MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products

Application#:	N20-819	**Sponsor:**	Abbott
Application Type:	Pediatric Exclusivity	**Proprietary Name:**	Zemplar Injection
Date Submitted:	9/30/2003	**USAN Name:**	Paricalcitol
Date of Review:	01/23/2004	**Route of Use:**	Oral
Standard/Priority:	Priority	**Indication:**	Secondary HPTH
UF Goal Date:	03/29/2004	**Reviewer:**	Eric Colman

Review Summary:

See Executive Summary

Outstanding Issues: None

Recommended Regulatory Action: Approve

Signatures:	
	Medical Reviewer:
	Team Leader:

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CLINICAL REVIEW

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1 Recommendations of Approvability

Approve

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None

2. SUMMARY OF CLINICAL PROGRAM

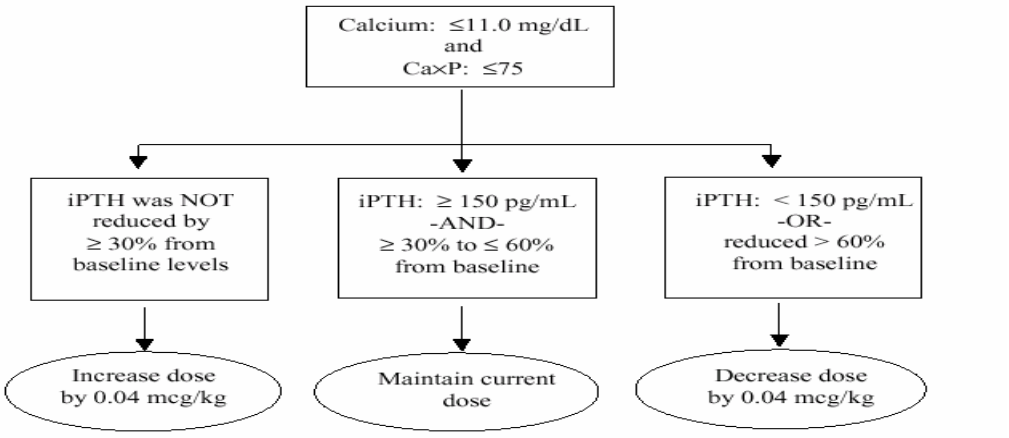
2.1 Brief Overview of Clinical Program

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-one percent of the placebo patients were discontinued due to inappropriate elevations in iPTH levels (i.e., 2 consecutive iPTH levels > 700 pg/ml and greater than baseline after 4 weeks of treatment).

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).

I. INTRODUCTION AND BACKGROUND

Zemplar injection was approved in April 1998, for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. Abbott is currently developing Zemplar capsules under IND.

Although the number of pediatric patients with secondary hyperparathyroidism due to chronic kidney disease is much smaller than the adult chronic kidney disease population, children and adolescents with impaired renal function do require vitamin D therapy to help control iPTH levels.

The Agency issued a 15 September 1999 Written Request for calcitriol (Calcijex injection), another vitamin D compound manufactured by Abbott, to obtain information about its efficacy and safety in pediatric patients with chronic kidney disease. The study was completed as requested and the product labeling for Calcijex was updated to include the information from the pediatric study.

Because the Agency believed health care providers would benefit from having data on the use of Zemplar in pediatric patients with chronic kidney disease, a Written Request for a clinical study was issued on February 22, 2001. The study is similar in design to that conducted with Calcijex.

II. EVALUATION OF FINANCIAL DISCLOSURE

The applicant of this supplemental NDA has submitted confirmation that each investigator required to disclose to the sponsor whether the investigator had a proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. Further, the sponsor has certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

III. REVIEW OF CLINICAL STUDY

Title: A Phase 4, Double-Blind, Placebo-Controlled, Multi-Center Study to Determine the Safety and Effectiveness of Zemplar (Paricalcitol Injection) in Decreasing Serum Intact Parathyroid Hormone Levels in Pediatric End Stage Renal Disease Subjects on Hemodialysis - Protocol 2001022

Study Initiated: 28 January 2002

Study Objective: To characterize the efficacy and safety of Zemplar as compared to placebo in lowering iPTH levels in pediatric subjects with end-stage renal disease (ESRD)

undergoing hemodialysis (HD).

