MEDICAL TEAM LEADER REVIEW

NDA: 21-688

DRUG: Cinacalcet (Sensipar™)

INDICATIONS: Treatment of (1) secondary hyperparathyroidism; (2) primary hyperparathyroidism when parathyroidectomy is not an option; and (3) hypercalcemia of parathyroid carcinoma

PRIMARY REVIEWERS: Patricia Beaston, MD, PhD, and Theresa Kehoe, MD

DATE NDA SUBMITTED: 5 September 2003

DATE OF REVIEW: 14 February 2004

1.0 BACKGROUND

1.1 Proposed Indications

Cinacalcet is a first-in-class oral caclimimetic drug that Agmen plans to market for the following 3 indications:

1. The [redacted] treatment of secondary hyperparathyroidism in patients with chronic kidney disease, receiving or not receiving dialysis.
2. The treatment of primary hyperparathyroidism when parathyroidectomy is not a treatment option.
3. The treatment of hypercalcemia in patients with parathyroid carcinoma.

1.2 Priority Review

Amgen requested and received a priority review for this NDA. Several vitamin D compounds are approved for the treatment of secondary hyperparathyroidism (secondary HPT); however, for many patients, the doses of vitamin D required to adequately lower serum intact PTH (iPTH) levels cause hypercalcemia and an elevated calcium X phosphorus ion product (Ca X P). This problem is often aggravated by the use of calcium-based phosphate binders, and is not entirely obviated by the use of sevelamer, a non-calcium-based phosphate binder. Epidemiological data have linked an elevated Ca x P ion product to an increased risk for cardiovascular death.

Because Cinacalcet interacts directly with the calcium-sensing receptors on the parathyroid gland, the drug lowers iPTH levels without increasing serum calcium or Ca X P levels.

The Division believes that Cinacalcet may prove to be an effective therapy for some patients with secondary HPT who are unable to reach treatment goals with the currently available vitamin D and phosphate-binder therapies.

1.3 Pharmacology and Pharmacokinetics

Cinacalcet lowers iPTH levels by increasing the sensitivity of the calcium sensing receptor to extracellular calcium. The reduction in iPTH is associated with a concomitant decrease in serum calcium levels. Reduction in iPTH levels correlated with Cinacalcet concentrations. The nadir in iPTH level occurs approximately 2 to 6 hours post-dose, corresponding with the C_{max} of Cinacalcet. The T_{max} of the drug is 3-4 hours post-dose. After absorption, Cinacalcet concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady state drug levels are achieved within 7 days. The AUC and C_{max} of Cinacalcet increase linearly over the dose range of 30 to 180 mg once daily. The drug has a large volume of distribution.

1.4 Dose Selection

In phase-2 investigations of patient with secondary HPT, doses of cinacalcet less than 25 mg did not suppress iPTH over a 24-hour interval in subjects with secondary HPT and doses above 200 mg daily did not increase exposure to the drug. Therefore, a dose range of 30 mg to 180 mg once daily was selected for the pivotal phase-3 studies.

1.5 Treatment Guidelines for Patients with CKD

The following table outlines the current treatment goals for patients with mild-severe CKD.

Table 1. K/DOQI Target Values for Secondary HPT Metabolic Parameters

Metabolic Parameter	Target Level CKD Stage 3[a]	Target Level CKD Stage 4[b]	Target Level ESRD[c]
iPTH (pg/mL)	30 to 70	70 to 110	150 to 300
Ca x P (mg/dL)[2]	Not in guideline	Not in guideline	≤ 55
Calcium (mg/dL)	8.4 to 10.3[d]	8.4 to 10.3[d]	8.4 to 9.5
Phosphorus (mg/dL)	2.7 to 4.6	2.7 to 4.6	3.5 to 5.5

CKD = chronic kidney disease, ESRD = end-stage renal disease, iPTH = intact parathyroid hormone, Ca x P = calcium x phosphorus

[a] glomerular filtration rate (GFR) 30 to 60 mL/min/1.73 m^2

[b] GFR 15 to 29 mL/min/1.73 m^2

[c] GFR < 15 mL/min/1.73 m^2 or dialysis

[d] within normal range for the laboratory used

2.0 OVERVIEW OF CLINICAL STUDIES

2.1 Secondary Hyperparathyroidism

2.1.1 Chronic Kidney Disease Receiving Dialysis

The efficacy and safety of Cinacalcet in the treatment of secondary HPT in patients on dialysis were examined in three, 6-month, placebo-controlled trials of similar design: Studies 172, 183, and 188. For a subset the patients who completed studies 172 and 183, and additional 6 months of double-blind treatment was obtained in study 240.

Studies 172, 183, and 188

Objective: To evaluate the efficacy of cinacalcet compared with placebo by determining the proportion of subjects with a mean iPTH value $\leq$ 250 pg/mL during the Efficacy-Assessment phase.

Patient Population and Study Design: To be eligible for the three phase-3 studies of patients with CKD on dialysis, patients had to be at least 18 years of age and have a iPTH $\geq$ 300 pg/ml and a serum calcium $\geq$ 8.4 mg/dl within 30 days of the trial. Exclusion criteria included a change in brand or dose of phosphate binder or oral calcium supplement within 30 days of the start of the trial; a change in dialysate calcium concentration within 30 days of trial initiation; receipt of vitamin D therapy for < 30 days before start of the study, or a change in the brand or dose of vitamin D within 30 days of study start.

As shown in Figure below, the studies were comprised of a 12-week dose-titration phase (Titration) and a 14-week efficacy phase (Efficacy-Assessment). Beginning on day 1, subjects received study medication at a starting dose of 30 mg Cinacalcet or placebo once daily. Tablets were taken with food or shortly after a meal if feasible. Study medication was taken at approximately the same time of day each day. On study visit days, study drug was administered after blood collection and study evaluations, approximately 24 hours after the last dose (at the nadir drug concentration).

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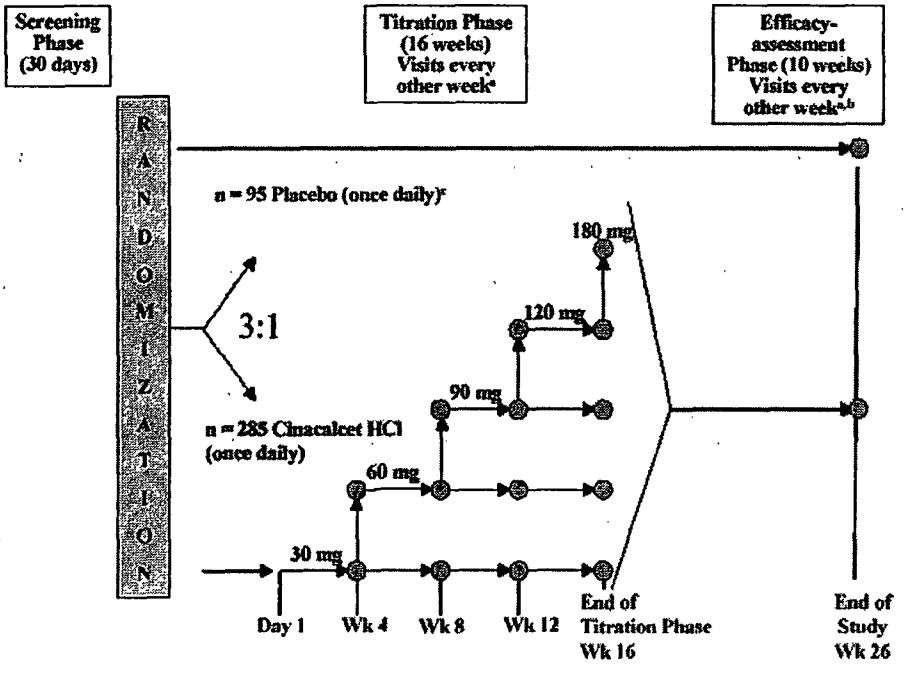


