CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-223

STATISTICAL REVIEW(S)

MAY 30 2000

Statistical Review and Evaluation[1]

NDA #: 21-223/1-P

Applicant: Novartis Pharmaceuticals Corporation

Name of the Drug: Zometa™ (zoledronic acid) for injection

Indication: Treatment of tumor-induced hypercalcemia

Documents Reviewed: Volumes 1.1, 1.61, 1.64 to 1.74, 1.140 to 1.159, amendments dated 01-07-00, 02-28-00, 04-07-00, 04-13-00, 04-14-00, and 04-28-00

Clinical Reviewer: Eric Colman, M.D. (HFD-510)

Statistical Reviewer: Japobrata Choudhury, Ph.D. (HFD-715)

The issues in this review have been discussed with the reviewing medical officer, Eric Colman, M.D. (HFD-510).

Sections in this review are as follows:

I. Background/Introduction

[ ]

The sponsor also states (Vol. 1.1) that data from three clinical trials in 320 patients with tumor-induced hypercalcemia (TIH,

[1] Key words: clinical studies, NDA review, active control

defined as a corrected serum calcium (CSC) level ≥ 3.0 mmol/L) demonstrate that Zometa is safe and effective in the target population and that safety data for 2423 patients are presented.

Study CJ/HC1 was an open-label, phase I, dose finding study conducted in Europe. Patients received single i.v. infusions of 0.002 to .04 mg/kg of zoledronic acid over 20 minutes.

The two adequate and well-controlled phase II studies 036 and 037 provide the pivotal data. Study 036 was conducted in Europe and Australia and Study 037 was an identical study conducted in the United States and Canada. Both studies were randomized, double-blind, parallel group, double-dummy studies of zoledronic acid at two doses (4 and 8 mg) and pamidronate 90 mg administered as i.v. infusions in patients with TIH. Summary information of these two studies, which are reviewed here, is attached as Table 0.1.1[2].

II. Clinical Studies

All analyses referred to in this report are the sponsor's analyses, except where specifically mentioned as done by this reviewer.

1. Study 036

A table showing some design and enrollment information is in the Appendix, Table 0.1.1.

Study 036 was a randomized, double-blind, parallel group, double-dummy study of zoledronic acid at two doses (4 and 8 mg) as a 5-minute i.v. infusion and pamidronate (Aredia) 90 mg administered as a 2-hour i.v. infusion in patients with TIH.

Of the two stages of this study, stage 1 was the initial treatment of patients with hypercalcemia with zoledronic acid or pamidronate. In stage 2, patients with refractory or relapsed hypercalcemia could be treated with 8 mg of zoledronic acid.

If the study drug treatment resulted in a complete response, the patient was followed for 8 weeks (to Day 56), or until the

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[2] In the Table (or Appendix or Figure; no separate numbering systems have been created for these) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

patient's CSC increased to ≥2.90 mmol/L (11.6 mg/dL), whichever occurred first. Patients who had not achieved a complete response by Day 10, but whose CSC concentration was <2.90 mmol/L on Day 10, were followed in Stage 1 of the trial to Day 56 (Visit 8) or until the patient's CSC level was ≥2.90 mmol/L (11.6 mg/dL).

Patients were eligible to enter the retreatment stage within the 56 days of stage 1 if their TIH was refractory to the initial zoledronic acid (either dose) or pamidronate treatment, or when their CSC concentration increased to ≥2.90 mmol/L (11.6 mg/dL) after having achieved a complete response (relapse).

All efficacy analyses, summaries, and figures were based upon the "corrected day" using the following time windows:

Days	2-5	6-8	9-11	12-15	16-18	19-22	23-25	26-29
Corrected Day	4	7	10	14	17	21	24	28

Days	30-32	33-36	37-39	40-43	44-46	47-50	51-53	>54
Corrected Day	31	35	38	42	45	49	52	56

1A. Objectives

The primary objective of this trial was to assess the ability of two different zoledronate doses (4.0mg and 8.0mg) as therapy for TIH to achieve a complete response rate > 70%. A zoledronate dose will be considered effective if the lower bound of the 95% confidence interval (CI) for complete response is > 70%. A complete response is defined as a corrected serum calcium concentration ≤ 2.70 mmol/L (10.8 mg/dl) by trial day 10.

(The confidence intervals mentioned above were 2-sided).

1B. Disposition of Patients

The sponsor stated, "Therefore, 108 patients (36 per treatment group) were required for the per protocol analysis of the primary variable, complete response. … An additional twelve patients per treatment group were randomized to increase the data available for an assessment of the safety, and for performing a newly planned pooled analysis of the pooled data from two TIH trials."

The patient disposition shows that 149 patients were randomized and treated and 127 patients completed the stage 1 of the study.

The number {percent} of discontinuation due to unsatisfactory

therapeutic effect was much higher in the Aredia 90mg (9 {17.3%}) group than 4mg (1 {2.2%}) and 8mg (1 {2.0%}) zoledronate groups.

The complete response was defined relative to Day 10 only. In one (first Table of Disposition in the NDA), complete responders were considered completers. The numbers (percentages) of discontinued patients from among the complete responders (second Table of Disposition in the NDA) in Stage 1 (prior to Day 56) due to unsatisfactory therapeutic effect were 10 (25.6%), 9 (22.0%), and 3 (6.5%), respectively, for the Aredia 90mg, zoledronate 4mg and 8mg groups. The corresponding numbers (percentages) due to death were 10 (25.6%), 8 (19.5%), and 15 (32.6%) and due to adverse events were 3 (7.7%), 1 (2.4%), and 6 (13.0%).