Study Design: This was a Phase 4, double-blind, placebo-controlled, multi-center study in pediatric ESRD subjects with 2° HPT who were undergoing HD. The study was divided into 4 phases: Screening Phase, Pre-treatment Phase, Treatment Phase, and Follow-Up Phase. The Pre-treatment Phase was defined as the 2- to 6-week period prior to the start of study drug administration. The purpose of the Pre-treatment Phase was to "wash out" any remaining vitamin D compounds and their carry-over effects from the subject's system and to establish baseline values. The length of the Pre-treatment Phase was dependent on the time it took the subject to achieve the appropriate lab criteria for entry into the Treatment Phase (Ca =10.5 mg/dL, Ca....P =70, and iPTH =300 pg/mL).

Subjects satisfying all inclusion/exclusion criteria were eligible for entry into the Treatment Phase. Qualified subjects were randomized in a 1:1 ratio to receive either Zemplar or placebo. Study drug was administered as a bolus dose 3 x weekly (no more frequently than every other day) at any time during HD. The initial dose of study drug was determined based on the degree of 2° HPT, as determined by the subject's baseline iPTH value. Decisions to maintain, increase, or decrease the dose were based on limited chemistry results collected weekly. The initial dose level was maintained for Treatment Weeks 1 and 2. Dose decreases could have occurred weekly and dose increases could have occurred no more frequently than every other week, starting at Treatment Week 3. 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. Safety was monitored through adverse event monitoring, the change from baseline in laboratory assessments, and the change from baseline in vital signs. After the Treatment Phase, subjects entered the Follow-Up Phase. Subjects returned for study procedures at the Follow-Up Visit (approximately 2-7 days after the last dose of study drug) and were not to restart any vitamin D treatment until after the Follow-Up Visit was complete.

If the subject prematurely discontinued from the study, the procedures outlined for the Follow-Up Visit must have been completed within 2-7 days of the last dose of study drug, and prior to the initiation of vitamin D therapy.

An independent Data Safety Monitoring Board (DSMB) was used to monitor the ongoing safety of the trial as specified in the DSMB charter. The final recommendation of the DSMB encouraged the sponsor to evaluate the data of pre-puberty patients (under the age of 12 or 13) as a subgroup. Therefore, separate subgroup analyses were performed for subjects less than 13 years of age; this was complemented with subgroup analyses for subjects 13 years of age or older.

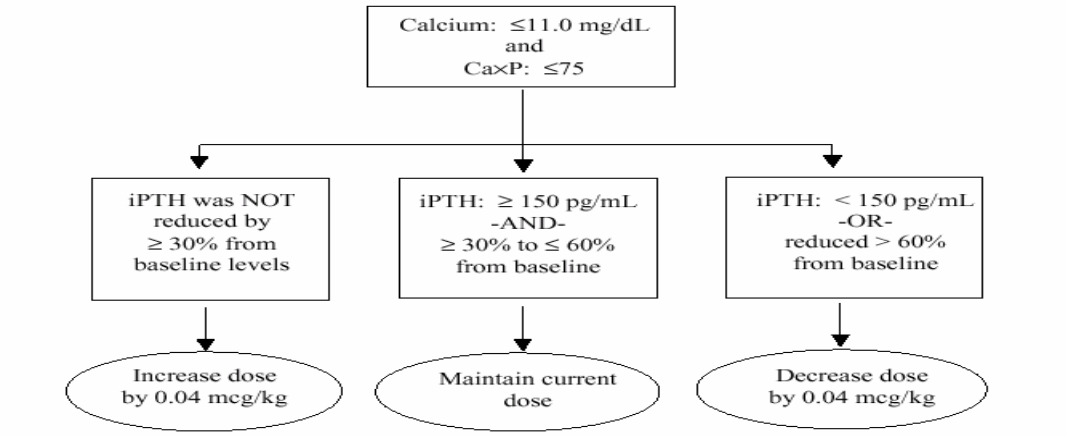
Study Population: Male and female patients with ESRD, aged 2 to 20 years, and receiving hemodialysis for at least one month prior to screening were eligible for trial enrollment. For entry into the Pre-treatment Phase the subject must have had: iPTH level of >=100 pg/mL, a corrected calcium level <=10.5 mg/dL, and a Ca X P product level <=70. For entry into the Treatment Phase the subject must have had iPTH level of >=300 pg/mL, a corrected calcium level <=10.5 mg/dL, and a Ca X P level <=70. The last iPTH, calcium, and Ca X P values were obtained at the final week of the Pre-treatment Phase.