Subjects could be titrated up to the next sequential dose level of cinacalcet (60 mg, 90 mg, 120 mg, and 180 mg)/placebo at the week 4, 8, 12, 16, 20, and 24 study visits. For each of these visits, a site representative called the interactive voice response system (IVRS) within 5 days before and 3 days after the scheduled visit in order for a subject to receive the next bottle number(s). The site personnel were asked for subject information that included central laboratory iPTH and serum calcium values and safety information. If any of the following criteria applied, a subject's dose was not increased:

For weeks 4, 8, 12, 16, 20, and 24:

- The central laboratory iPTH value from the preceding study visit was $\leq$ 200 pg/mL.
- The highest dose of study medication was reached.
- The serum calcium was < 7.8 mg/dL or the subject was experiencing symptoms of hypocalcemia.
- The subject was experiencing an adverse event that precluded a dose increase.

If iPTH values were < 100 pg/mL for 2 consecutive study visits, study medication was reduced to the next lower dose.

If a subject experienced an intolerable adverse event that was considered related to the dose of study drug (other than hypocalcemia), study drug was decreased to the next lower dose. If a

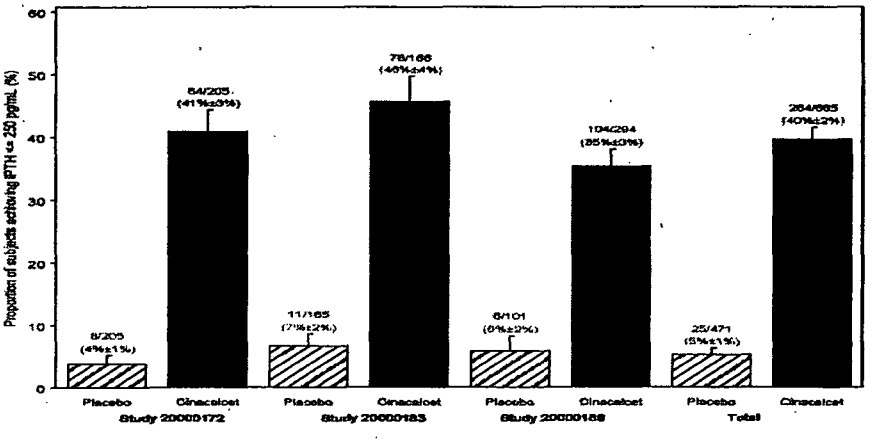
subject experienced symptoms of hypocalcemia and/or a serum calcium < 8.4 mg/dL, calcium supplements and/or phosphate binders could be increased to resolve the symptoms (if present) or to increase serum calcium to ≥ 8.4 mg/dL. If these measures were insufficient, the vitamin D dose could be increased. Figure 7.2 in the Appendix provides the algorithm for management of hypocalcemia.

Baseline Demographics and Disposition: A total of 471 patients were randomized to placebo and 665 to cinacalcet in the three, 6-month studies. The baseline demographic characteristics were well-matched for the placebo and Cinacalcet groups. The mean age of the participants was 54 years, 62% were male, and 52% were Caucasian. The average duration of dialysis prior to study enrollment was 67 months and 96% of the patients were receiving hemodialysis; 4% were on peritoneal dialysis. The baseline iPTH level was 712 pg/ml, with 26% of subjects having baseline iPTH levels > 800 pg/ml, and the baseline Ca X P product was approximately 61. Sixty-six percent of the subjects were receiving vitamin D therapy at baseline, and 93% were on some type of phosphate binder.

Seventy-eight percent of placebo patients and 71% of the Cinacalcet patients completed the 6-month studies. Fourteen percent of the Cinacalcet-treated patients and 8% of the placebo patients discontinued early due to an adverse event - a large proportion of which were nausea or vomiting or both.

Exposure to Study Drug: The distribution of patients by dose of drug at the end of the Titration and Efficacy-Assessment periods of the studies are shown in Figures 1 and 2 in the Appendix.

Primary Efficacy Outcome: The primary efficacy outcome variable was the proportion of patients in each group who achieved a mean iPTH value ≤ 250 pg/ml during the Efficacy-Assessment phase of the trials. In the ITT population, 40% of cinacalcet subjects vs. 5% of placebo subjects achieved a mean iPTH value of < 250 pg/ml during the Efficacy-Assessment phase ($p<0.001$). The following figure provides the results of the primary efficacy assessments for each of the three pivotal studies and for studies combined.



Ca x P Ion Product: The mean percent reductions from baseline to Week 26 in the Ca x P product ion were -0.02% in the placebo group and -14.0% in the cinacalcet group.

K/DOQI Treatment Goals: The following table provides the proportion of patients in the two treatment groups who achieved the various K/DOQI treatment goals during the Efficacy-Assessment Phase. A larger percentage of patients treated with Cinacalcet met the new treatment goals than did patients who received placebo.

	Study 20000172		Study 20000183		Study 20000188		Total	
	Placebo (N = 205) n(%)	Cinacalcet (N = 205) n(%)	Placebo (N = 165) n(%)	Cinacalcet (N = 166) n(%)	Placebo (N = 101) n(%)	Cinacalcet (N = 294) n(%)	Placebo (N = 471) n(%)	Cinacalcet (N = 665) n(%)
iPTH (pg/mL) 150 - 300	18 (9)	76 (37)	15 (9)	46 (28)	8 (8)	84 (29)	41 (9)	206 (31)
Serum calcium (mg/dL) 8.4 - 9.5	55 (27)	106 (52)	37 (22)	87 (52)	26 (26)	121 (41)	118 (25)	314 (47)
Serum phosphorus (mg/dL) 3.5 - 5.5	62 (30)	79 (39)	50 (30)	76 (46)	45 (45)	134 (46)	157 (33)	289 (43)
Ca x P (mg/dL)[2] ≤ 55	69 (34)	123 (60)	58 (35)	109 (66)	45 (45)	186 (63)	172 (37)	418 (63)
Concurrent achievement of iPTH 150-300 pg/mL and Ca x P ≤ 55 (mg/dL)[2]	9 (4)	58 (28)	11 (7)	31 (19)	5 (5)	67 (23)	25 (5)	156 (23)

Adverse Events: There were no meaningful differences between treatment groups in the incidence of deaths or serious AEs during the 3 trials. Fifteen percent of Cinacalcet subjects and 8% of placebo subjects discontinued prematurely due to adverse events. A large percentage of patients in the Cinacalcet groups withdrew because of nausea or vomiting or both. Nausea and vomiting were also the two most commonly reported treatment-emergent adverse events, with 31% and 27% of Cinacalcet subjects reporting these events, respectively. This compares with 19% and 15% of placebo-treated patients who reported at least one episode of nausea and vomiting. There was a clear dose-response relationship for vomiting, but not nausea.

