria, see table 1. For ethical reasons, no placebo group was included in this study.

Patients

Study centres in the US (15), France (3), Italy (3), Canada (1), Spain (1) and Switzerland (1) recruited a total of 46 patients in the study, 29 (63 %) with parathyroid carcinoma and 17 (63 %) with intractable primary HPT.

Objectives of study 20000204

The primary objective was to assess the ability of cinacalcet to reduce serum calcium concentrations, recorded as the proportion of subjects with a ≥ 1 mg/dl reduction in serum calcium from baseline to the end of titration phase.

Secondary objectives were:

- To assess the effect of cinacalcet on plasma iPTH concentration
- To assess the effect of cinacalcet on the bone turnover markers serum N-telopeptide (Ntx) and bone-specific alkaline phosphatase (BALP)
- To assess the long-term safety of cinacalcet in this population
- To assess the pharmacokinetics (PK) of cinacalcet in this population
- To assess the effect of cinacalcet on patient reported outcome (PRO) domains

Statistics

Descriptive statistics were used to summarize safety and efficacy data.

Subject disposition

Table 3. Discontinuations from study 20000204

	Cinacalcet		
	Parathyroid Carcinoma n (%)	Intractable pHPT n (%)	Total n (%)
Subjects enrolled	29 (100)	17 (100)	46 (100)
Subjects who completed study	6 (21)	9 (53)	15 (33)
Subjects who are on-going	0 (0)	0 (0)	0 (0)
Subjects who discontinued study	23 (79)	8 (47)	31 (67)
Subjects who discontinued study during titration phase[a]	10 (34)	3 (18)	13 (28)
Protocol deviation	1 (3)	0 (0)	1 (2)
Noncompliance	2 (7)	0 (0)	2 (4)
Adverse event	4 (14)	1 (6)	5 (11)
Consent withdrawn	1 (3)	0 (0)	1 (2)
Administrative decision	1 (3)	0 (0)	1 (2)
Lost to follow-up	0 (0)	1 (6)	1 (2)
Death	1 (3)	1 (6)	2 (4)
Subjects who discontinued study during maintenance phase	13 (45)	5 (29)	18 (39)
Noncompliance	1 (3)	0 (0)	1 (2)
Adverse event	1 (3)	3 (18)	4 (9)
Consent withdrawn	2 (7)	1 (6)	3 (7)
Administrative decision	2 (7)	0 (0)	2 (4)
Lost to follow-up	3 (10)	1 (6)	4 (9)
Death	4 (14)	0 (0)	4 (9)

a Includes one patient who discontinued after the titration phase, prior to the maintenance phase

Only 3 patients in this study were identified by the investigator as having contraindications to surgery.

Discontinuation rate was high, especially among patients with parathyroid carcinoma which could partly be explained by the mortality rate in this group of severely ill patients.

Baseline characteristics

Table 4. Baseline demographics, study 20000204

	Cinacalcet		
	Parathyroid Carcinoma (N=29)	Intractable pHPT (N=17)	Total (N=46)
Sex - n(%)			
Male	15 (52)	8 (47)	23 (50)
Female	14 (48)	9 (53)	23 (50)
Race - n(%)			
White	28 (97)	16 (94)	44 (96)
Black	1 (3)	1 (6)	2 (4)
Age - years			
n	29	17	46
Mean	51.0	65.7	56.4
SD	14.4	9.0	14.5
SE	2.7	2.2	2.1
Median	50.0	65.0	58.0
Q1, Q3	41.0, 59.0	59.0, 71.0	49.0, 68.0
Min, Max	24.0, 79.0	52.0, 88.0	24.0, 88.0
Age Category - n(%)			
18 to 29 years	3 (10)	0 (0)	3 (7)
30 to 39 years	4 (14)	0 (0)	4 (9)
40 to 49 years	5 (17)	0 (0)	5 (11)
50 to 59 years	10 (34)	6 (35)	16 (35)
60 to 64 years	2 (7)	2 (12)	4 (9)
65 to 74 years	3 (10)	7 (41)	10 (22)
75 years or more	2 (7)	2 (12)	4 (9)
Geriatric Age Group - n(%)			
≥ 65	5 (17)	9 (53)	14 (30)
≥ 75	2 (7)	2 (12)	4 (9)

No children or adolescents were included in the study. Patients with parathyroid carcinoma were much younger than those with primary intractable HPT, mean age 51 vs. 66 years.

Table 5. Selected baseline laboratory values, study 20000204

	Cinacalcet		
	Parathyroid Carcinoma (N=29)	Intractable pHPT (N=17)	Total (N=46)
Serum calcium (mg/dL)			
n	29	17	46
Mean	14.13	12.72	13.61
SD	2.31	0.75	2.00
Median	13.90	12.50	13.30
Q1, Q3	13.30, 14.60	12.30, 13.00	12.50, 14.10
Min, Max	8.6, 20.2	11.8, 14.5	8.6, 20.2
iPTH (pg/mL)			
n	28	16	44
Mean	697.29	243.38	532.23
SD	496.98	105.08	455.76
Median	491.00	266.50	365.00
Q1, Q3	365.00, 947.50	135.50, 300.50	242.50, 713.00
Min, Max	133.0, 2106.0	100.0, 499.0	100.0, 2106.0
Serum phosphorus (mg/dL)			
n	28	17	45
Mean	2.44	2.18	2.34
SD	0.71	0.39	0.62
Median	2.40	2.30	2.30
Q1, Q3	1.95, 2.85	2.00, 2.40	2.00, 2.60
Min, Max	1.1, 4.0	1.3, 2.9	1.1, 4.0
BALP (ng/mL)			
n	29	16	45
Mean	72.61	60.40	68.27
SD	110.80	110.66	109.64
Median	37.00	18.50	25.00
Q1, Q3	17.00, 71.00	11.50, 27.00	15.00, 65.00
Min, Max	7.1, 588.0	9.4, 388.0	7.1, 588.0
NTx (nM)			
n	29	17	46
Mean	110.31	78.76	98.65
SD	143.94	158.58	148.56
Median	50.00	25.00	31.00
Q1, Q3	23.00, 120.00	15.00, 31.00	15.00, 116.00
Min, Max	8.0, 560.0	8.3, 620.0	8.0, 620.0