A subject was excluded from the study if he/she met any of the following criteria:

1. Subject had a history of an allergic reaction or significant sensitivity to drugs similar to the study drug.
2. Subject had received partial parathyroidectomy within 1 year prior to the Screening Phase.
3. Subject had acute renal failure within 3 months of the Screening Phase.
4. Subject had taken aluminum-containing phosphate binders for > 3 weeks in the last 3 months prior to the Screening Phase, or required such medications for > 3 weeks during the study.
5. Subject had a current malignancy, or clinically significant liver disease, in the opinion of the Investigator.
6. Subject had a history of drug or alcohol abuse within 6 months prior to the Screening Phase.
7. Subject was known to be human immunodeficiency virus (HIV) positive.
8. Subject had evidence of poor compliance with diet, medication or HD that may have interfered, in the Investigator's opinion, with adherence to the protocol.
9. Subject had received any investigational drug within 30 days prior to the Screening Phase.
10. Subject was taking maintenance calcitonin, glucocorticoids, or other drugs that may have affected calcium or bone metabolism.
11. For any reason, subject was considered by the Investigator to be an unsuitable candidate to receive Zemplar injection.

Study Drug Administration: Treatment consisted of an IV bolus injection of Zemplar or placebo 3 times weekly, during the subject's regularly scheduled HD session. Doses could have been given after blood draws for laboratory samples, before, during, or after HD. The initial dose of study drug was based on the degree of 2° HPT, as determined by the last iPTH value obtained at the final week of Pre-treatment (baseline iPTH), and the physician's prescribed-dry weight from that same week (see Table 2). This weight was to be used for all dose calculations throughout the study. The initial dose level was to be maintained for Treatment Weeks 1 and 2.

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.

Study Endpoints (see Table in Appendix): The primary efficacy endpoint was the proportion of subjects in each group who achieved 2 consecutive =30% decreases from baseline iPTH levels. The secondary efficacy endpoint was the proportion of subjects in each group who achieved 2 consecutive iPTH values below 300 pg/mL. Serum levels of

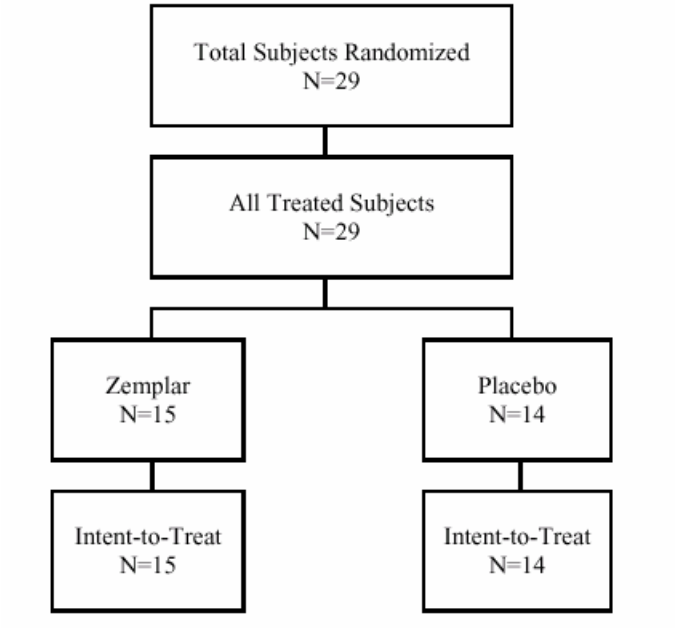
calcium, phosphorus, iPTH, and albumin were samples weekly during the Treatment phase. Hypercalcemia was defined as at least one corrected serum calcium level greater that 11.2 mg/dL.