Serum Calcium Levels: Given Cinacalcet's mechanism of action, hypocalcemia would be an expected safety issue. In the pooled data from Studies 172, 183, and 188, 66% of Cinacalcet subjects vs. 25% of placebo patients developed at least one serum calcium level $\leq$ 8.4 mg/dl. Approximately 5% of Cinacalcet and 0.9% of placebo patients had 2 consecutive serum calcium values < 7.5 mg/dl. Seven percent of subjects receiving Cinacalcet and 0.9% of subjects receiving placebo had study drug withheld due to decreased serum calcium. All of these subjects subsequently resumed study medication. There was no major imbalance between groups in the incidence of adverse events that could be attributed to hypocalcemia.

Among the Cinacalcet subjects who experienced a serum calcium < 8.4 mg/dL, a majority (64%) had only one or two values below this level during the 6-month trial period. It appears that the risk of hypocalcemia (< 8.4 mg/dl) was similar during the Titration and Efficacy-Assessment phases of the studies.

Seizures: Five percent of the patients in both the placebo and Cinacalcet groups reported having a history of a seizure disorder at baseline. During the trials, 2 patients in the placebo groups and 11 subjects in the Cinacalcet groups were coded as having had at least one "seizure" - the majority of which were described as grand mal (nominal p = 0.054).

[For the entire population of patients who participated in any of the secondary HPT + dialysis studies, 5/738 (0.7%) of placebo patients and 17/1166 (1.5%) of Cinacalcet patients were coded as having had at least one "seizure" (nominal p = 0.12).]

In Studies 172, 183, and 188, 5 of the 11 cinacalcet-treated subjects who experienced an on-study seizure had a previous history of a seizure disorder. Of these 5 subjects, 3 had one or more clinical conditions that were *possible* confounding factors, such as subdural hematoma secondary to head trauma; ventriculo-peritoneal shunt and concurrent urinary tract infection; isoniazid administration; promethazine administration; and cefazolin administration. Two of the 5 subjects with a history of seizures were on anticonvulsant medications at the time of study enrollment. The 2 placebo subjects who experienced convulsions also had a history of convulsions and were on anticonvulsant medications at the time of study enrollment.

Preclinical data indicate that Cinacalcet crosses the blood brain barrier. In preclinical studies, seizures associated with acute and severe reductions in serum calcium were observed in rats and dogs at the highest Cinacalcet dose levels. As shown in the following table, 4 of the Cinacalcet subjects had low serum calcium levels prior to or after the reported seizure.

Subject	Study No.	History of Seizures	Confounding Factors	Calcium[a] (mg/dL)	Dose level (mgs)	Treatment Relationship[b]
Cinacalcet						
30608	20010240		isoniazid	11.8 / 10.2	30	No
33510	20000183	X	subdural hematoma	8.6 / ---	60	No
31602	20000183	X	HTN, tramadol	8.0 / 10.0	120	Yes
30202	20000183		VP shunt, UTI	9.1 / 7.8	120	No
34204	20000183		cefazolin	9.6 / 8.0	60	Yes
10602	20000172		HTN	8.6 / 9.5	30	No
10706	20000172/ 20010240	X		8.3 / 8.6 7.3 / 9.2	180 180	Yes
20511	20000188	X	low phenytoin level	7.4 / 9.7 9.7 / 8.8	60 60	No
10911	20000188			9.0 / 8.5 9.6 / 10.7	60 90	Yes
16708	20010240			9.4 / 11.0	90	No
13107	20000188	X		7.8 / 9.3	90	No
Placebo						
14302	20000172			8.2 / 8.9	90	Yes
13105	20000172	X	promethazine	9.0 / 8.6	90	No

[a] Nearest on-study serum calcium values before and after event
[b] Investigator's assessment

Of the 11 Cinacalcet subjects who reportedly suffered an on-study seizure, 2 were receiving 30 mg Cinacalcet, 3 were receiving 60 mg, 2 were receiving 90 mg, 3 were receiving 120 mg, and 1 was receiving 180 mg at the time of the seizure.

No studies have been done to examine whether Cinacalcet induces the activity of enzymes that metabolize common anti-seizure medications.

COMMENT: With the available data, it's not possible to accept of reject the hypothesis that cinacalcet increases the risk for seizure. If the drug does in fact increase the risk for seizure, it most likely dose so by way of hypocalcemia. Despite the uncertainty of a cause and effect relationship between cinacalcet and seizures, several measures should be taken in response to the findings from the phase 3 CKD studies. First, a series of *in vitro* enzyme induction studies should be conducted to determine whether cinacalcet increases the activity of enzymes known to metabolize common anti-seizure medication. Second, the Warnings section of the labeling should include a clear description of the seizure findings from Studies 172, 183, and 188, along with a recommendation that serum calcium levels be closely monitored, particularly in patients with a known seizure disorder. Third, following approval, Amgen should commit to providing the Division with regular (i.e., semi-annual) analyses of all seizure data from cinacalcet clinical trials and MedWatch reports.

Cardiac Repolarization (QT): There is a growing interest within CDER to closely scrutinizing new molecular entities for their potential to adversely affect cardiac repolarization. The Cinacalcet NDA contains some data on cardiac repolarization, but by no means does it include a comprehensive assessment of the drug's proarrhymthmic potential.

The *in vitro* testing included 7 ion channel assays. For details of these studies please see Dr. Gemma Kuijper's review. According to Dr. Kuijper's, 4 of the 7 ion channel studies (3 K^+ and 1 Na^+) were "positive". Although only one drug concentration was tested in the HERG assay, the IC_{50} was > 500 ng/mL, a concentration that is 10 times the free plasma levels obtained with the maximum proposed clinical dose of 180 mg. No additional *in vitro* testing was done.

Regarding *in vivo* data, in a 3-month study of monkeys, a QT prolonging effect (> 20 ms) was observed in animals that received the two highest doses of Cinacalcet: 100 mg/kg/day and 150 mg/kg/day. In a 12-month of monkeys, dosed at 0 mg, 5 mg/kg/day, 50 mg/kg/day, 100 mg/kg/day Cinacalcet, there were QT prolonging effects noted for the higher doses at Months 3 and 6, but not at Months 9 and 12. The company attributed the prolongation of the QT interval to drug-induced reductions in serum calcium levels, which is a plausible explanation. Of note, it is unknown when the ECGs were obtained relative to T_{max} of Cinacalcet.

Electrocardiogram (ECG) data were collected in a larger proportion of the 1126 patients who took part in the three, 6-month phase 3 CKD - dialysis studies. The ECGs were read manually and obtained at trough drug levels. The mean QT_{cb} intervals at baseline were 426 ms and 427 ms in the placebo and cinacalcet patients, respectively. The mean changes in QT_{cb} from baseline to Endpoint were 4.4 ms and 5.7 ms in the placebo and cinacalcet groups, respectively.

The following table provides the percentage of patients within each category of change in QT_{cb} from baseline to Endpoint.

Endpoint	Placebo n = 470	Cinacalcet n = 656
Decrease	46%	42%
Increase < 30 ms	34%	37%
Increase 30 - 60 ms	15%	17%
Increase > 60 ms	5%	4%
> 450 ms (♂) > 470 ms (♀)	21%	24%
> 500 ms	3%	3%

The following table provides the proportion of subjects with normal baseline QT_{cb} intervals but prolonged QT_{cb} intervals [> 450 ms (♂) > 470 ms (♀)] by serum calcium levels at Week 14/18 and Week 26.