A total of 34 patients entered Stage 2 of the study (all to receive zoledronate 8mg). Of these, 10 had received zoledronate 4mg, 5 had received zoledronate 8mg, and 19 had received Aredia 90mg (more than those in the other groups) in Stage 1. More details are in the sponsor submission dated 2-28-00.

Of the 14 discontinuations (Stage 2) from the non "complete responders" (in Stage 2), 11 discontinued due to unsatisfactory therapeutic effect. From the 19 complete responders during Stage 2, 8 discontinued Stage 2, of which 5 were due to unsatisfactory therapeutic effect and 2 were due to death.

1C. Baseline Comparability of Treatment Groups

For the primary objective of the study, baseline comparability is not at all an issue. Only when zoledronate doses are compared to Aredia, baseline comparability may be an important issue.

The mean Urea/creatinine ratio (correction statement on p.2 top of amendment 2-28-00) at baseline was 49.2, 41.2, and 39.5 for zoledronate 4 mg, 8 mg, and Aredia 90 mg, respectively, (p-value for baseline comparison: p=0.011).

All imbalances were accounted for in alternative analyses (Section 9.3 of the study report and amendment dated 2-28-00).

1D. Efficacy Results (Sponsor's Analyses)

According to the protocol, a zoledronate dose will be considered effective if the lower bound of the 95% confidence interval (CI) for complete response (by Day 10, by definition of Response in 3.6.3) is > 70%. The per-protocol analysis was to be the primary analysis (Section 5.1).

Both doses of zoledronate met the criteria for effectiveness. The 95% confidence intervals for the complete response rates were (80.14 to 98.13) and (80.94 to 98.23), respectively, for 4 mg and 8 mg of zoledronate, the lower limits being much above 70%.

The corresponding 95% confidence interval for Aredia 90 mg was (61.84 to 86.16).

The number of patients were:

	Zoledronate 4 mg	Zoledronate 8 mg	Aredia 90 mg
Per protocol	46	48	50
ITT	46	51	52

The intent-to-treat results were similar or more favorable for zoledronate.

Following are the 95% confidence intervals and p-values for the difference between treatment groups with respect to the percent of complete responders:

Summary of between treatment analysis of percentage of complete responders
Stage: 1 (Initial treatment)
(Per protocol population)

Treatment	Estimate	95% confidence Interval (1)		p-value (2)
Zoledronate 4 mg - Aredia 90 mg	15.1	0.01 -	30.25	0.062
Zoledronate 8 mg - Aredia 90 mg	15.6	0.67 -	30.50	0.128
Zoledronate 8 mg - Zoledronate 4 mg	0.5	-12.02 -	12.93	0.933

J. Normal approximation to binomial distribution
(2) p- value is from Cochran- Mantel Haenszel test adjusting for baseline Corrected serum calcium (group)

Zoledronate doses are numerically superior but not statistically superior to Aredia 90mg.

1E. Reviewer's Comments and Conclusions on Study 036

Study 036 satisfied the criterion for primary efficacy mentioned in the protocol.

The sponsor used the estimate p(1-p)/n for the variance of the sample proportion p, which is biased. This reviewer recalculated the 95% confidence intervals with the unbiased estimate p(1-p)/(n-1). This difference in the method of estimation was of no material consequences.

The study was not properly designed to comment statistically about the efficacy of retreatment.

The four covariates examined were : presence of bone metastases at baseline (yes, no); primary cancer group (other, breast/ hematological); baseline CSC group ($\geq$3.4 mmol/L, <3.4 mmol/L); and PTHrP group (>2pmol/L , $\leq$2pmol/L).

There was some (non-significant) baseline differences among treatment groups with respect to baseline CSC (two subgroups with cut-off at 3.4 mmol/L). This stratification for analysis (and not for randomization because of small numbers) was mentioned in the protocol p. 35. Numerically, 4mg showed better results than those for 8mg zoledronate, in the CSC $\geq$3.4 mmol/L subgroup. Aredia 90 mg results were much better (84% complete responders) in the other subgroup (still, not as good as the zoledronate results) of baseline CSC than in this subgroup with CSC $\geq$3.4 mmol/L (64% complete responders).

PTHrP was an important covariate; i.e. efficacy results were better when patients had PTHrP <2 pmol/L. The presence of bone metastases and cancer group seems to have little or no effect on the efficacy variables.

2. Study 037

A table showing some design and enrollment information is in the Appendix, Table 0.1.1.

Study 037 was a randomized, double-blind, parallel group, double-dummy study of zoledronic acid at two doses (4 and 8 mg) as a 5-minute i.v. infusion and pamidronate 90 mg administered as a 2-hour i.v. infusion in patients with TIH.

Of the two stages of this study, stage 1 was the initial treatment of patients with hypercalcemia with zoledronic acid or pamidronate. In stage 2, patients with refractory or relapsed hypercalcemia could be treated with 8 mg of zoledronic acid.

If study drug treatment resulted in a complete response, the patient was followed for 8 weeks (to Day 56), or until the patient's CSC increased to ≥2.90 mmol/L (11.6 mg/dL), whichever occurred first. Patients who had not achieved a complete response by Day 10, but whose CSC concentration was <2.90 mmol/L on Day 10, were followed in Stage 1 of the trial to Day 56 (Visit 8) or until the patient's CSC level was ≥2.90 mmol/L (11.6 mg/dL), whichever occurred first.