Statistical Analyses: The primary efficacy endpoint was to be evaluated with statistical hypothesis testing utilizing subjects in the Intent-to-Treat population (Full Analysis Set). A Fisher's exact test was to be used to test for a difference between treatment groups in the proportion of subject's achieving the efficacy endpoint. The proportion of subjects in each treatment group who achieved 2 consecutive iPTH values below 300 pg/mL, a secondary efficacy endpoint, was to be evaluated with descriptive summary statistics.

The Intent-to-Treat population (Full Analysis Set) was to be used to establish efficacy, *i.e.,* all randomized subjects with a baseline and who had at least 2 on-treatment iPTH assessments. The all treated subject population was to be used in the safety assessment, *i.e.,* all randomized subjects who received at least 1 dose of study drug.

Results

Patient Disposition: Twenty-nine subjects were randomized in the study by 11 investigative sites in the US. Each of these 29 subjects received at least 1 dose of study drug; 15 received Zemplar and 14 received placebo. Subject disposition is presented in the following Figure.



Among the 29 (15 Zemplar, 14 placebo) randomized and treated subjects, a greater

proportion of Zemplar-treated subjects completed the study compared to placebo-treated subjects (10/15, 67% *vs.* 2/14, 14%, respectively). Seventeen (5 Zemplar, 12 placebo) subjects prematurely terminated from the study. A notably higher proportion of subjects in the placebo group prematurely terminated due to increasing iPTH (10/14, 71%) compared to subjects in the Zemplar group (4/15, 27%). One (7%) placebo subject prematurely terminated due to missing 3 consecutive doses of study medication; 1 (7%) subject in each group prematurely terminated due to "other" reasons. The pharmacist inadvertently opened the envelope of Subject #101 (Zemplar) and broke the blind on Day 19. No other blind breaks were reported during the study. Per Investigator's request, Subject #114 (placebo) was prematurely terminated due to preparation for transplant.

As shown in the below table, a much larger percentage of patients randomized to placebo than Zemplar discontinued study participation prematurely - mostly because of elevated iPTH levels.

Reason for Premature Termination	**Zemplar (N=15)**	**Placebo (N=14)**
Increased iPTH	4 (27%)	10 (71%)
Missed 3 consecutive doses of study drug	0 (0%)	1 (7%)
Other	1 (7%)	1 (7%)
Total Prematurely Terminated	5 (33%)	12 (86%)
Total Completed 12 weeks of Treatment	10 (67%)	2 (14%)

COMMENT: The much larger number of subjects in the placebo group vs. the Zemplar group who discontinued prematurely due to elevated iPTH levels must be taken into account when interpreting the efficacy results. For example, the results of the LOCF analyses will differ substantially from the Completers results, with the former providing a more accurate assessment of drug efficacy (see figures below).

Protocol deviations occurring during the study were mainly associated with errors in study drug administration or mistiming and/or inadvertent omission of clinical evaluations. The observed deviations are unlikely to have affected the integrity of the data.

Baseline Demographics:

Baseline Demographic Characteristics			
Characteristic	Zemplar	Placebo	p-value
Age yr	13.6	14.3	0.7
Gender % Male	87%	64%	0.2
Race % Black	47%	43%	1.0
Time since first HD yr	2.8	2.3	0.5
SBP mmHg	126	131	0.4
DBP mmHg	75	81	0.2
Calcium-based P Binder	93%	79%	0.7
Height cm	137	149	0.2
iPTH pg/ml	841	740	0.5
Weight kg	42	46	0.5

COMMENT: The two groups were well-matched for baseline demographic characteristics.

Primary Efficacy Endpoint

The mean and median doses of Zemplar administered during the study were 4.6 mcg and 4.7 mcg, respectively.