Calcium Level	Placebo n = 470	Cinacalcet n = 656
Week 14/18		
< 7.5 mg/dl	0.3%	0.9%
≥ 7.5 to < 8.4 mg/dl	0.6%	6%
≥ 8.4 to 10.3 mg/dl	7%	9%
> 10.3 mg/dl	3%	2%
Week 26		
< 7.5 mg/dl	0%	0.2%
≥ 7.5 to < 8.4 mg/dl	1%	3%
≥ 8.4 to 10.3 mg/dl	9%	11%
> 10.3 mg/dl	3%	2%

The table below provides the proportion of subjects with QT_{cb} intervals > 500 ms by serum calcium levels at Week 14/18 and Week 26.

Calcium Level	Placebo n = 470	Cinacalcet n = 656
Week 14/18		
< 7.5 mg/dl	0%	0.2%
≥ 7.5 to < 8.4 mg/dl	0.2%	2%
≥ 8.4 to 10.3 mg/dl	2%	1%
> 10.3 mg/dl	0.5%	0.2%
Week 26		
< 7.5 mg/dl	0%	0.2%
≥ 7.5 to < 8.4 mg/dl	0%	2%
≥ 8.4 to 10.3 mg/dl	3%	0.6%

> 10.3 mg/dl	0.5%	0.4%

As shown in the following table of potential adverse events that could be related to a prolongation of the QT interval, there were no major imbalances between the two groups.

Preferred Term	Placebo (N = 470) n (%)	Cinacalcet (N = 656) n (%)
Number of Subjects Reporting an Adverse Event	87 (19)	116 (18)
Arrhythmia	5 (1)	3 (<1)
Av Block	3 (<1)	2 (<1)
Bradycardia	2 (<1)	9 (1)
Cardiac Arrest	6 (1)	9 (1)
Convulsions	2 (<1)	8 (1)
Death Cause Unknown	3 (<1)	0 (0)
Dizziness	36 (8)	64 (10)
Extrasystoles Ventricular	0 (0)	1 (<1)
Fibrillation Atrial	7 (1)	12 (2)
Myocardial Infarction	8 (2)	5 (<1)
Palpitation	11 (2)	13 (2)
Status Epilepticus	0 (0)	1 (<1)
Syncope	4 (<1)	15 (2)
Tachyarrhythmia	1 (<1)	0 (0)
Tachycardia	16 (3)	21 (3)
Tachycardia Supraventricular	0 (0)	2 (<1)
Tachycardia Ventricular	1 (<1)	0 (0)

COMMENT: The *in vitro* data suggest that Cinacalcet has the capacity to inhibit some ion channels. The *in vivo* data indicate that high-doses of Cinacalcet are associated with prolongation of the QT interval. The phase-3 data demonstrate that treatment with Cinacalcet is associated with a small increase in the mean QT interval and with a slightly higher percentage of "outliers" (increases > 450 ms and 470 ms). It is entirely plausible, as the company contends, that these findings are due to Cinacalcet-induced reductions in serum calcium levels.

While the preclinical and clinical data do not raise serious concern that Cinacalcet is a clinically significant QT-interval prolonging drug, the database examining this question is incomplete. Furthermore, the phase-3 ECG data that are available are of limited value because the ECGs were obtained at trough, rather than peak drug levels.

Another factor that should be kept in mind when evaluating the Cinacalcet-QT issue, is the fact that Cinacalcet is metabolized by the CYP3A4 and 2D6 enzyme systems. Despite warnings to the contrary, once the drug is in wide-spread use, it is inevitable that some patients will be exposed to supratherapeutic concentration of Cinacalcet following concomitant use with drugs that inhibit the 3A4 or 2D6 enzyme systems.

A thorough QT study, if properly designed, would allow one to separate the intrinsic effect of Cinacalcet on the QT interval (if one exists) from effects due to the lowering of serum calcium concentrations. Lacking a strong signal from the available data, I believe a thorough QT study could be done post-approval. In this scenario, approval would be limited to the treatment of secondary HPT in patients with CKD receiving dialysis. This was the population for which

Cinacalcet was granted a priority review. This is the population for which one could argue that a small risk for QT prolongation would be outweighed by the drug's unique ability to simultaneously lower both serum iPTH and the Ca x P ion product. (the poor prognosis and lack of effective therapies for parathyroid carcinoma-related hypercalcemia also argues for approval of this indication before completion of a thorough QT study).

Serum Testosterone: In a long-term monkey study, serum testosterone levels were noted to have decreased significantly in the Cinacalcet compared with the placebo-treated animals. To evaluate this finding further, Amgen measured serum levels of total testosterone, free testosterone, LH, and FSH in 240 men who participated in Study 188.

Baseline levels of total and free testosterone were similar in the two groups. The median changes from baseline to Week 26 in total testosterone were 2 pg/ml and -49 pg/ml in the placebo and Cinacalcet groups, respectively (nominal p=0.0004); the median changes from Baseline to Week 26 in free testosterone were -8 pg/ml and -18 pg/ml in the placebo and Cinacalcet groups, respectively (nominal p=0.02).

Baseline levels of LH were similar in the two groups: approximately 11.3 mIU/ml. The mean values at Week 26 were 12.3 mIU/ml and 9.9 mIU/ml in the placebo and Cinacalcet groups, respectively. There were very small, insignificant changes in the levels of FSH from baseline to Week 26 in both groups.

COMMENT: Abnormalities in the hypothalamic-pituitary-gonadotropin axis are well documented in male patients with CKD receiving dialysis. Reduced libido and erectile dysfunction are two common manifestations of this altered endocrine milieu. Given the abnormal baseline endocrine profile of male dialysis patients, it may be difficult to assess the clinical significance of modest cinacalcet-induced reductions in testosterone levels. Nevertheless, future long-term studies (i.e., > 1 year) should, at a minimum, include assessments of bone mineral density and sexual function in male dialysis patients taking cinacalcet.

2.1.2 See the Appendix for a summary of Study 240, a 6-month extension trial.

2.1.3 Chronic Kidney Disease Not Receiving Dialysis

Two studies, 236 and 239, were conducted in patients with secondary HPT not yet receiving dialysis.

3 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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2.1.4 Parathyroid Carcinoma and "Intractable" Primary Hyperparathyroidism

A total of 10 patients with parathyroid carcinoma are currently being studied in trial 204, an open-label, single-arm, 3-year study. Five patients with primary hyperparathyroidism, 2 of whom reportedly had undergone unsuccessful parathyroidectomies and 3 whom Amgen claims parathyroidectomy was not a treatment option, were also enrolled into this study. The company refers to these five patients as having "intractable" primary hyperparathyroidism. Data up to 31 January 2003 are included in the NDA submission.

Study 204

Objective: to assess the ability of cinacalcet to reduce serum calcium concentrations in subjects with parathyroid carcinoma or intractable primary HPT.

Patient Population and Study Design: Male and female subjects with a diagnosis of parathyroid carcinoma or intractable primary HPTH with a serum calcium level > 12.5 mg/dl were eligible for study participation.