Patients were eligible to enter the retreatment stage within the 56 days of stage 1 if their TIH was refractory to the initial zoledronic acid (either dose) or pamidronate treatment, or when their CSC concentration increased to ≥2.90 mmol/L (11.6 mg/dL) after having achieved a complete response (relapse).

2A. Objectives

The primary objective of this trial was to assess the efficacy of two different zoledronate doses (4.0mg and 8.0mg) as 5-minute intravenous infusions as therapy for TIH. A zoledronate dose will be considered effective if the lower bound of the 95% confidence interval (CI) for the proportion of complete responders is > 70%. A complete response is defined as a corrected serum calcium concentration ≤ 2.70 mmol/L (10.8 mg/dl) by trial day 10.

2B. Disposition of Patients

The patient disposition shows that 138 patients were randomized and treated and 113 (81.9%) patients completed the stage 1 of the study by continuing to study day 56 or by having a complete response.

Aredia 90mg group had a much higher number {percent} of discontinuation (14 {27.5%} vs 4 {10%} and 5 {15%} in Zometa doses) and discontinuation due to unsatisfactory therapeutic effect (7 {13.7%} vs 3 {7.5%} and 1 {2.1%} in Zometa doses). The number {percent} of discontinuation due to death from 8mg zoledronic acid (5 {10.6%}) was statistically significantly higher than in the Aredia 90mg (0%; p=.023, done by the reviewer) and was marginally statistically significantly higher (p= .059 by Fisher's exact test and .011 by Liklihood Ratio Chi-Square test, both done by the reviewer) than in the zoledronic acid 4mg (0%).

The complete responders were defined relative to Day 10 only. In one (first Table of Disposition in the NDA), they were considered completers. The numbers (percents) of discontinued patients from among the complete responders (second Table of Disposition in the NDA) in Stage 1 (prior to Day 56) due to unsatisfactory therapeutic effect were 12 (35.3%), 6 (17.1%), and 6 (15.4%), respectively, for the Aredia 90mg, zoledronate 4mg and 8mg groups. The corresponding numbers (percents) due to death were 7 (20.6%), 5 (14.3%), and 8 (20.5%) and due to adverse events were 2 (5.9%), 2 (5.7%), and 3 (7.7%).

A total of 36 patients entered Stage 2 of the study (all to receive zoledronate 8mg). Of these, 9 had received zoledronate 4mg, 8 had received zoledronate 8mg, and 19 had received Aredia 90mg (more than those in the other groups) in Stage 1. More details are in the sponsor's submission dated 2-28-00.

Of the 16 discontinuations (Stage 2) from the non-"complete responders" (in Stage 2), 13 discontinued due to unsatisfactory therapeutic effect. From the 18 complete responders during Stage 2, 12 discontinued Stage 2, of which 5 were due to death and 3 were due to unsatisfactory therapeutic effect.

2C. Baseline Comparability of Treatment Groups

For the primary objective of the study, baseline comparability is not at all an issue. Only when zoledronate doses are compared to Aredia, baseline comparability may be an important issue.

There was a statistically significant (p=.039) baseline imbalance among treatment groups with respect to Cancer Group (Breast/ Hematological vs. Other). Various categories of "Primary Site of Cancer" with percentages of patients (baseline) are on page 41 of the report for study 037 (this reviewer is unable to judge the clinical significance of these imbalances). There was a statistically significant (p=.025) baseline imbalance among treatment groups also with respect to baseline parathyroid hormone. The p-value for the comparison with respect to baseline calculated serum creatinine clearance (ml/min) was .095 (not statistically significant but it is somewhat small).

All imbalances were accounted for in alternative efficacy analyses (Appendix 5 of NDA and amendment of 2-28-00).

2D. Efficacy Results (Sponsor's Analyses)

According to the protocol, a zoledronate dose will be considered

effective if the lower bound of the 95% confidence interval (CI) for complete response is > 70%.

Both doses of zoledronate met the criteria for effectiveness. The 95% confidence intervals for the complete response rates were (77.3 to 97.8) and (72.1 to 94.6), respectively, for 4 mg and 8 mg of zoledronate, the lower limits being above 70%.

The corresponding 95% confidence interval for Aredia 90 mg was (52.0 to 78.6).

The number of patients were:

	Zoledronate 4 mg	Zoledronate 8 mg	Aredia 90 mg
Per protocol	40	42	49
ITT	40	47	51

The intent-to-treat results were similar (for Aredia, just a little better than the per-protocol results).

Following are the 95% confidence intervals and p-values for the difference between treatment groups with respect to the percent of complete responders:

Summary of between treatment analysis of percentage of complete responders
Stage: 1 (Initial treatment)
(Per protocol population)

Treatment	Estimate	95% confidence interval (1)		p-value (2)
Zoledronate 4 mg - Aredia 90 mg	22.2	5.38	39.01	0.018
Zoledronate 8 mg - Aredia 90 mg	18.0	0.57	35.48	0.069
Zoledronate 8 mg - Zoledronate 4 mg	-4.2	-19.40	11.07	0.602

and 4mg zoledronate was statistically superior to Aredia 90mg.

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2E. Reviewer's Comments and Conclusions on Study 037

Study 037 satisfied the criterion for primary efficacy mentioned in the protocol.