In an analysis of the ITT population, 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).

Secondary Efficacy Endpoints

Although the sample sizes are low for subgroup analyses of the responses to treatment by baseline iPTH level, the results are of interest.

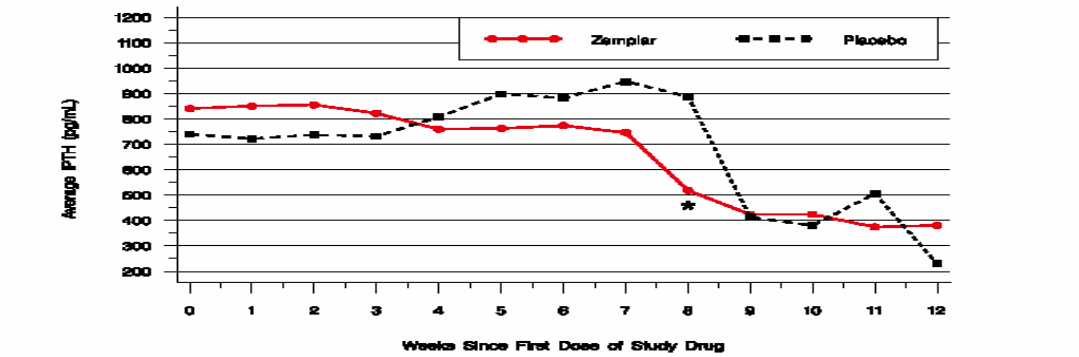
Primary Efficacy Outcome by Baseline iPTH level		
Baseline iPTH	Zemplar	Placebo
< 500 pg/ml	25%	20%
500 to < 1000 pg/ml	67%	20%
> 1000 pg/ml	80%	25%

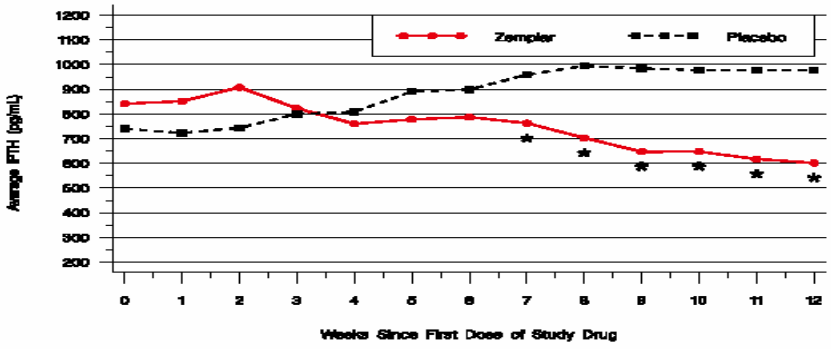
The mean change in iPTH levels from baseline to Endpoint were -164 pg/ml in the Zemplar group and 238 in the placebo group (nominal p=0.03).

COMMENT: Although the favorable results of the primary efficacy analysis were of borderline statistical significance (0.06) in this pediatric study, there is ample evidence that Zemplar is efficacious in adult subjects with secondary hyperparathyroidism and CKD requiring dialysis. This *a priori* experience suggests to this reviewer that the sample size of the pediatric study was inadequate to demonstrate a robust statistically significant effect of Zemplar vs. placebo.

LOCF vs. Completers

As shown in the two figures below, because of the high dropout rate due to lack of efficacy in the placebo group, the pattern of the change in the mean levels of iPTH in the LOCF (top) vs. the Completers (bottom) populations are very different.





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.

Safety

Deaths

There were no deaths reported.

Serious Adverse Events

Three Zemplar and 3 placebo subjects had at least one 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.

Adverse Events Leading to Patient Withdrawal

No subjects withdrew from the study due to an adverse event.

Treatment-Emergent Adverse Events

Sixty-seven percent of Zemplar subjects reported a total of 17 AEs, while 43% of placebo subjects reported a total of 15 AEs.

The following table provides all treatment-emergent AEs in descending order for Zemplar-treated patients.

