CLINICAL REVIEW

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1 Recommendations of Approvability

Approve

1.2 Recommendations of Postmarketing Studies/or Risk Management

None

2. SUMMARY OF CLINICAL PROGRAM

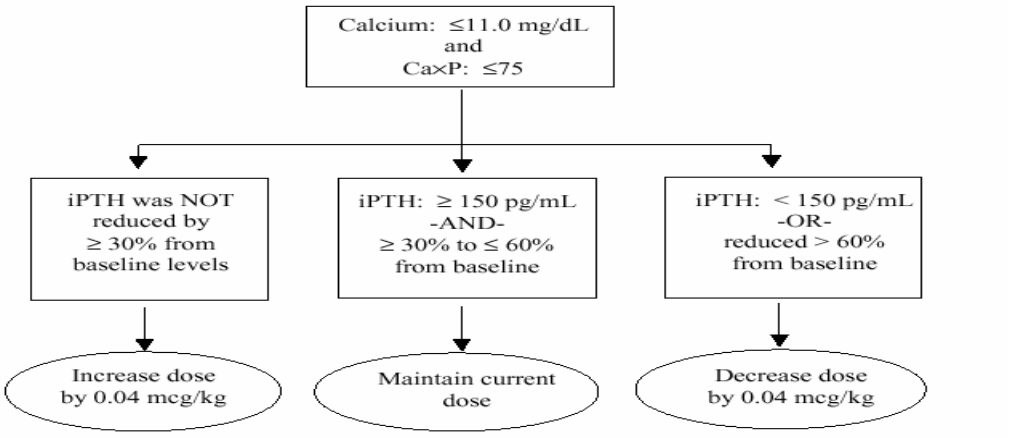
2.1 Brief Overview of Clinical Program

As part of the Pediatric Exclusivity provision of FDAMA, the Agency issued a 22 February 2001 Written Request to Abbott, requesting that the company conduct a clinical study to examine the efficacy and safety of Zemplar injection in the treatment of pediatric patients with secondary hyperparathyroidism associated with chronic kidney disease. The requested study was a randomized, double-blind, placebo-controlled investigation comprised of a 2-6-week Pre-Treatment phase, a 12-week Treatment phase, and a 4-week Follow-Up phase. The study enrolled male and female patients, aged 2 to 20 years, who had been receiving hemodialysis for at least one month prior to screening. For entry into the Treatment phase of the study, subjects had to have a serum iPTH level of >=300 pg/mL, a corrected serum calcium level <=10.5 mg/dL, and a Ca X P product level <=70.

Study drug treatment consisted of an IV bolus of Zemplar injection or placebo 3 times weekly, during the subject's regularly scheduled hemodialysis sessions. The initial dose of study drug was determined by the degree of secondary hyperparathyroidism, as determined by the last iPTH value obtained at the final week of Pre-Treatment

Decisions to maintain, increase or decrease the subject's dose were to be based upon the previous week's laboratory results and were to be implemented on the

first dialysis session (Monday or Tuesday) of the following week. Dose increases were limited to once every 2 weeks (starting at Treatment Week 3) and dose decreases could have occurred once per week. All doses were to be rounded to the nearest 10th mcg. The method for determining dose maintenance, increase, or decrease is illustrated in the Figure below.



In addition to the parameters provided in the Figure, the following criteria applied: If calcium was >=11.0 mg/dL and Ca X P Product > 75, the dose was to be decreased by 0.04 mcg/kg; If calcium was > 11.0 mg/dL at any time, the dose was to be withheld until the calcium level returned to =10.5 mg/dL. The dose may have been restarted at 0.04 mcg/kg less than the dose at which the therapy was withheld. If a subject's dose needed to be decreased and the new calculated dose, based on a 0.04 mcg/kg reduction, equaled zero, then the dose was to be decreased by 50% rather than by 0.04 mcg/kg. If the new calculated dose, based on the 50% reduction criteria, was < 0.5 mcg, the subject was to be discontinued from the study.

To limit exposure to inappropriately high levels of iPTH, subjects were to be withdrawn from the study if they had 2 consecutive iPTH values > 700 pg/mL after 4 weeks of treatment and if this level represented an increase from baseline, regardless of their phosphorus level.

The primary efficacy endpoint was the proportion of patients in each group who achieved 2 consecutive $\geq$ 30% decreases from baseline iPTH level.

2.2 Efficacy

A total of 29 patients were randomized to either placebo (n=14) or Zemplar (n=15) injection 3 times per week. The two groups were well-matched for baseline characteristics. The mean age was 14 years (range 5-20 yr),

approximately 70% of the patients were male, almost 50% were Black, and the average duration of hemodialysis was 2.5 years. Most of the subjects were taking a calcium-based phosphate binder, and the mean iPTH level was approximately 800 pg/ml.

Ten of the 15 Zemplar-treated patients and only 2 of the 14 placebo-treated subjects completed the trial. Seventy percent of the premature discontinuations in the placebo group were due to inappropriate elevations in iPTH levels.

The mean dose of Zemplar administered during the study was 4.6 mcg.

In a Last-Observation-Carried-Forward analysis, 9 (60%) of the Zemplar subjects and 3 (21%) of the placebo subjects had two consecutive $\geq$ 30% decreases from baseline in iPTH (95% CI for the difference -1.0%, 63%; p=0.06).

The mean change in iPTH levels from baseline to Endpoint were -164 pg/ml in the Zemplar group and 238 in the placebo group (nominal p=0.03).

The proportion of subjects who achieved 2 consecutive iPTH values below 300 pg/ml were 20% in the Zemplar group and 14% in the placebo group.

2.3 Safety

There were no deaths in this study. Three Zemplar and 3 placebo subjects had at least one serious adverse event (SAE) during the Treatment and Follow Up Phases. The events in these subjects were all related to clotted venous access requiring hospitalization. The SAEs in the placebo group included: bleeding post A-V graft placement, cellulitis, depression, and sepsis. All these events also required hospitalization. No subject withdrew from the study due to an adverse event.

Sixty-seven percent of Zemplar subjects reported a total of 17 AEs, while 43% of placebo subjects reported a total of 15 AEs. There were no meaningful differences between groups in the reporting of adverse events.

In categorical analyses, 23% of Zemplar vs. 31% of placebo patients had at least one serum calcium level > 10.3 mg/dl (p=1.0); 75% of Zemplar compared with 43% of placebo patients had at least one serum phosphorus value above normal during the study (p=0.3); and 40% vs. 14% of Zemplar vs. placebo subjects had a least one Ca x P ion product > 72 (nominal p=0.2).

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/s/

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for Dr. Orloff