The study was not properly designed to comment statistically about the efficacy of retreatment.

The four covariates examined were : presence of bone metastases at baseline (yes, no); primary cancer group (other, breast/ hematological); baseline CSC group ($\geq$3.4 mmol/L, <3.4 mmol/L); and PTHrP group (>2pmol/L , $\leq$2pmol/L).

The sponsor stated, "For complete response, none of the key covariates had an important effect on efficacy." (037 CSR p.52).

The treatment groups differed statistically significantly with respect to baseline cancer group (two subgroups breast/hematological vs Other). Numerically, 4mg and 8mg Zometa showed better results in the "Other" group than those in the breast/hematological group. In both subgroups 4 mg and 8 mg zoledronic acid did much better than Aredia 90 mg (037 CSR p.320).

The treatment groups differed statistically significantly with respect to baseline parathyroid hormone also.

On request, the sponsor performed further exploration of covariation effects on complete response (especially, of the factors in which there was imbalance among the treatment groups in any of the studies separately or pooled) and stated, "None of the 7 covariates were found to be statistically significant … . Since the main effects were not statistically significantly related to complete response rate, the interaction terms with treatment were not examined further."

For the Time to Relapse, baseline CSC and "cancer group" were important covariates. The time to relapse was shorter in the subgroup with baseline CSC$\geq$3.4 mmol/L than in the other subgroup. The time to relapse was also shorter for the cancer group "Other" when compared to the cancer group "breast/hematological". (037 CSR p.52)

III. Overall Reviewer's Comments and Discussions

Both studies 036 and 037 satisfied the protocol mentioned criterion for primary efficacy (the US/Canada Study 037 results were not as strong as those of the other study).

Pooled data from these two studies provided statistical evidence for the superiority of zoledronate doses to Aredia 90mg (at least numerical superiority was there in both studies separately). The following is copied from the sponsor's CD-Rom:

Table 2-16. Summary of between-treatment analysis of complete responders in the pooled analysis

	Difference Zoledronic acid 4 mg - pamidronate 90 mg	Difference Zoledronic acid 8 mg - pamidronate 90 mg	Difference Zoledronic acid 8 mg - Zoledronic acid 4 mg
Estimate (%)	18.7	17.0	-1.7
95% confidence interval	7.4-30.0	5.5-28.4	-11.5-8.1
p-value	0.002	0.015	0.674

"Change from baseline corrected serum calcium", without the words "within Day 10", was mentioned as a secondary variable on page 33 of the protocol. Also, since almost all efficacy variables were based on corrected serum calcium, I requested CSC results even after Day 10 with the statements of their limitations.

In response, the sponsor stated, "... CSC data collected after Corrected Day 10 were used in the assessment of secondary efficacy, i.e., time to relapse and duration of complete response and duration of response for the subset of responders. Any analyses on CSC after Corrected Day 10 are biased since, by trial design, only responders continue in the study after Day 10. This bias will have an even greater impact as the days on the study increase."

With these limitations (only responders), the graphs for (1) Percentage of Patients with CSC in the Appendix, Figure 0.2.1 and (2) Mean CSC without carried forward values in the Appendix, Figure 0.3.1 are provided for the pooled data from the two studies (Days 31,38,45, and 52 were really not visit days by the protocol).

The sponsor stated, "Onset of normalization of CSC was more rapid, and the time to relapse and duration of response was prolonged, in the zoledronic acid 8 mg group versus zoledronic acid 4 mg group; however the differences were relatively small and the 4 mg dose of zoledronic acid was at least as effective as the 8 mg dose, in terms of complete response rates, in the TIH population as a whole, and in all subgroups tested. Thus, zoledronic acid 4 mg dose is the recommended dose, since minimal additional benefit was obtained with the 8 mg dose."

In Study 037, the 4mg dose results were numerically better than those for the 8mg zoledronate.

In both studies, there were **more deaths in the 8mg** zoledronate group (than the other groups). In study 036, the numbers (percentages) of death were 4 (7.8%), 3 (6.5%), and 3 (5.8%), respectively, in the 8mg, 4mg zoledronate, and Aredia 90mg. The corresponding numbers (percentages) for Study 037 were 5 (10.6%) (statistically significantly more than the other groups), 0 (0%), and 0 (0%). These did not include deaths (within Day 56 of stage 1) among the complete responders. Including those, the corresponding numbers (percentages) were 19 (37.3%), 11 (23.9%), and 13 (25.0%) in Study 036 and 13 (27.7%; vs. 4mg 2-sided p-value is about .08), 5 (12.5%), and 7 (13.7%) in Study 037.

It turned out that, in both the studies, slightly more patients were randomized in the Aredia group (still, about the same size).

In the pooled data set, there were statistically significant baseline imbalances among the treatment groups (ISE p.592) with respect to cancer group (Breast/Hematological vs. Other) and baseline CSC (<3.4mmol/L or not, this stratification for analysis and not for randomization was mentioned in the protocol). The corresponding p-value with respect to baseline BUN/creatinine ratio was .021 (significant) and with respect to baseline calculated serum creatinine clearance (ml/min) was .053 (only marginally non-significant).

This reviewer's analyses, performed with the data supplied by the sponsor electronically, did not reveal any concern with respect to the conclusion about the primary efficacy.

Covariate or Subgroup Analyses

Subgroup and covariance analyses discussed here are those performed after pooling data from studies 036 and 037. Individual study results are discussed under each study separately. The percentage of complete responders at Day 10 was considered for these analyses.