COSTART V Term[a]	Number (%) of Subjects	
	Zemplar (N=15)	Placebo (N=14)
Peripheral Vascular Disorder	4 (27%)	1 (7%)
Infection	2 (13%)	0 (0%)
Infection Bacterial	2 (13%)	0 (0%)
Rash	2 (13%)	1 (7%)
Accidental Injury	1 (7%)	0 (0%)
Allergic Reaction	1 (7%)	0 (0%)
Hemorrhage	1 (7%)	2 (14%)
Myalgia	1 (7%)	0 (0%)
Parathyroid Disorder	1 (7%)	0 (0%)
Pharyngitis	1 (7%)	0 (0%)
Sepsis	1 (7%)	1 (7%)
Abnormal Vision	0 (0%)	1 (7%)
Cellulitis	0 (0%)	1 (7%)
Depression	0 (0%)	1 (7%)
Edema	0 (0%)	1 (7%)
Fever	0 (0%)	1 (7%)
Neck Pain	0 (0%)	1 (7%)
Pain	0 (0%)	1 (7%)
Skin Disorder	0 (0%)	1 (7%)
Taste Perversion	0 (0%)	1 (7%)
Viral Infection	0 (0%)	1 (7%)

COMMENT: It's important to keep in mind the large number of placebo patients who discontinued prematurely from the study due to lack of efficacy when trying to interpret the AE profiles. Peripheral vascular disorder, for example, may not have been reported by as many placebo as Zemplar subjects simply because the number of days of on-study treatment was lower in the placebo group, 67 vs. 47 days, respectively.

Laboratory Parameters

The principal laboratory parameters of interest include serum calcium, phosphorus, and Ca X P product. The mean changes from baseline to Endpoint are provided in the following table.

There were no clinically meaningful differences between treatment groups in the mean changes from baseline to Endpoint in routine chemistry and hematology parameters.

	Zemplar (N=15)	Placebo (N=14)	ANOVA p-value[a]
Calcium (mg/dL)			
Mean Baseline Value	9.49	9.21	
Baseline Range	7.8 - 10.5	6.4 - 10.5	
Mean Final Value	9.49	9.50	
Change from Baseline (SE)	-0.00 (0.262)	0.29 (0.271)	0.455
Ca×P			
Mean Baseline Value	51.31	50.09	
Baseline Range	38.8 - 67.2	23.1 - 70.3	
Mean Final Value	49.97	53.31	
Change from Baseline (SE)	-1.35 (3.641)	3.21 (3.769)	0.392
Phosphorus (mg/dL)			
Mean Baseline Value	5.42	5.46	
Baseline Range	4.0 - 7.7	2.2 - 8.0	
Mean Final Value	5.27	5.64	
Change from Baseline (SE)	-0.15 (0.349)	0.18 (0.361)	0.514
Albumin (g/dL)			
Mean Baseline Value	3.97	4.16	
Baseline Range	3.4 - 4.6	3.6 - 5.0	
Mean Final Value	3.97	4.07	
Change from Baseline (SE)	-0.01 (0.102)	-0.09 (0.106)	0.595

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 (p=0.2).

No subject in either treatment group had a serum calcium level > 11.2 mg/dl.

Vital Signs

No statistically significant differences were observed between the treatment groups for the mean change from baseline to the Endpoint in systolic blood pressure, diastolic blood pressure, pulse, and weight using ANOVA. In addition, when vital sign variables were presented by age group, results were consistent with those seen in the overall analysis.

I. LABELING

The following text represents the language that Abbott is proposing to include in the package insert.

Medical Officer's Proposed Language

The information from the pediatric study should be moved to the Pediatric subsection of the Precautions section, as follows.

The company has also proposed minor, and acceptable, changes to the Precautions and Dosage and Administration sections of the labeling.