This is a multi-center, open-label, single-arm study that consists of a 30-day screening period, a 2 to 16-week titration phase, and a long-term maintenance phase (planned duration of study is 3 years)(see Figure below). Subjects initially received 30 mg cinacalcet BID and then every 2 weeks were titrated up to the next sequential dosage depending upon the previous week's serum calcium concentration and an adverse event assessment. Subsequent dosages in the titration sequence were 50 mg BID, 70 mg BID, 90 mg BID, 70 mg TID, 90 mg TID, 70 mg QID, and 90 mg QID. Dosage escalation continued until the serum calcium concentration was $\leq$ 10.3 mg/dL (2.5 mmol/L), the subject reached the highest possible dosage, or adverse events precluded further dosage increases. During the maintenance phase, visits were scheduled every 8 weeks. If serum calcium increased to an unacceptable level and the subject was not already at the maximum dosage, additional dosage increases were permitted using the same procedures as used in the titration phase.

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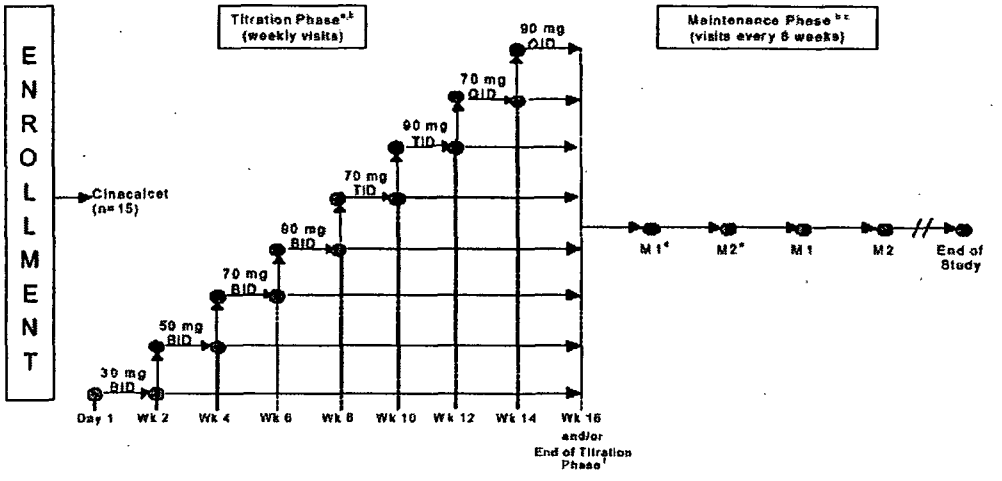


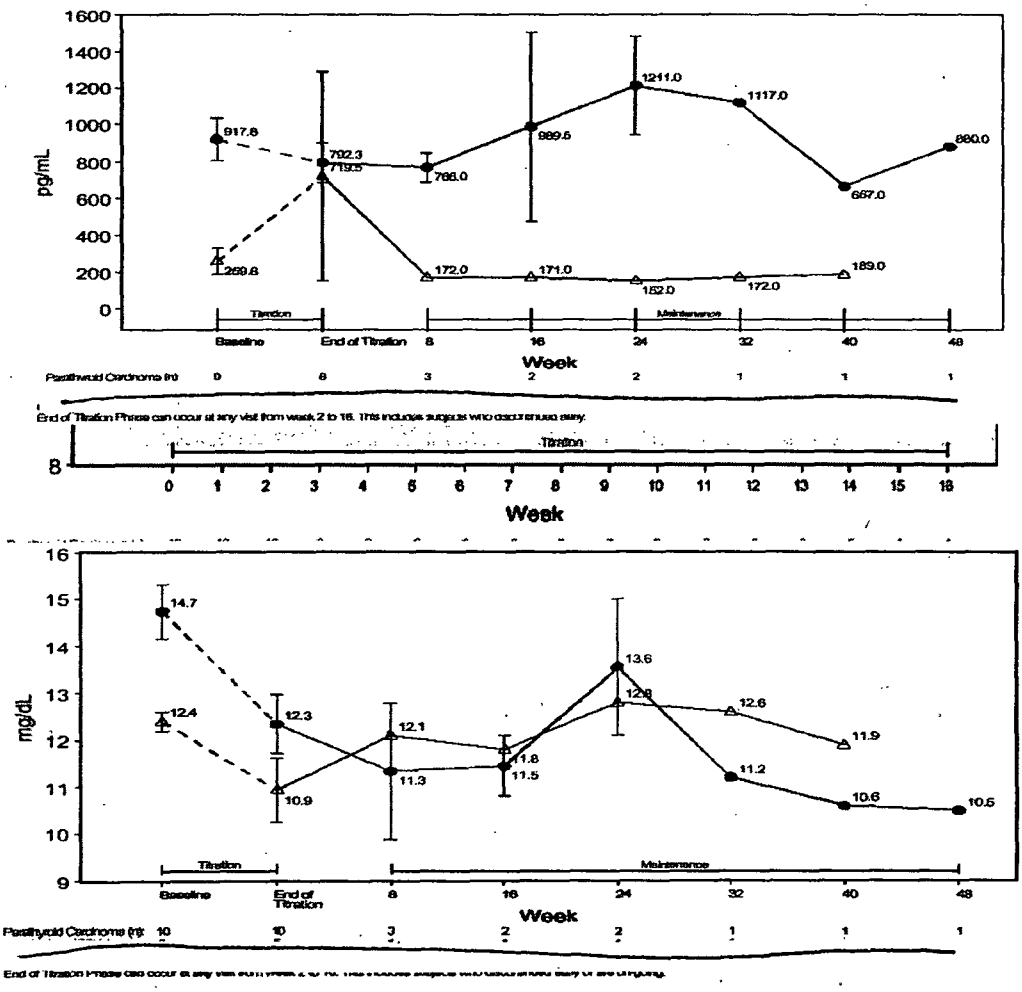
Exposure to Study Drug: At the completion of the titration phase in the carcinoma patients, 1 subject was receiving 30 mg BID, 1 was receiving 70 mg BID, 1, 70 mg TID, 3, 90 mg TID, 2, 70 mg QID, and 2, 90 mg QID. For the patients with intractable primary HPTH, 1 patient was receiving 30 mg BID, 1, 70 mg BID, 2, 70 mg TID, and 1, 90 mg TID.

Baseline Demographics and Disposition: Fifteen patients entered the study: 10 with parathyroid carcinoma and 5 with intractable primary HPTH. Sixty-seven percent were male and 93% were Caucasian. The average age of the patients with carcinoma was 48 years, and the average age of subjects with intractable HPTH was 67 years. Two of the 5 subjects who had intractable primary HPT had undergone parathyroid surgery, indicating that the remaining 3 subjects were contraindicated for parathyroidectomy. All but 1 subject had used bisphosphonates. Plasma iPTH concentrations at baseline were highly variable across subjects, with a mean of 918 pg/mL in subjects with parathyroid carcinoma . The mean serum calcium level in the subjects with carcinoma was 15.0 mg/dl
Of the 10 subjects with carcinoma who entered the trial, 5 remain on-study; of the 5 patients with intractable HPTH who entered the trial, 2 remain on-study. Two of the premature withdrawal (one from each group) were due to death.