Per protocol analyses were the protocol mentioned primary analyses.

The four covariates examined were : presence of bone metastases at baseline (yes, no); primary cancer group (other, breast/ hematological); baseline CSC group ($\geq$3.4 mmol/L, <3.4 mmol/L); and PTHrP group (>2pmol/L , $\leq$2pmol/L).

The sponsor stated (2-28-00), "The original protocol stated that baseline corrected serum calcium level would be included in the analysis as a covariate. The other covariates were selected based on the Novartis clinical team's opinion of important baseline variables which could possibly have an effect on efficacy. This determination was made by the clinical team, prior to the unblinding of the patients' treatment assignments."

About the results, the sponsor stated that none of the covariates had an important influence on the complete response rate.

However, there was some effect of a few factors on Time to Relapse. For example, the median Time to Relapse was shorter in the subgroup of baseline CSC <3.4 mmol/L than in the other subgroup, in the subgroup of PTHrP > 2 pmol/L than in the other subgroup, in the subgroup of "Bone Metastases = No" than in the other subgroup. The sponsor stated, "For all above subgroups, time to relapse is always longer for zoledronate-treated patients. The differences in time to relapse between the subgroups reflect the underlying effect of that prognostic variable; there is no evidence of any treatment by subgroup interaction."

Although the 8mg zoledronate and 90mg Aredia were somewhat dissimilar with respect to "Presence of Bone Metastases," (p=.062), the pairwise between-treatment comparison, controlling for the presence of bone metastases , with respect to the primary efficacy variable. [02-28-00]

In all subgroups, zoledronate doses were at least numerically superior to pamidronate 90 mg. For Race, the number of subjects in "other races" is so small that the little discrepancy does not deserve a mention.

Within each treatment, the complete response rate varied over the subgroups based on the factors like Age, Sex, Race, Cancer Group, intake of loop diuretics, etc. This reviewer is not sure how meaningful those subgroup variations are clinically (Integrated Summary of Efficacy, pages 490 to 495).

On request, the sponsor performed further exploration of covariation effects on complete response (especially, of the factors in which there was imbalance among the treatment groups in any of the studies

separately or pooled) and stated, "None of the 7 covariates were found to be statistically significant … . Since the main effects were not statistically significantly related to complete response rate, the interaction terms with treatment were not examined further."

IV. **Overall Conclusion**

Both doses 4 mg and 8 mg of zoledronic acid satisfied the protocol mentioned criterion for primary efficacy, in both the studies 036 and 037. Pooled data from these two studies provided statistical evidence for the superiority of zoledronate doses to Aredia 90mg. The dose recommended by the sponsor is 4 mg which showed statistical superiority to Aredia 90mg (even without pooling but without multiple comparison adjustments) in Study 037. The 8mg dose had a somewhat higher death rate.

These studies were not properly designed to make statistical conclusions about the efficacy of retreatment.

/S/ 5-25-00

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot /S/ 5/30/00

Dr. Nevius /S/ 5/25/00

CC:
Archival NDA 21-223

HFD-510/Dr. Colman
HFD-510/Mr. Hedin
HFD-715/Dr. Nevius
HFD-715/Dr. Sahlroot
HFD-715/Dr. Choudhury
HFD-715/Chron

This review consists of 14 pages of text and 4 pages of Tables, Figures, etc.