Following several discussions with Abbott, the following labeling represents mutually-agreed upon language:

The safety and effectiveness of Zemplar ® were examined in a 12-week randomized, double-blind, placebo-controlled study of 29 pediatric patients, aged 5-19 years, with end-stage renal disease on hemodialysis and nearly all had received some form of vitamin D prior to the study. Seventy-six percent of the patients were male, 52% were Caucasian and 45% were African-American. The initial dose of Zemplar ® was 0.04 mcg/kg 3 times per week, based on baseline iPTH level of less than 500 pg/mL, or 0.08 mcg/kg 3 times a week based on baseline iPTH level of $\geq$500 pg/mL, respectively. The dose of Zemplar ® was adjusted in 0.04 mcg/kg increments based on the levels of serum iPTH, calcium, and Ca $\times$ P. The mean baseline levels of iPTH were 841 pg/mL for the 15 Zemplar ® treated patients and 740 pg/mL for the 14 placebo-treated subjects. The mean dose of Zemplar ® administered was 4.6 mcg (range: 0.8 mcg - 9.6 mcg). Ten of the 15 (67%) Zemplar-treated patients and 2 of the 14 (14%) placebo-treated subjects

completed the trial. Ten of the placebo patients (71%) were discontinued due to excessive elevations in iPTH levels as defined by 2 consecutive iPTH levels > 700 pg/ml and greater than baseline after 4 weeks of treatment. In the primary efficacy analysis, 9 of 15 (60%) patients in the Zemplar ® group had 2 consecutive 30% decreases from baseline iPTH compared with 3 of 14 (21%) patients in the placebo group (95% CI for the difference between groups -1%, 63%). Twenty-three percent of Zemplar patients vs. 31% of placebo patients had at least one serum calcium level > 10.3 mg/dl, and 40%of Zemplar patients vs. 14% of placebo patients had a least one Ca x P ion product > 72 $(mg/dl)^2$. The overall percentage of serum calcium measurements >10.3 mg/dL was 7% in the Zemplar® group and 7% in the placebo group; the overall percentage of patients with Ca x P product >72 mg^2/dL^2 was 8% in the Zemplar® group and 7% in the placebo group. No patients in either the Zemplar group or placebo group developed hypercalcemia (defined as at least one calcium value >11.2 mg/dL) during the study.

VI. CONCLUSIONS

The results from this small, short-term study suggest that Zemplar is relatively safe and effective in the treatment of secondary hyperparathyroidism in pediatric patients with CKD undergoing dialysis.

VII. Recommendation

Approve

Appendix

Procedures	Screening	Pre-treatment Phase (weeks)		Treatment Phase (weeks)		Follow-Up Phase[b]
		1	2-6[a]	1	2-12	
Informed Consent[c]	X					
Inclusion/Exclusion Criteria		X	X[d]	X	X	
Medical History		X				
Physical Examination and Vital Signs		X				X
Adverse Event Monitoring[e]			X	X	X	X
Serious Adverse Event Monitoring[f]	X	X	X	X	X	X
Concurrent Medication		X		X	X	X
Bone Specific Alkaline Phosphatase				X[g]		X[h]
Complete Chemistry and Hematology		X[g]		X[g]		X[h]
Limited Chemistry: Ca, P, Albumin, and iPTH	X[h]		X[i]	X[i]	X[i]	
Serum Pregnancy Test[j]		X				
Study Drug Administration[k]				X	X	

a Duration was dependent on the length of time it took for the subject's lab values to reach the levels required for entering into the Treatment Phase.

b Within 2 to 7 days following final dose of study drug or at the next scheduled HD session for all subjects who completed or prematurely discontinued from the study.

c Must have been performed prior to any study procedures.

d Treatment Phase criteria only.

e Monitored at every HD session beginning with first administration of study drug and continued through 30 days post study drug administration.

f Monitored at every HD session beginning when the informed consent was signed and continued through 30 days post study drug administration.

g At the first HD session, prior to HD.

h Prior to HD.

i At the second HD session, prior to HD.

j Pubescent females or females ≥ 10 years of age of child bearing potential.

k At the 1st, 2nd, and 3rd HD session at anytime during HD. Dose no more frequently than every other day.

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/s/

Eric Colman
3/31/04 02:52:16 PM
MEDICAL OFFICER

Mary Parks
3/31/04 02:58:04 PM
MEDICAL OFFICER