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

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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

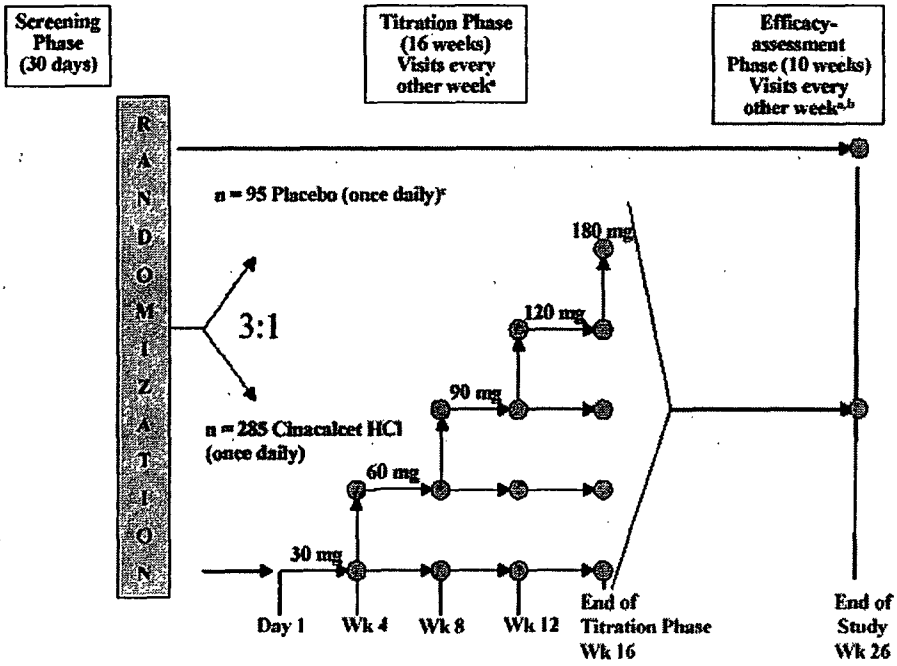
The efficacy and safety of Cinacalcet in the treatment of secondary HPT in patients on dialysis were examined in three, 6-month, placebo-controlled trials of similar design: Studies 172, 183, and 188. For a subset the patients who completed studies 172 and 183, and additional 6 months of double-blind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



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

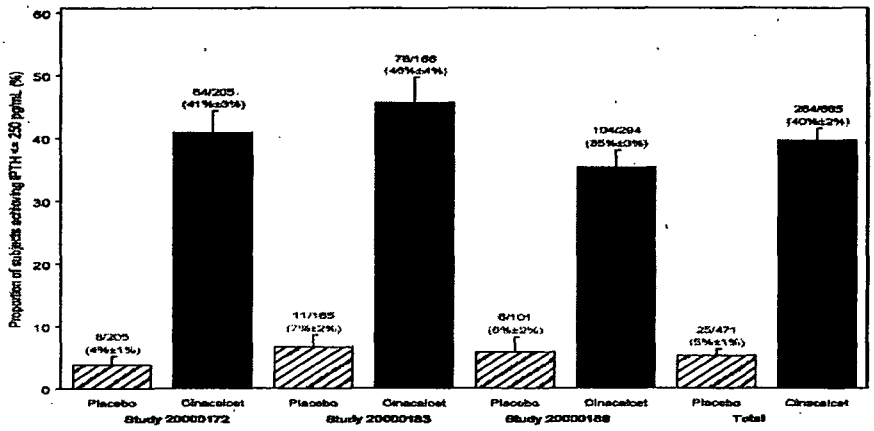
subject experienced symptoms of hypocalcemia and/or a serum calcium < 8.4 mg/dL, calcium supplements and/or phosphate binders could be increased to resolve the symptoms (if present) or to increase serum calcium to ≥ 8.4 mg/dL. If these measures were insufficient, the vitamin D dose could be increased.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



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