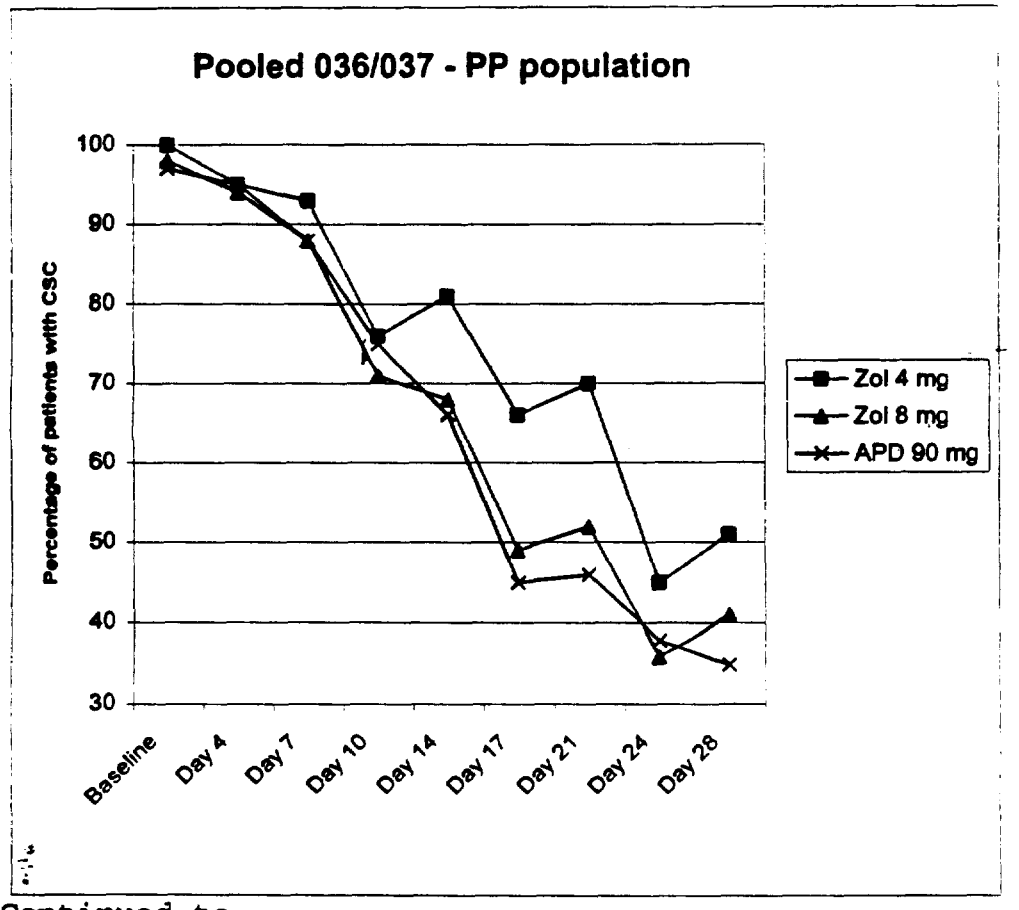
Appendix

Table 0.1.1

Company: NOVARTIS Finished Product: zoledronic acid Active Substance: CGP 42446		REFERENCE THERAPY CONTROLLED STUDIES IN PATIENTS			Page 10	
Ref. (Vol. & Page)	Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No. & Race (w,b,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen Duration of Therapy Dosage	General Results & Adverse Events % AEs	 % SAEs
1.6. Reference therapy controlled studies in patients						
report: Doc. Vol listings: Doc. Vol p	protocol: 036 invest.: Dr A. Lortholary, France start: 23-Dec-97 end: 13-Oct-99	design, goal & population: randomized, double-blind study of 2 doses of zoledronate and Aredia in treatment of tumor-induced hypercalcemia evaluations: corrected serum calcium concentration, safety and tolerability	total: 149 (143w, 2b, 4o) age: 26-84 (58.7) yr groups: 46 (20m,26f) 51 (28m,23f) 52 (27m,25f)	form: intravenous duration: once in Stage 1; -- once 56 days later for Stage 2 (retreatment) for relapse or refractory TIH doses: zol. 4 mg zol. 8 mg Aredia 90 mg	Both zoledronate doses are highly efficacious. Zoledronate 4 mg is the recommended dose for the initial treatment of TIH 94 96 90	54 63 46
report: Doc. Vol listings: Doc. Vol p	protocol: 037 invest.: Dr. P Major, Canada start: 07-Jan-98 end: 19-Sep-99	design, goal & population: randomized, double-blind study of 2 doses of zoledronate and Aredia in treatment of tumor-induced hypercalcemia evaluations: corrected serum calcium concentration, safety and tolerability	total: 138 (95w, 43b, 1Do) age: 21-94 (59.1) yr groups: 40 (26m,14f) 47 (37m,10f) 51 (31m,20f)	form: intravenous duration: once in Stage 1: once 56 days later for Stage 2 (retreatment) for relapse or refractory TIH doses: zol. 4 mg zol. 8 mg Aredia 90 mg	Both zoledronate doses are highly efficacious. Zoledronate 4 mg is the recommended dose for the initial treatment of TIH. 95 96 94	50 49 37

Appendix

Figure 0.2.1



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Appendix

Figure 0.2.1 (Continued)