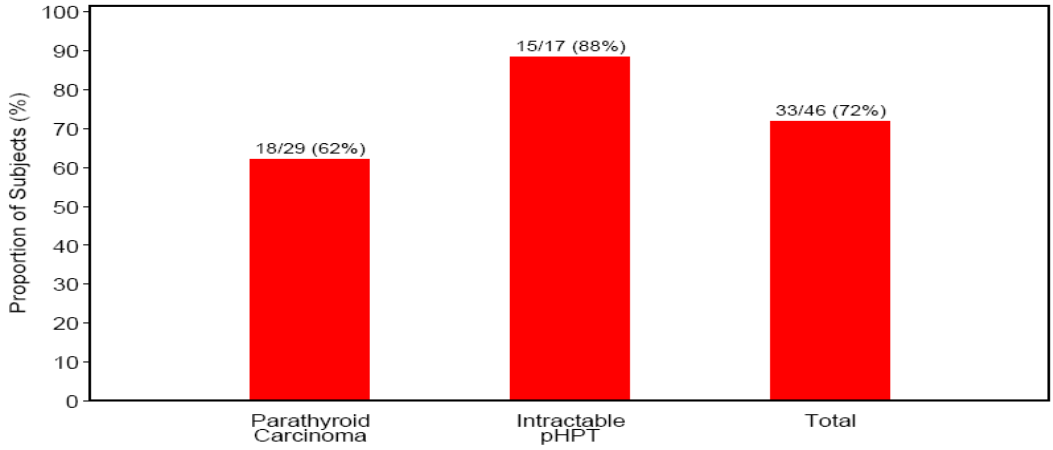
Serum calcium levels, plasma iPTH, serum phosphorus, BALP and NTx at baseline were higher in patients with parathyroid carcinoma than in those with intractable primary HPT. Standard deviations were great.

Efficacy results

Efficacy data are given for the intent-to-treat population. No extrapolation of missing values was used for the maintenance phase.

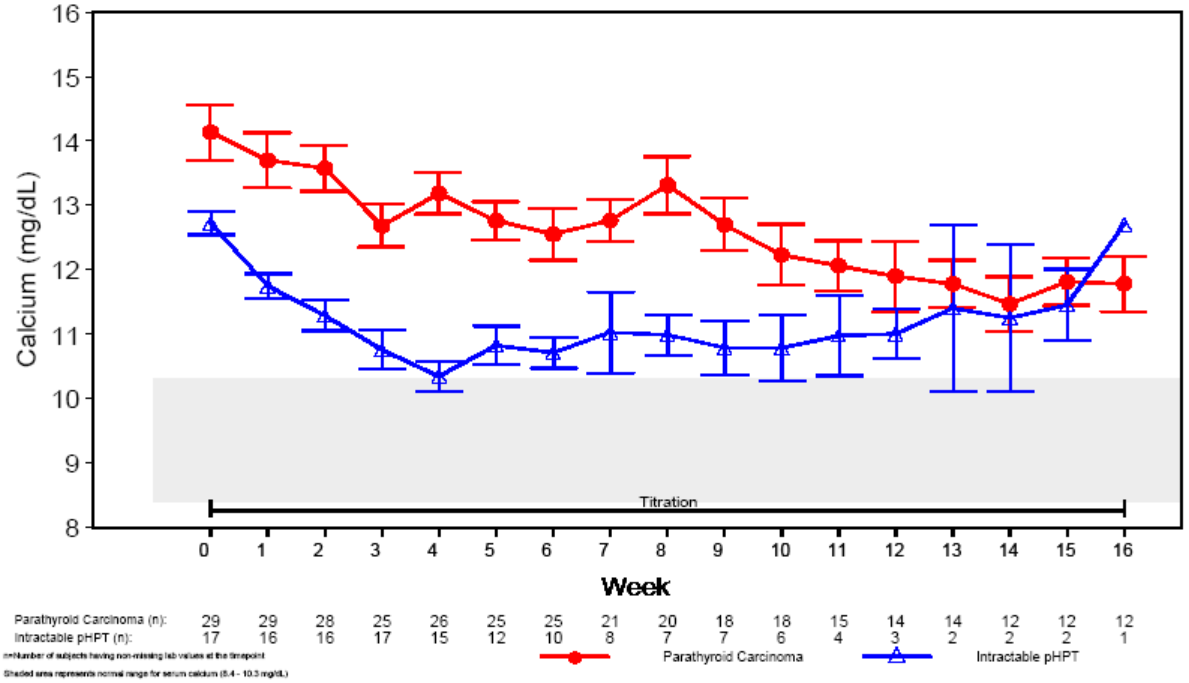
The greatest reductions in serum calcium levels were noted in patients with the highest baseline calcium concentrations (in subjects with parathyroid carcinoma).

Figure 1. Proportion of subjects with serum calcium reduction ≥ 1 mg/dl at the end of titration phase



The proportion of subjects with serum calcium reduced by ≥ 1 mg/dl remained relatively stable through the maintenance phase, ranging from 60 % to 86 % for subjects with parathyroid carcinoma and from 67 to 83 % for subjects with intractable primary HPT.

Figure 2. Mean serum calcium concentrations at each scheduled visit during the titration phase (Standard Error = SE)



Study patients achieved modest but significant reductions of their serum calcium levels. Patients with intractable primary HPT had a faster reduction of their serum calcium levels during the titration phase than patients with parathyroid cancer. Both patient categories remained relatively stable during the maintenance phase. Interindividual variations were great, especially among patients with intractable primary HPT.