COMMENT: Unlike the diagnosis of parathyroid carcinoma, which is well-defined and based on histological findings, intractable primary HPT,

Primary Efficacy Outcome: At the end of the titration phase, 7/10 carcinoma patients had a decrease in serum calcium of ≥ 1.0 mg/dl,

Secondary Efficacy Outcome: The following figures provides the mean serum iPTH (top) and calcium (bottom) concentrations for each group of patient throughout the study.



3.0 SUMMARY AND CONCLUSIONS

Efficacy

The National Kidney Foundation recently updated the treatment guidelines for patients with CKD and secondary HPT. Per these guidelines, patients on dialysis should strive for iPTH levels of 150 pg/ml to 300 pg/ml. The Ca x P ion product in dialysis patients should be below 55 $(mg/dl)^2$. These treatment goals aim primarily to reduce the risk for osteitis fibrosa while avoiding iatrogenic adynamic bone disease, and reduce the occurrence of soft tissue calcification, including that involving the coronary arteries and cardiac valves. Effective management of secondary HPT is presumed to reduce the risks for cardiovascular disease and fractures, though no controlled trials have been conducted to verify this assumption.

Data from three randomized, double-blind, placebo-controlled, 6-month trials of more than 1000 patients with CKD and secondary HPTH receiving dialysis, indicate that Cinacalcet, when initiated at 30 mg QD and titrated to a dose as high as 180 mg QD, reduces serum iPTH by approximately 50% relative to placebo. A much higher percentage of Cinacalcet-treated patients (40%) compared with placebo-treated subjects (5%) were able to achieve a serum iPTH level $\leq$ 250 pg/ml, and nearly twice as many Cinacalcet as placebo patients attained a serum Ca x P ion product of less than 55 mg/dl^2. Cinacalcet's calcimimetic action allows for the simultaneous reductions of serum iPTH and the Ca x P ion product - a duel treatment effect that is rarely achieved with current vitamin D and phosphate-binder therapies. For example, whereas 5% of placebo subjects had concurrent reductions of iPTH to 150 to 300 pg/ml and Ca x P < 55 mg/dl^2, almost 25% of Cinacalcet patients achieved these therapeutic goals.

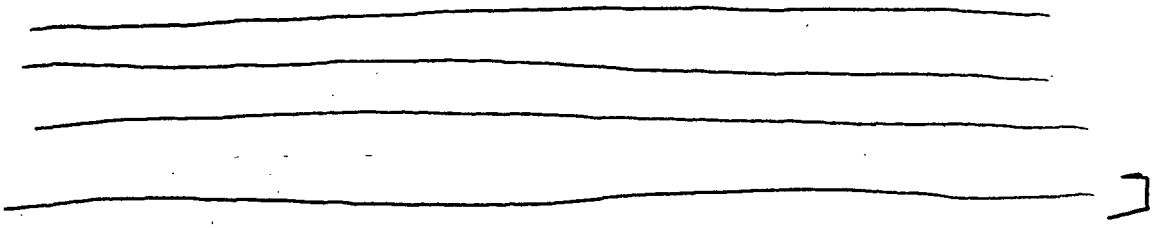
Based on the favorable changes in these biomarkers, it's not unreasonable to speculate that a treatment regimen that includes Cinacalcet might decrease cardiovascular morbidity and mortality. While evidence of such a benefit is lacking, the Division nevertheless accepts these biochemical changes as demonstration of efficacy for Cinacalcet in this population.

High doses of Cinacalcet had marginal efficacy in lowering serum calcium levels in 10 patients with parathyroid carcinoma. At the end of a 16-week, open-label, titration phase, 7 out of the 10 patients had reductions in serum calcium of $\geq$ 1.0 mg/dL. None of the patients, however, normalized their serum calcium levels.

To state the obvious, the data upon which Amgen is requesting approval for the treatment of parathyroid carcinoma are very limited. Yet, parathyroid carcinoma is a rare disease and

patients have few treatment options for the hypercalcemia associated with the condition. Cinacalcet offers the potential to satisfy an unmet medical need in this population of seriously ill patients.

In addition to the indications for the treatment of secondary HPT and the hypercalcemia of parathyroid carcinoma, Amgen is seeking approval for the treatment of patients with primary hyperparathyroidism for whom parathyroidectomy is not a treatment option.



Safety

Nausea and vomiting were the two most commonly reported adverse events and the most frequent reasons for premature withdrawal from the trials. Vomiting was dose-related, nausea was not.

The risk of hypocalcemia (< 8.4 mg/dL) is clearly increased in patients treated with Cinacalcet. The risk does not appear to be dose-related, but is does appear higher in pre-dialysis vs. dialysis patients. This is particularly true in pre-dialysis patients with relatively mild elevations in iPTH who are aggressively treated (i.e., goal iPTH < 65 pg/ml). In one study, nearly 50% of the Cinacalcet patients developed serum calcium levels less than 7.4 mg/dl, whereas none of the placebo subjects became hypocalcemic. Because calcium levels were monitored weekly in the trials and low levels were managed with supplemental calcium and/or vitamin D, it would seem appropriate for the labeling to recommend frequent, perhaps even weekly, measurement of serum calcium levels in patients at particular risk for hypocalcemia because of relatively mild hyperparathyroidism until a stable dose of Cinacalcet is achieved.

There was an imbalance between the Cinacalcet and placebo groups in the number of patients who reportedly suffered a "seizure" during the studies of patients with CKD who were receiving dialysis. It is unknown if this imbalance is a chance finding or reflects a true drug-induced risk, perhaps by way of hypocalcemia. At this point the most appropriate action would be to include the seizure information in the labeling, reinforce the need to regularly measure serum calcium levels, and closely monitor ongoing clinical trial and post-approval data for reports of seizures. Insofar as several of the patients who had seizures while treated with Cinacalcet had histories of epilepsy and two were on anticonvulsant therapy it would also be worthwhile for Amgen to conduct *in vitro* enzyme induction studies to rule out the possibility that Cinacalcet enhances the activity of enzymes responsible for the metabolism of common anti-seizure medications.

Regarding cardiac repolarization, limitations of the preclinical and clinical data do not allow for a comprehensive assessment of Cinacalcet's potential to significantly prolong the QT interval. It is unclear if the minor QT prolongation observed in the phase-3 trials is due to lowering of serum calcium levels or to direct effects of Cinacalcet or its metabolites. Given this degree of uncertainty, a thorough QT would provide valuable information regarding the overall risk - benefit relationship of this drug. While admittedly a conservative approach, until a thorough QT study is completed, it would be prudent to limit approval of Cinacalcet to patients with secondary HPT and CKD receiving dialysis and to patients with parathyroid carcinoma - the populations who stand to benefit the most from the drug and for which a small risk for QT prolongation would therefore be acceptable.

Not only do patients with pre-dialysis CKD have less severe hyperparathyroidism than those CKD requiring dialysis, and therefore in theory have a less favorable benefit-to-risk profile, but they may also be at greater risk for Cinacalcet-induced hypocalcemia - itself a potential trigger of a malignant arrhythmia. This is yet another reason to thoroughly characterize the QT-prolonging potential of Cinacalcet before approving it for patients with less serious forms of disease.

Conclusions

Based upon the data presented in this NDA, I conclude that the benefit-to-risk profile of Cinacalcet supports approval for the treatment of secondary HPT in patients with CKD receiving dialysis and the treatment of hypercalcemia associated with parathyroid carcinoma. I consider the following two indications approvable [redacted]

4.0 REGULATORY RECOMMENDATIONS

I recommend approval of cinacalcet for the indication: The treatment of secondary HPT in patients in patients with CKD receiving dialysis.