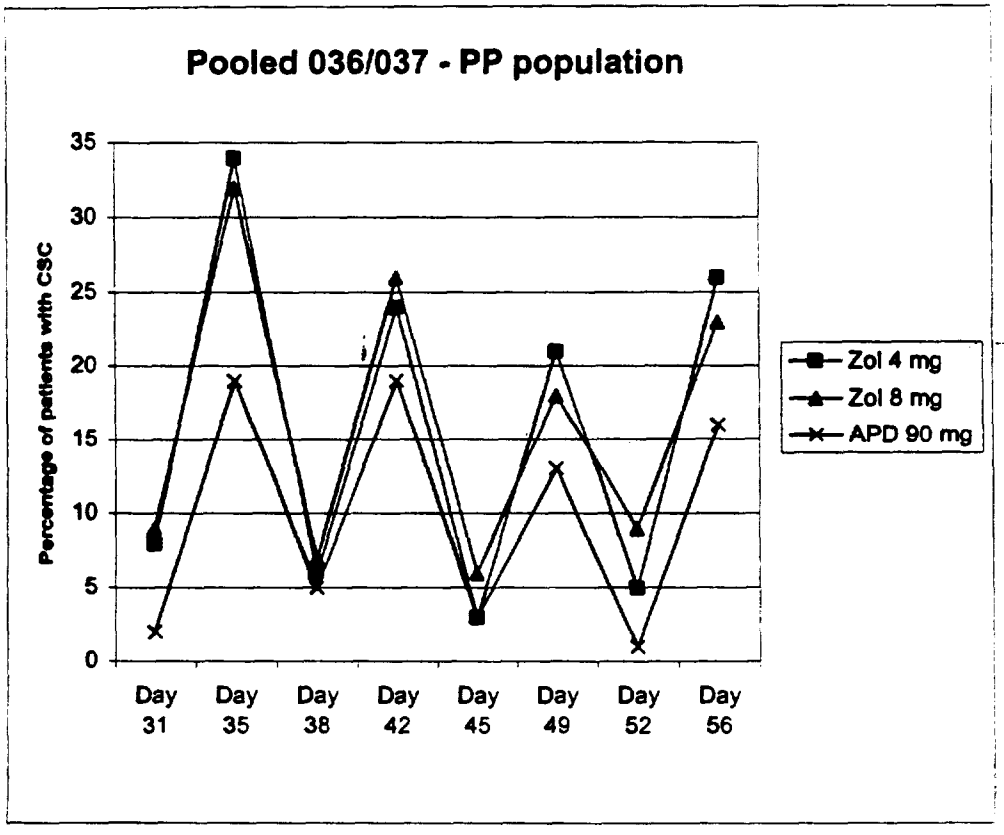

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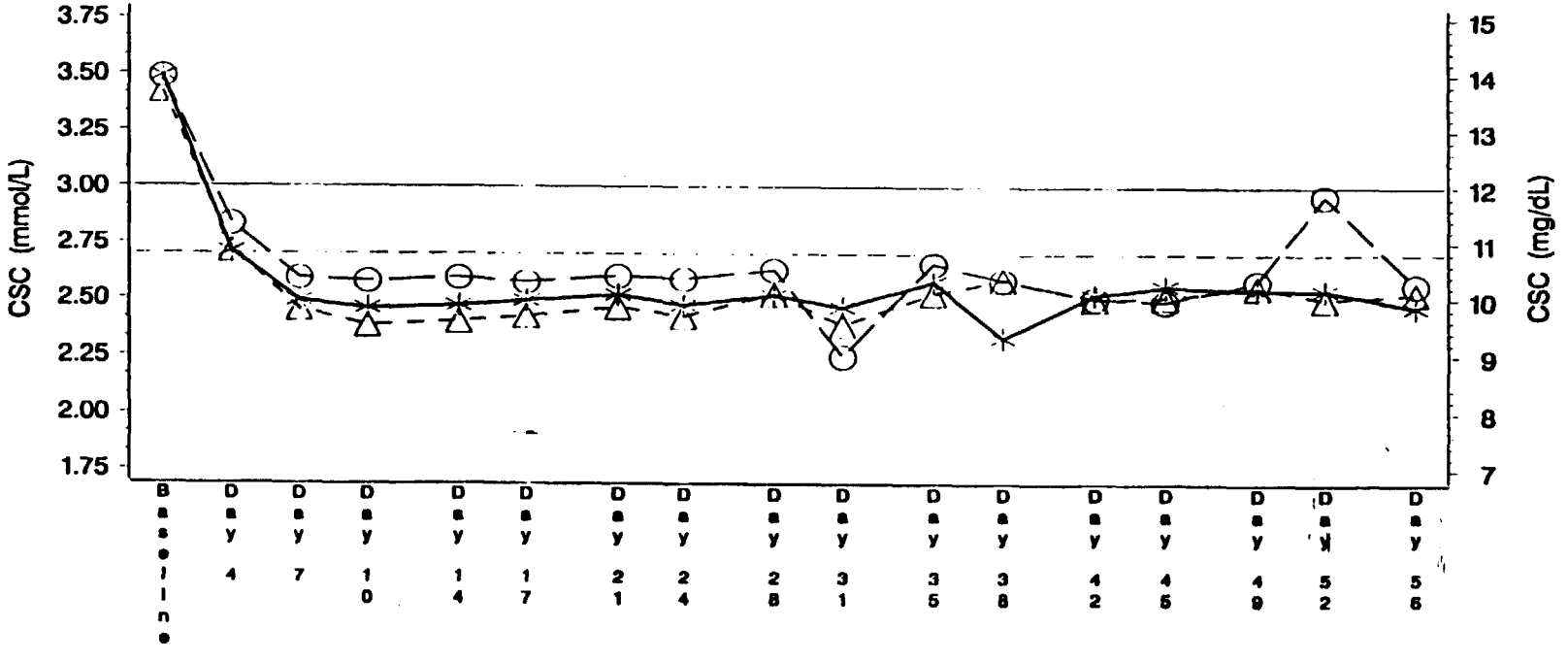
Figure 0.3.1

Figure 3
Mean corrected serum calcium without carried forward values by corrected day (all days)
Stage: 1 (initial treatment) (Per protocol population)



Corrected day

Treatment group: Zol 4 mg Zol 8 mg APD 90 mg

If multiple values appeared within the same window, the last one was used.
Note: Patients with only baseline were excluded.

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5327, FAX (301) 594-5494

Memorandum

DATE: 4.18.01

FROM: Douglas C. Throckmorton, M.D., Deputy Division Director
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Ray Lipicky, M.D., Ph.D., Division Director
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TO: Randy Hedin, Project Manager
Eric Colman, M.D., Medical Officer
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Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Renal toxicity of zoledronic acid
NAME OF DRUG: Zoledronic acid/ zoledronate
TRADE NAME: Zometa
FORMULATION: IV
NDA: 21-223

RELATED APPLICATIONS: IND [redacted] submitted to HFD-510
APPROVED INDICATIONS: N/A
SPONSOR: Novartis Pharmaceutical Corporation

DOCUMENTS USED FOR REVIEW:

1. NDA 21-223, Complete Response to Approvable Letter, dated 2.19.01.
2. My previous consultations for HFD-510, dated 7.25.00 and for HFD-150, dated 10.26.00.
3. Fax containing 2.01 update of Renal Deterioration Events, received 4.13.01.