Plasma iPTH concentrations at baseline were highly variable and no consistent changes in predose plasma iPTH concentrations were seen during the titration phase. Plasma iPTH concentrations at baseline and at the end of the titration phase were 697 (SE 93.9) pg/ml and 593 (SE 67.7) pg/ml respectively, for patients with parathyroid carcinoma. The mean change from baseline was -6.1 % (SE 7.27 %). Subjects with intractable primary HPT had mean plasma iPTH concentrations at baseline and the end of the titration phase of 243 (SE 26.3) pg/ml and 396 (SE 158.2) pg/ml, respectively, and for these patients, the mean change from baseline was -2.5 % (SE 13.65 %). The mean plasma iPTH concentrations during the maintenance phase were similar to those observed at the end of the titration phase.

Serum NTx was generally increased or constant over the titration phase. Mean (SE) serum NTx at baseline and at the end of the titration phase were 110.3 (26.7) nM and 142.9 (37.8) nM, respectively, for patients with parathyroid carcinoma. For subjects with intractable primary HPT, mean (SE) serum NTx concentrations at baseline and at the end of the titration phase were 78.8 (38.5) nM and 168.1 (118.9) nM, respectively. During the maintenance phase, mean serum NTx concentrations did not change notably from the end of the titration phase in subjects with parathyroid carcinoma but decreased among subjects with intractable primary HPT.

Serum BALP concentrations generally increased or remained constant over the titration phase. For subjects with parathyroid carcinoma, mean (SE) serum BALP concentrations at baseline and the end of the titration phase were 72.6 (20.6) ng/mL and 114.2 (28.9) ng/ml, respectively. For subjects with intractable primary HPT, mean (SE) serum BALP concentrations at baseline and the end of the titration phase were 60.4 (27.7) ng/ml and 82.2 (37.0) ng/ml, respectively. During the maintenance phase, mean serum BALP concentrations did not change notably from the end of the titration phase in subjects with parathyroid carcinoma but decreased among subjects with intractable primary HPT.

PK assessments: The limited exposure data obtained in this study was consistent with the previously obtained PK profile of cinacalcet. Across subjects, cinacalcet concentrations appeared to increase with increasing dose. As expected, the frequent dosing utilized in this study resulted in low peak-to trough fluctuation and notable accumulation of cinacalcet. At the end of the titration phase, iPTH concentrations at both 2 and 4 hours postdose were lower than the predose concentration, suggesting that cinacalcet can elicit a transient reduction in iPTH in these populations. Although serum calcium levels decreased from day 1 to the end of the titration phase, calcium levels remained relatively constant over the 4 hour sampling period on both sampling days.

Quality of life: At baseline, the patients with parathyroid carcinoma or intractable primary HPT had relatively poor functional status, 1 SD below the mean for a US population on the SF-36 QoL scale. The Physical Component Summary score was more than 1 SD below the general population mean in both populations. The Mental Component Summary score was more than 1 SD below the general population mean only for the patient group with intractable primary HPT. Most scales showed minimal improvement at the end of titration phase for subjects with parathyroid carcinoma. Of the 15 subjects with evaluable data in this group, 27 to 67 % had an improvement at the end of titration, depending on the scale. Among subjects with intractable primary HPT, all mean scale scores improved from baseline. Of the 15 subjects in this group, 33 to 80 % had an improvement at the end of titration, depending on scale.

Results for bone turnover markers were insignificant as these were PK results. There was a positive trend for QoL parameters, especially for patients with intractable primary PTH. However, study 20000204 did not have a control group and in addition, a large number of post-baseline QoL assessments were incomplete which makes definitive evaluation of QoL data from this study impossible.

Analysis performed across trials

Integrated analyses of data from studies 980125, 990120, 990160 and 10000159 were performed to provide support for the efficacy of cinacalcet in the now proposed additional indication, analysing the ability of cinacalcet to decrease elevated serum calcium and iPTH concentrations in the following categories of subjects:

• Patients with persistent or recurrent primary HPT after parathyroidectomy, “failed parathyroidectomy” = category 1

• Patients who met at least one criterion (according to the NIH criteria) for consideration of surgical intervention but had not undergone a parathyroidectomy, “indicated for parathyroidectomy” = category 2

• All other study participants = category 3

About 46 % of the subjects in these 4 studies fulfilled at least one criterion for consideration of surgical intervention but had not undergone parathyroidectomy. It should be noted that data on medical contraindications to surgery were not collected in 3 of these 4 studies.

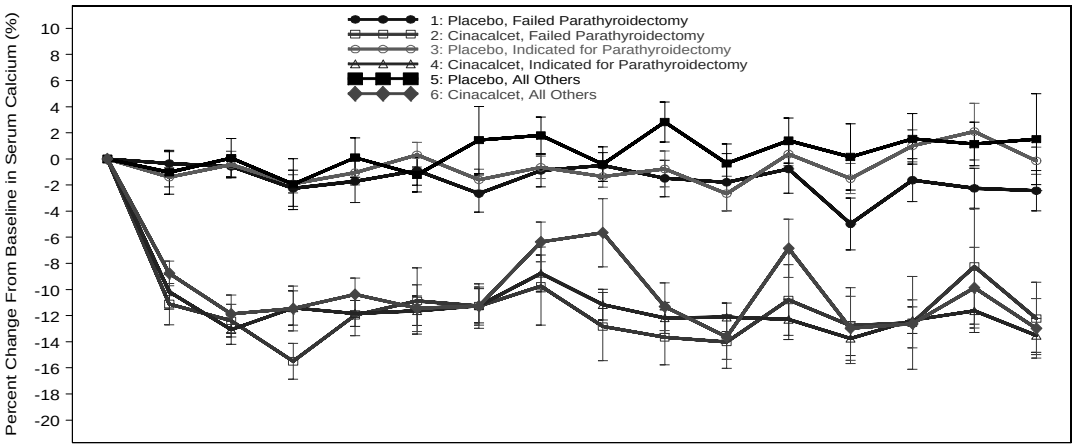
Although the primary and secondary endpoints of these studies varied, the studies all assessed the absolute values and percentage changes in calcium and iPTH concentrations over time. Most studies also assessed the proportion of subjects who reduced their serum calcium to within normal limits.
Statistics: Descriptive statistics was used for the studies on primary HPT. In studies 980125 and 990120, hypothesis testing was also performed.