I recommend approval of cinacalcet for the indication: The treatment of hypercalcemia associated with parathyroid carcinoma.

I recommend approvable for the indication: The treatment of secondary HPT in patients in patients with pre-dialysis CKD,

I recommend approvable for the indication: The treatment of patients with primary hyperparathyroidism for whom parathyroidectomy is not an option,

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Appendix

Figure 7-2. Guidelines for Treating Hypocalcemia

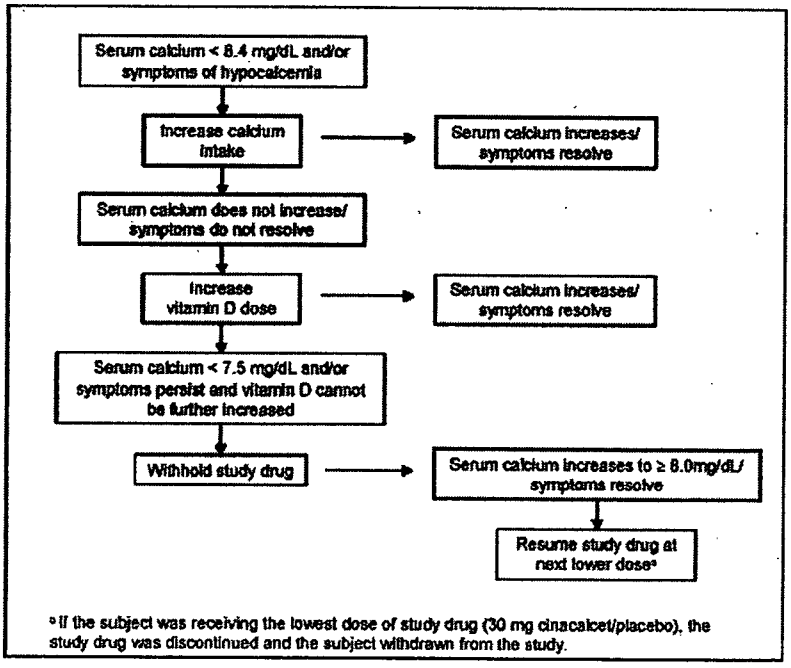

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Figure 1. Number (Percent) of Subjects Receiving Each Dose at the End of the Titration Phase

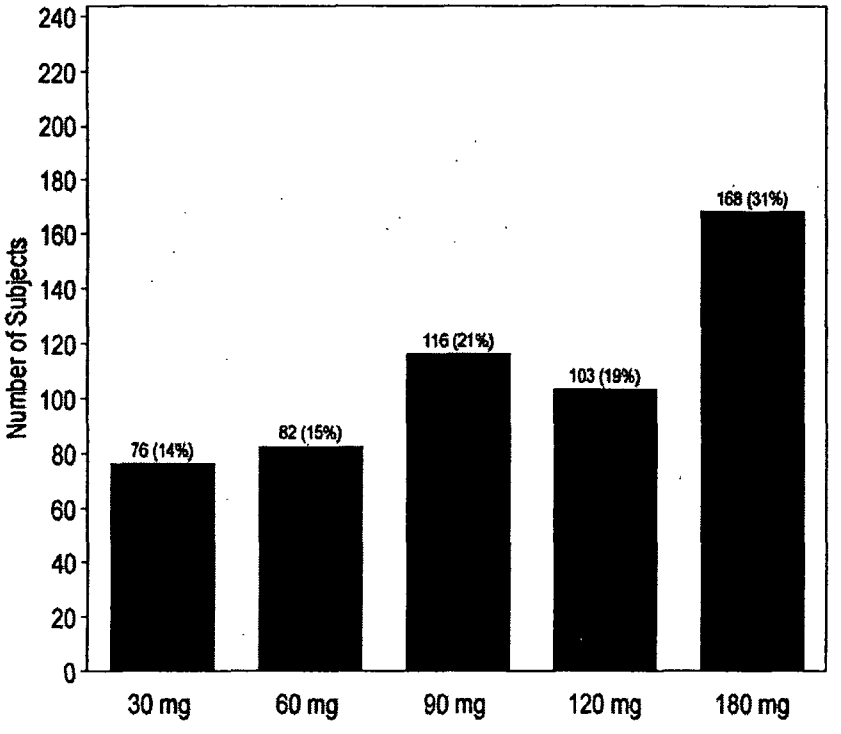

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Figure 2. Number (Percent) of Subjects Receiving Each Dose at the End of the Efficacy Assessment Phase

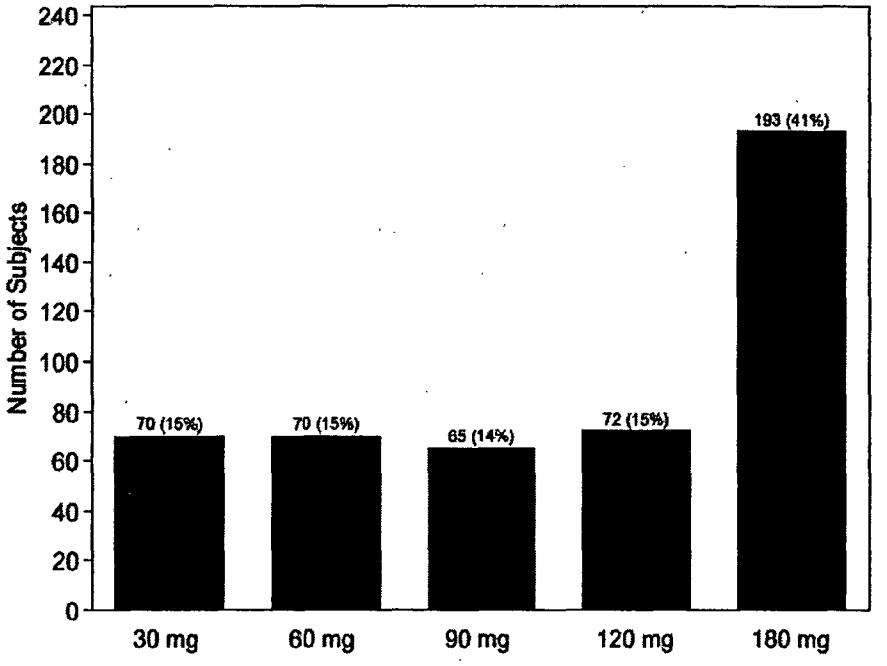

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Table 14. Frequency of Measurement of PTH and Calcium/Phosphorus by Stage of CKD

CKD Stage	GFR Range (mL/min/1.73 m²)	Measurement of PTH	Measurement of Calcium/Phosphorus
3	30-59	Every 12 months	Every 12 months
4	15-29	Every 3 months	Every 3 months
5	<15 or dialysis	Every 3 months	Every month

Table 15. Target Range of Intact Plasma PTH by Stage of CKD

CKD Stage	GFR Range (mL/min/1.73 m²)	Target "Intact" PTH (pg/mL [pmol/L])
3	30-59	35-70 [3.85-7.7 pmol/L] (OPINION)
4	15-29	70-110 [7.7-12.1 pmol/L] (OPINION)
5	<15 or dialysis	150-300 [16.5-33.0 pmol/L] (EVIDENCE)