Efficacy results of each of the studies in the broader primary HPT population are presented as representative of the effects of cinacalcet in the narrower population included in the proposed new indication. Two sets of integrated analyses were performed. The first set assessed efficacy over 6 months, using all data from studies 980125 and 990160 plus data from the 12-week titration and 12-week maintenance phases of study 990120. The other set assessed efficacy over 5.75 years, using all data from studies 990120 and 20000159.

For each integrated dataset, absolute concentrations and percentage changes from baseline over time were summarized for serum calcium and plasma iPTH concentrations. The proportion of subjects having a decrease in serum calcium concentration to within the normal range (8.4 – 10.3 mg/dl) at each study visit and the proportion of subjects having a ≥1 mg/dl reduction from baseline in serum calcium concentration at each study visit were summarised.

Patients in studies 980125, 990120, 990160 and 10000159 had mild or moderate primary HPT, in contrast to patients in study 20000204, who had a more severe disease, according to inclusion criteria in the studies. Also, the patients in study 20000204 had a variable length titration phase. The efforts made to pick out patients who are supposed to have a contraindication to surgery from primary HPT studies other than 20000204 can be questioned as data were not collected prospectively.

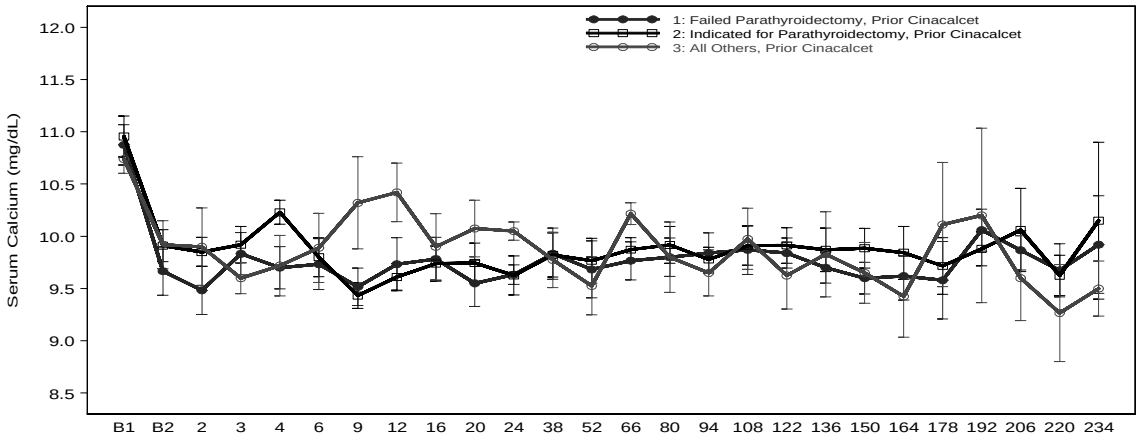
Figure 3. Mean (SE) of percent change from baseline in serum calcium concentration at each scheduled Visit during first 6 months: studies 980125 + 990160 + 990120



Group 1 (N):	10	10	10	9	9	8	8	9	7	7	6	6	6	6	6	6
Group 2 (N):	21	19	17	11	17	10	14	12	10	9	10	10	8	8	8	8
Group 3 (N):	26	26	23	20	23	20	19	21	20	19	20	19	17	17	15	15
Group 4 (N):	38	38	36	27	28	23	25	23	18	19	19	19	18	18	16	16
Group 5 (N):	14	13	14	10	14	10	12	12	11	11	9	11	8	8	8	7
Group 6 (N):	26	25	24	11	21	8	20	20	13	13	13	13	7	7	7	7

B=Baseline. For Study 980125, the first available baseline cycle measurement is used.
Twenty-two subjects enrolled into Study 990120 from Study 980125 and are counted in both studies.
For Study 990120, only the titration and maintenance phases are included.
Program: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/graphs/programs/g_lab_week_shortterm.sas
Output: g1-02_001_cachp_week_shortterm.cgm (Date Generated: 28AUG2007:13:46:09)
Source Data: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/statdata/crt/weekly.sas7bd

Figure 4. Mean (SE) serum calcium concentration over time, long-term assessment for patients from studies 990120 continuing into study 20000159

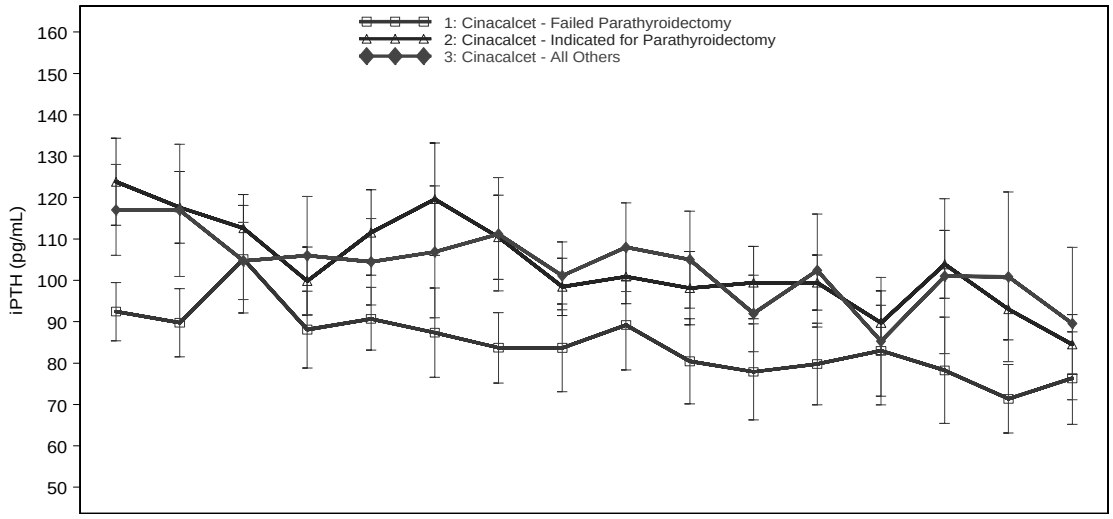


Group 1 (N):	6	6	6	6	6	6	6	6	6	6	6	6	6	6	5	5	5	5	5	5	5	5	5	4	5
Group 2 (N):	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	8	8	7	7	6	5	5	4	2
Group 3 (N):	5	5	5	5	5	5	5	5	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	3	3

B1=Study 990120 baseline, B2=Study 20000159 baseline. Prior placebo/cinacalcet: prior treatment in Study 990120.
Only subjects who rolled over from Study 990120 to Study 20000159 are included.
Scheduled visits displayed refer to the scheduled visits in Study 20000159.
Program: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/graphs/programs/g_lab_week_longterm_calci.sas
Output: g1-01_002_001_ca_week_longterm_calci.cgm (Date Generated: 28AUG2007:13:46:16)
Source Data: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/statdata/crt/weekly.sas7bdat, baseline.sas7l

All cinacalcet groups had an immediate decrease in serum calcium concentration from baseline that was maintained during the study period, although with great inter-individual variations and great standard errors.

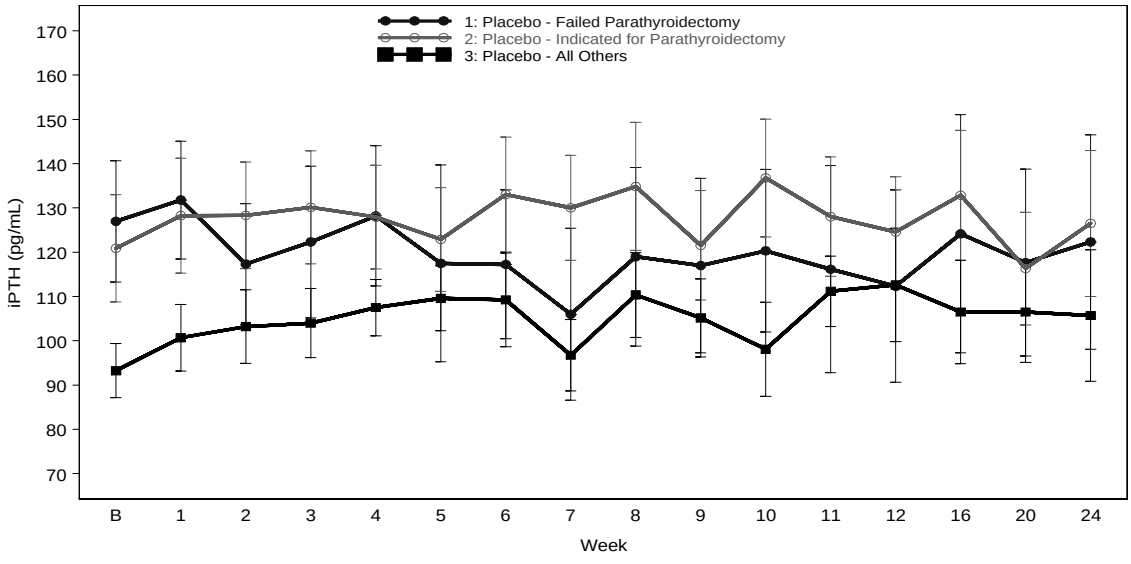
Figure 5. Mean (SE) plasma iPTH concentration at each scheduled visit during first 6 months: studies 980125 + 990160 + 990120, cinacalcet groups



	B	1	2	3	4	5	6	7	8	9	10	11	12	16	20	24
Group 1 (N):	21	19	17	11	17	9	13	12	10	9	9	10	8	8	8	8
Group 2 (N):	38	38	36	25	28	22	24	23	20	19	19	19	18	18	16	16
Group 3 (N):	26	25	23	11	21	8	18	20	14	13	12	13	7	7	7	7

B=Baseline. For Study 980125, the first available baseline cycle measurement is used.
Ten cinacalcet subjects enrolled into Study 990120 from Study 980125 and are counted in both studies.
For Study 990120, only the titration and maintenance phases are included.
Program: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/graphs/programs/g_lab_week_shortterm_calci.sas
Output: g1-03_001_001_pth_week_shortterm_calci.cgm (Date Generated: 28AUG2007:13:46:25)
Source Data: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/statdata/crt/weeklv.sas7b

Figure 6. Mean (SE) plasma iPTH concentration at each scheduled visit during first 6 months: studies 980125 + 990160 + 990120, placebo groups