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Study 239

Table 11-4. Vitamin D Sterol, Phosphate Binder, and Calcium Supplement Use

	Placebo (N = 27) n (%)	Cinacalcet (N = 27) n (%)
Never used vitamin D during the study	18 (67)	14 (52)
Started using vitamin D after the first dose of study drug	0 (0)	7 (26)
Used/Started vitamin D during the study	9 (33)	13 (48)
Oral Alfacalcidol only	5 (19)	7 (26)
Oral Calcitriol/Rocaltrol only	3 (11)	4 (15)
Doxercalciferol/Hectorol only	1 (4)	1 (4)
Combination of vitamin D above	0 (0)	1 (4)
Never used phosphate binder during the study	19 (70)	21 (78)
Started using phosphate binder after the first dose of study drug	0 (0)	1 (4)
Used/Started phosphate binder during the study	8 (30)	6 (22)
Calcium Containing only	7 (26)	6 (22)
Sevelamer HCl/Renagel only	1 (4)	0 (0)
Never used calcium supplement during the study	20 (74)	9 (33)
Started using calcium supplement after the first dose of study drug	1 (4)	13 (48)
Used/Started calcium supplement during the study	7 (26)	18 (67)

Study 236

Table 11-4. Summary of Vitamin D and Phosphate Binder Use During the Study

	Placebo N= 31	AMG 073 N= 30
Never used vitamin D during the study	27 (87%)	11 (37%)
Used / started vitamin D during the study	4 (13%)	19 (63%)
Hectorol	0 (0%)	3 (10%)
Rocaltrol	2 (6%)	12 (40%)
Other	1 (3%)	2 (7%)
Used Combination of Vitamin D Above	1 (3%)	2 (7%)
Never used phosphate binder during the study	27 (87%)	18 (60%)
Used / started phosphate binder during the study	4 (13%)	12 (40%)
Calcium containing	4 (13%)	12 (40%)
Vitamin D dose increased / subjects receiving vitamin D at baseline	0/ 3	1/ 4
Phosphate binder dose increased / subjects receiving phosphate binder at baseline	0/ 3	2/ 5

Study 240

This was a placebo-controlled, double-blind, 6-month extension study to assess the long-term safety of cinacalcet in patients with CKD receiving dialysis. Subjects retained their assigned treatment from the previous cinacalcet studies (20000172 and 20000183) and began this study on their final dose of study drug from the previous study. End-of-study assessments for the previous study were considered day 1 assessments for the current study. Study visits occurred at weeks 4, 8, 12, 16, 20, 24, and 26. During the current study, doses of cinacalcet or placebo were titrated based on plasma intact parathyroid hormone (iPTH) response and safety profile. Safety assessments were used to evaluate the frequency, severity, and relationship to treatment of all adverse events and changes in laboratory parameters. At the end of the current study, a physical exam and an electrocardiogram (ECG) were performed. iPTH, serum calcium, and serum phosphorus concentrations were determined to assess the long-term efficacy of cinacalcet in maintaining reductions in the levels of iPTH, the product of serum calcium and phosphorus concentrations (Ca x P), and calcium and phosphorus concentrations compared with placebo.

A total of 128 subjects were randomized to cinacalcet and 138 to placebo. The mean age was 54 years; about 60% were male; and approximately 50% were Black. Doses of 30 through 180 mg were possible depending on tolerance to the drug.

Seventy-six percent of the subjects in the cinacalcet group and 82% of the subjects in the placebo group completed the study.

Mean iPTH concentrations at the beginning of the current study were 295 and 699 pg/mL for the cinacalcet and placebo groups, respectively. The proportion of subjects with a mean iPTH $\leq$ 250 pg/mL at week 26 was 54% in the cinacalcet group and 13% in the placebo group at the end of the study.

Mean Ca x P values at baseline of the current study were 51.4 and 59.3 (mg/dL)2 for the cinacalcet and placebo groups, respectively. Relative to the baseline values in the previous studies, the cinacalcet group had mean Ca x P values that were decreased by 9% compared with a 1% decrease in the placebo group by the end of the study. Reductions in Ca x P values in the cinacalcet group resulted from decreases in both serum calcium (5%) and phosphorus (4%) concentrations.

Most adverse events were mild to moderate in severity and were typical for the subject population. Thirteen subjects (10%) in the cinacalcet group and 0 subjects from the placebo

group withdrew because of adverse events; the most common adverse events that lead to withdrawal (cinacalcet, placebo) included nausea (4%, 0%), and/or vomiting (3%, 0%). The most common adverse events in the cinacalcet group were (cinacalcet, placebo) nausea (30%, 15%), vomiting (27%, 9%), diarrhea (20%, 17%), upper respiratory infection (17%, 13%), limb pain (16%, 15%), hypotension (12%, 14%), and headache (11%, 15%). Serious adverse events were reported by 34% and 32% of subjects who received cinacalcet and placebo, respectively. Thirty-two percent of subjects in the cinacalcet group and 31% of subjects in the placebo group had adverse events that were classified as (cinacalcet, placebo) severe (28%, 24%), life-threatening (1%, 2%), or fatal (3%, 5%). No clinically relevant differences were noted between treatment groups in clinical laboratory measurements, other than expected differences in plasma iPTH, serum calcium, and serum phosphorus concentrations.

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David Orloff
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MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Consultative Clinical Review

NDA: 21-688 (cinacalcet)

Sponsor: Amgen

Submission: NDA supplementary information in submission of 21 January 2004.

Review date: 9 February 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Concurrence: DC Throckmorton, MD, Division Director

Distribution: NDA 21-688

HFD-510/Hedin/Beaston/Kehoe

Cinacalcet is a small-molecule agonist at the parathyroid's calcium sensor. It is under NDA review for use in primary and secondary hyperparathyroidism. The Division of Cardio-Renal Drug Products is asked to comment on the need for a "thorough" QT study.

Doses in phase I-III studies ranged up to 180 mg once-daily or 90 mg four-times-daily. Peak levels are reached after about 4 hours and the primary half-life is about 6 hours. Factors potentially affecting plasma levels include renal failure, 3A4 inhibition, and 1A2 inhibition.

Sparse QT data were obtained in numerous studies. For post-phase I studies, the synopses are not adequate to describe the timing of the ECGs. Most or all of the QT data appear to have come from automated reading. The sponsor's analyses of QTcB by dose or plasma level detected no signal (mean or outlier), although it is not possible to quantify the magnitude of mean signal that could have been missed. The sponsor was, however, able to detect an effect of serum calcium on QTcB, about -10 ms per mg/dL. As the sponsor acknowledges, this effect may not be innocuous.

Safety data apparently reveal no adverse events with a clear relationship to QT effects, not surprising for a database as small as this.

A thorough evaluation of QT effects would appear to be quite relevant. Such a study ought to include a dosing regimen that challenges tolerability, allows for production of metabolites, has ECGs timed to, at least, peak plasma levels of parent and major metabolites, and includes an assay validation. To differentiate effects of hypocalcemia from true drug effects, this study might need external control of plasma calcium levels.

The Division of Cardio-Renal Drug Products appreciates the opportunity to comment upon this application. Please contact the Division for further clarification, if needed.

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Randy Hedin
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CSO

David Orloff
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