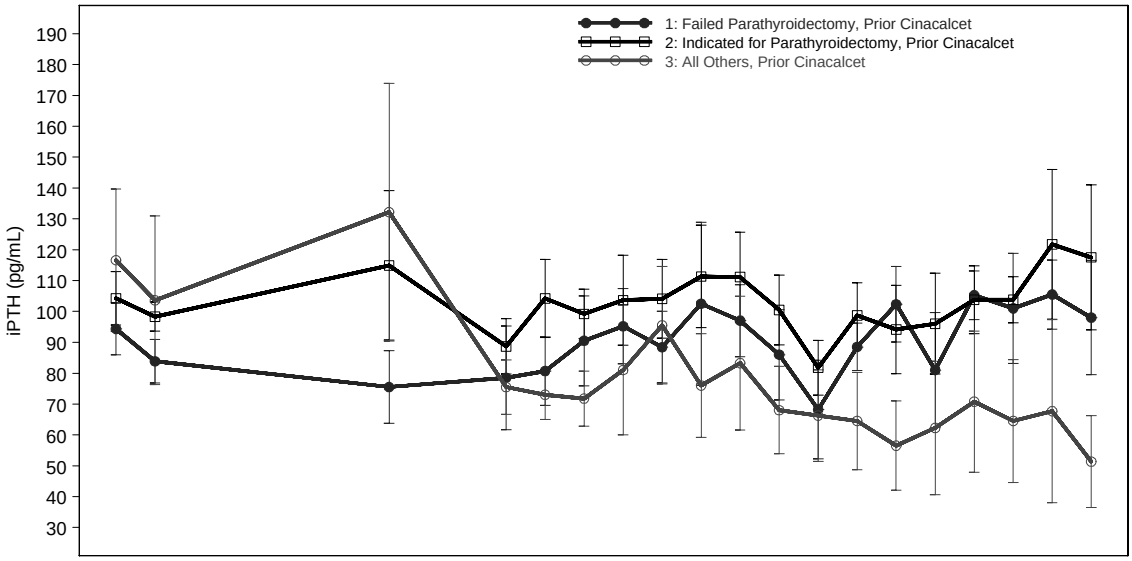


	B	1	2	3	4	5	6	7	8	9	10	11	12	16	20	24
Group 1 (N):	10	10	9	9	9	8	8	8	7	7	6	6	6	6	6	6
Group 2 (N):	26	25	24	19	23	20	19	21	20	18	20	19	17	17	15	15
Group 3 (N):	14	14	14	10	14	10	12	12	11	11	10	11	8	8	8	7

B=Baseline. For Study 980125, the first available baseline cycle measurement is used.
Four placebo subjects enrolled into Study 990120 from Study 980125 and are counted in both studies.
For Study 990120, only the titration and maintenance phases are included.
Program: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/graphs/programs/g_lab_week_shortterm_placebo.sas
Output: g1-03_001_002_pth_week_shortterm_placebo.cgm (Date Generated: 28AUG2007:13:46:38)
Source Data: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/statdata/crt/weeklv.sas7bda

There was no significant difference in plasma iPTH concentrations between cinacalcet treated patients and placebo treated patients in pooled data from studies 980125 + 990160 and 990120 for patient categories 1, 2 and 3 (see p 11). Standard errors were great.

Figure 7. Mean (SE) plasma iPTH concentration over time, long-term assessment for cinacalcet patients from study 990120 continuing into study 20000159



Group 1 (N):	6	6						6			6	6	6	5	5	4	5	5	5	4	3	4	4	4	4	4
Group 2 (N):	10	10						9			9	9	9	9	9	9	9	8	8	7	7	6	5	5	4	2
Group 3 (N):	5	5						5			4	4	4	4	4	4	4	4	4	4	4	4	4	4	3	3

B1=Study 990120 baseline, B2=Study 20000159 baseline. Prior placebo/cinacalcet: prior treatment in Study 990120.
Only subjects who rolled over from Study 990120 to Study 20000159 are included.
Scheduled visits displayed refer to the scheduled visits in Study 20000159.
Program: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/graphs/programs/g_lab_week_longterm_calci.sas
Output: g1-03_002_001_pth_week_longterm_calci.cgm (Date Generated: 28AUG2007:13:46:16)
Source Data: /stat/calci/pHPT/EMEA_2007/analysis/p_ISSISE/statdata/crt/weeklv.sas7bdat, baseline.sas7t

There was a trend towards higher long term values for iPTH in patients indicated for parathyroidectomy but not operated and for patients with failed parathyroidectomy compared to all others. Again, standard errors were great.

4. Clinical safety

Patient exposure

On the cut-off data of the most recent PSUR report, 28 February 2007, the worldwide postmarketing exposure to cinacalcet up to 28 February 2007 is estimated to 138.354 patient-years.

Table 6. Approximate exposure to cinacalcet post-marketing by geographic area, by patient-years

	Cumulative Since Launch[a]
United States	97,803
Canada	1,289
Europe	38,652
Australia and New Zealand	610
Total patient-years	**138,354**

[a] From date of commercial launch through 28 February 2007. Market experience with cinacalcet was estimated by determining the number of patients and patient-years of exposure from monthly product distribution and prescription data by region.

The number of subjects who received cinacalcet and the number of subjects who received placebo in the five studies performed to evaluate cinacalcet in subjects with primary HPT are presented by study in Table 1.

Study 20000204

Adverse events

Twenty-four (83 %) parathyroid carcinoma patients and 15 patients with intractable HPT (88 %) had AEs that were considered by the investigator to be treatment-related. The most common treatment-related AEs (≥ 10 %) included nausea, vomiting and paresthesia. The overall incidence of treatment-related AEs was similar among subjects with parathyroid cancer and subjects with intractable primary HPT.

Table 7. Incidence of AEs (≥ 10 %), study 20000204

	Cinacalcet		
Preferred Term	Parathyroid Carcinoma (N = 29) n (%)	Intractable pHPT (N = 17) n (%)	Total (N = 46) n (%)
Number of Subjects Reporting Adverse Events	28 (97)	17 (100)	45 (98)
Nausea	19 (66)	10 (59)	29 (63)
Vomiting	15 (52)	6 (35)	21 (46)
Paresthesia	4 (14)	5 (29)	9 (20)
Fatigue	6 (21)	2 (12)	8 (17)
Fracture	6 (21)	2 (12)	8 (17)
Hypercalcaemia	6 (21)	2 (12)	8 (17)
Anorexia	6 (21)	1 (6)	7 (15)
Asthenia	5 (17)	2 (12)	7 (15)
Dehydration	7 (24)	0 (0)	7 (15)
Anaemia	5 (17)	1 (6)	6 (13)
Arthralgia	5 (17)	1 (6)	6 (13)
Constipation	3 (10)	3 (18)	6 (13)
Depression	3 (10)	3 (18)	6 (13)
Headache	6 (21)	0 (0)	6 (13)
Infection Upper Respiratory	3 (10)	2 (12)	5 (11)
Pain Limb	3 (10)	2 (12)	5 (11)
N=Number of subjects receiving at least one dose of study drug.			

Altogether nine subjects withdrew from the study due to AEs. Five patients with parathyroid cancer withdrew due to AEs including nausea, vomiting, hypercalcaemia and urticaria, Four patients with intractable primary HPT withdrew due to AEs including nausea, vomiting, hypercalcaemia, hyperparathyroidism, muscle weakness and neoplasm.

Nausea and vomiting were the most common AEs. The pattern of AEs did not differ between the patient groups.

Serious adverse events and deaths *(study 20000204)*

Eight deaths (7 patients with parathyroid cancer, 1 with intractable primary HPT) occurred in study 20000204. The fatal events were recorded as due to cardiac arrest (2) and one case each of cardiac failure, gastrointestinal haemorrhage, hypotension, metastatic neoplasm and multi-organ failure. The fatal outcome for the patient with intractable primary PTH was initially coded as arrhythmia but later re-classified as heart failure as cause of death. Narratives were provided for all these patients. None of the deaths were considered by the investigator to be related to the investigational product.
Twenty subjects with parathyroid cancer (69 %) and 6 with intractable primary HPT (35 %) experienced SAEs. Four of the subjects with carcinoma had SAEs that were considered by the investigator to be treatment-related, including nausea and dehydration; vomiting and dehydration; hypercalcaemia, anorexia and asthenia; hypercalcaemia, dehydration and hypokalaemia.

Table 8. Incidence of SAEs by preferred term, study 20000204

		Cinacalcet	
Preferred Term	Parathyroid	Intractable	Total
	Carcinoma	pHPT	(N = 46)
	(N = 29)	(N = 17)	n (%)
	n (%)	n (%)	
Number of Subjects Reporting Serious Adverse Events	20 (69)	7 (41) [a]	27 (59) [a]
Hypercalcaemia	6 (21)	2 (12) [a]	8 (17) [a]
Fracture	6 (21)	1 (6)	7 (15)
Dehydration	4 (14)	0 (0)	4 (9)
Anaemia	3 (10)	0 (0)	3 (7)
Cardiac Arrest	3 (10)	0 (0)	3 (7)
Metastatic Neoplasm	3 (10)	0 (0)	3 (7)
Pneumonia	2 (7)	1 (6)	3 (7)
Abdominal Hernia	1 (3)	0 (0)	1 (2)
Anorexia	1 (3)	0 (0)	1 (2)
Arrhythmia	0 (0)	1 (6)	1 (2)
Asthenia	1 (3)	0 (0)	1 (2)
Cardiac Failure	1 (3)	0 (0)	1 (2)
Cerebrovascular Disorder	0 (0)	1 (6)	1 (2)
Coronary Artery Disorder	0 (0)	1 (6)	1 (2)
Dissem. Intravasc. Coagulation	1 (3)	0 (0)	1 (2)
Dyspnoea	1 (3)	0 (0)	1 (2)
Oedema Retinal	0 (0)	1 (6)	1 (2)
Fibrillation Atrial	1 (3)	0 (0)	1 (2)
Haemorrhage GI	1 (3)	0 (0)	1 (2)
Haemothorax	1 (3)	0 (0)	1 (2)
Hypokalaemia	1 (3)	0 (0)	1 (2)
Hypotension	1 (3)	0 (0)	1 (2)
Infection Urinary Tract	0 (0)	1 (6)	1 (2)
Intestinal Obstruction	1 (3)	0 (0)	1 (2)
Multi Organ Failure	1 (3)	0 (0)	1 (2)
Nausea	1 (3)	0 (0)	1 (2)
Neoplasm Malignant	1 (3)	0 (0)	1 (2)
Pain Back	1 (3)	0 (0)	1 (2)
Pain Chest, Cardiac	0 (0)	1 (6)	1 (2)
Pancreatitis	1 (3)	0 (0)	1 (2)
Renal Failure Acute	1 (3)	0 (0)	1 (2)
Septic Shock	1 (3)	0 (0)	1 (2)
Spinal Cord Compression	1 (3)	0 (0)	1 (2)
Thrombosis Arterial	1 (3)	0 (0)	1 (2)
Thrombosis Retinal	0 (0)	1 (6)	1 (2)
Vascular Disorder	0 (0)	1 (6)	1 (2)
Vomiting	1 (3)	0 (0)	1 (2)

Laboratory findings

No trends indicating treatment-related effects were seen for other laboratory values than for serum alkaline phosphatase (ALP). Elevated mean serum ALP concentrations were seen from baseline to the end of the titration phase. At baseline, the mean serum ALP concentration was 187.5 U/l and at the end of the titration phase, the mean ALP concentration was 284.5 U/l.

The CHMP agreed with the MAH that these elevations are due to cross-reactivity of the enzyme assay with the BALP isoform as no SGOT/SGPT or clinical sign of hepatic or biliary symptoms were observed.

Analysis performed across trials

Adverse events

The safety profile of cinacalcet was similar across the five studies in patient with primary HPT although subjects with intractable primary HPT or parathyroid carcinoma in study 20000204 tended to have a greater incidence of nausea and, in particular, of vomiting than subjects in the other studies.

However, patients in study 990160 also had a high incidence of nausea. This can be explained as subjects in studies 990160 and 20000204 had higher baseline serum calcium concentrations than subjects in the other studies and hypercalcaemia can cause nausea. Nausea is also a known common adverse reaction associated with cinacalcet.

In the double-blind studies 980125, 990120 and 990160, nausea, dizziness, fatigue, diarrhoea and paraesthesia were reported to be more common in the cinacalcet groups than in the placebo groups. The most common AE was nausea. These events are mentioned as common adverse effects in the SPC for cinacalcet. Most of these adverse effects are related to the calcium-lowering effect of cinacalcet.

Serious adverse events and deaths

The only SAEs reported in the double-blind studies occurred in study 990120. In this study, 8 % of patients in both the cinacalcet and the placebo groups experienced SAEs. These SAEs were: neck pain, sepsis, renal calculus (2), diverticulosis and dislocation. None of these SAEs were considered by the investigator to be treatment-related. In study 20000159, 8 subjects (38 %) who had received cinacalcet in the prior study and 8 (33 %) who had earlier received placebo had SAEs. One subject in each prior treatment group experienced syncope. None of the SAEs in this study were considered related to investigational drug by the investigator.

Two subjects died during the long-term extension study 20000159. The cause of death was metastatic colon cancer in one of the patient and cerebral ischemia in the other patient. None of these deaths was considered by the investigator to be related to cinacalcet.

Laboratory findings

With the exceptions of serum calcium and serum phosphorus, no clinically relevant trends in laboratory parameters were seen in subjects with primary HPT or parathyroid carcinoma.

Serum phosphorus concentrations were increased with cinacalcet due to renal retention of phosphorus caused by reduced PTH levels. The mean phosphorus concentrations still remain within the normal range, 2.2 to 5.1 mg/dl. Urine volume and urine calcium excretion were recorded in study 990120.

This study enrolled patients with normal kidney function (creatinine clearance > 50 ml/min) and no effect of cinacalcet on urine volume or urine calcium excretion over 24 hours was seen during 1 year of measurement.

Safety in special populations

Safety was not found to be different between the study subgroups: failed previous parathyroidectomy, indicated for parathyroidectomy and others in the studies for primary HPT. Children, adolescents or pregnant women were not included in any of the cinacalcet clinical studies.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system (version 2.1) as described by the MAH fulfils the legislative requirements.

Annex II has been updated accordingly.

Risk Management Plan

The MAH submitted a Risk Management Plan (version 1.0).

Table Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities
Important Identified Risks:		
Hypocalcaemia	Routine pharmacovigilance	Routine risk minimization in label (in the Posology and method of administration, Special warnings and precautions for use, Undesirable effects, and Overdose sections) and package leaflet
Convulsions/seizures	Routine pharmacovigilance; analysis of incidence rates of convulsions across completed clinical studies; analysis of convulsions in Study 20050182	Routine risk minimization in label (in the Special warnings and precautions for use, and Undesirable effects sections) and package leaflet
Hypotension and/or worsening heart failure	Routine pharmacovigilance; analysis of hypotension and worsening heart failure in Study 20050182	Routine risk minimization in label (in the Special warnings and precautions for use and Undesirable effects sections) and package leaflet
Important Potential Risks:		
Myocardial ischemia, ventricular arrhythmias	Routine pharmacovigilance; analysis of cardiac events in Study 20050182; analysis of progression of coronary artery calcification in Study 20060111	Routine risk minimization in label and package leaflet and additional actions, if warranted by nature of risk
Fractures	Routine pharmacovigilance; analysis of incidence rates of fractures across completed clinical studies; analysis of fractures in Study 20050182, analysis of changes in bone formation rate in Study 20050104	Routine risk minimization in label and package leaflet and additional actions, if warranted by nature of risk

Acute pancreatitis	Routine pharmacovigilance; analysis of acute pancreatitis in Study 20050182	Routine risk minimization in label and package leaflet and additional actions, if warranted by nature of risk
Serious hepatic events	Routine pharmacovigilance; analysis of hepatic events in Study 20050182	Routine risk minimization in label and package leaflet and additional actions, if warranted by nature of risk
Important Missing Information:		
Pregnant or lactating women	Routine pharmacovigilance	Communication of the lack of information for this population in the label (in the Pregnancy and lactation section) and package leaflet. Routine risk minimization in label and additional actions, if warranted by nature of risk.
Paediatric patients	Routine pharmacovigilance; evaluation of safety in paediatric subjects in Study 20030227, planned Study 20070208	Communication of the lack of information for this population in the label (in the Posology and method of administration section). Routine risk minimization in label and additional actions, if warranted by nature of risk.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Changes in the Product Information

Sections 4.2, 4.8 and 5.1 of the SPC have been updated as a consequence to the addition of the new indication.

There has been a substantial revision of the Package Leaflet further to the results of the readability testing performed in October 2007. The list of local representatives has been updated.

In addition, the MAH has submitted the Pharmacovigilance System (version 2.1) and a new Risk Management Plan (version 1.0). Annex II has been updated to reflect this.

7. Overall conclusions and Benefit / Risk Assessment

The treatment of choice for primary HPT is surgical parathyroidectomy. However, there is a limited number of patients for whom surgery for various reasons is not achievable. At present, no approved medical treatment exists in the EU for these patients with primary HPT.

Study 20000204 provides evidence that cinacalcet has a beneficial effect in patients with surgically intractable HPT, even if the individual variability is large. Twenty-nine patients with parathyroid carcinoma, fourteen patients with failed parathyroidectomy and three patients with documented medical contraindication for surgery were included in this study. Even if the number of included patients is still small, the mean observation time in the study was 328 days for patients with parathyroid cancer and 347 days for patients with primary intractable HPT.

This relatively long observation time plus the circumstance that the pattern of adverse effects was not different from what has been observed in patients with other, earlier approved indications, are favourable for an approval of an indication for cinacalcet in primary HPT patients for whom parathyroidectomy is indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not feasible. When pooling data from studies 980125, 990120, 990160 and 10000159, altogether 21 patients with failed parathyroidectomy and 38 patients with primary HPT and at least one indication for surgery but not operated were identified. Even if these studies were not designed to evaluate data from patients refractory to or contraindicated for curative parathyroid surgery, the pooled data for primary HPT patients with failed parathyroidectomy or indicated for surgery but not operated give some support to the conclusions from study 20000204.

The risk/benefit ratio is considered to be positive for the indication "reduction of hypercalcaemia in patients with 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".

8. Conclusion

On 24 April 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.