DATE CONSULT ASSIGNED: 2.21.01
DATE CONSULT COMPLETED: 4.15.01

1.0 BACKGROUND

Zoledronate is under development for the treatment of hypercalcemia of malignancy [redacted]

[redacted] The sponsor was issued an approvable letter dated 9.21.00. In the letter, additional information on the potential renal toxicity of zoledronate:

> 'Completion of the ongoing studies will allow for a more comprehensive evaluation of zoledronate's renal safety profile, including an assessment of the effect of the recently implemented protocol amendments.
>
> In order to address this outstanding safety concern [renal toxicity], you must provide the complete study reports for clinical trials 010, 011, and 039.' (from approvable letter)

To address this requirement, the sponsor has submitted updated safety data from the three ongoing trials (010, 011, and 035), trials examining [redacted]
The sponsor contends that the datasets reflect substantial long-term follow-up for these three trials; sufficient to address the issues relating to renal safety raised by the Agency (thus, the complete study reports are not required). There are three issues related to the renal toxicity of zoledronate:

1) How does the incidence of renal injury following zoledronate 4 mg administered over 15 minutes compare to placebo and to pamidronate in the treatment of tumor-induced hypercalcemia?

2) How does the severity of renal injury following zoledronate 4 mg administered over 15 minutes compare to placebo and to pamidronate in the treatment of tumor-induced hypercalcemia?

3) How reversible is any renal injury associated with the use of zoledronate 4 mg?

2.1-2.2 Renal Effects of Zoledronate

What follows is a summary of the pertinent information regarding renal adverse events reported in the most recent submission, focusing on two sets of data: the long-term repeat infusion studies (010, 011, 039), and the completed studies in tumor-induced hypercalcemia (036, 037).

The first section will summarize the new data from the three trials 010, 011, and 039. These trials enrolled patients with either myeloma or breast cancer (protocol 010), patients with prostate cancer (protocol 039) and patients with other malignancies (protocol 011). Patients were randomized to receive zoledronate (4 or 8 mg), compared with either placebo (protocols 011 and 039), or pamidronate (protocol 010). The patients received repeated doses of study drug every 3 weeks (studies 011 and 039) or every 3-4 weeks (study 010). As a consequence of the observed renal toxicity, the dose of zoledronate, the rate of infusion and monitoring was changed to 15 minutes in June of 1999. The reader is referred to the primary medical review for additional details, including details of the changes in treatment schedule and monitoring. Within each of the three trials, the treatment groups were well-balanced with regard to age and serum creatinine. No unblinded clinical adverse events are available, as these trials are ongoing.

The second dataset that was submitted by the sponsor and requires comment is the additional follow-up for the completed trials of tumor-induced hypercalcemia. Included are two pivotal, randomized, double-blind, placebo-controlled trials (036, 037) in patients with tumor-induced hypercalcemia. These last two trials compared zoledronate (4 and 8 mg) with pamidronate (a previously approved bisphosphonate). At the request of the FDA additional follow-up information regarding those patients with renal injury has been obtained and submitted by the sponsor.

The renal adverse event data will be discussed in two categories: reported adverse events (including serious adverse events and discontinuations), and the occurrence of 'Renal Deteriorations Events, as defined by the sponsor and a 'Renal Safety Advisory Board' (RAB).

The RAB defined renal deterioration as follows:

1) In patient with normal renal function (baseline serum creatinine, SCr, <1.4 mg/dl), any increase in SCr ≥0.5 mg/dl.

2) In patients with abnormal renal function (baseline SCr ≥1.4 mg/dl), any increase of ≥1.0 mg/dl.

2.1 Ongoing Bone Metastasis Trials (Protocols 010, 011, 039)

The database used for the analyses from studies 010, 011 and 039 is summarized below, based on renal events reported to the sponsor through 'early' February, 2001. Compared with the database at the time of the NDA submission, the primary new data comes from additional cycles administered to patients. Patients in the three trials have received an average of 11 cycles of therapy.

Enrollment in Studies 010, 011, and 039 as of 2.19.01[a].

Study	All Treatments 15-Minute Infusion # Patients/ # Infusions	Zoledronate 4 mg, 15 Minute Infusion # Patients/ # Infusions
Study 010	795/ 9705	270/ 3384
Study 011	505/ 3686	164/ 1247
Study 039	257/ 3251	92/ 1222

a. Data from NDA submission dated 2.19.01.

1. Incidence of Renal Deterioration Events

The RAB defined renal deterioration as follows:

1) In patient with normal renal function (baseline SCr <1.4 mg/dl), any increase of ≥0.5 mg/dl.

2) In patients with abnormal renal function (baseline SCr ≥1.4 mg/dl), any increase of ≥1.0 mg/dl.

The incidence of these events is summarized in the table below, focusing on the post-amendment data (that is, the data from the 15 minute infusions). Protocol 10 is further sub-divided according to their primary disease. In study 010, the incidence of renal deterioration events was higher in the zoledronate 4 and 8 mg groups when compared with pamidronate. This result reflects differing incidences in the two populations enrolled (breast cancer or myeloma). In studies 011 and 039, the rate of renal adverse events was higher in zoledronate 4 mg than in placebo.

Renal Deterioration Events from Protocols 010, 011, and 039 (Ongoing Bone Metastasis Trials)[a,b].

Trials	Placebo	Zoledronate 4 mg	Zoledronate 8 mg	Pamidronate
Protocol 010	--	22/270 (8.1%)	48/262 (18.3%)	20/263 (7.6%)
Protocol 010 Breast Ca Pts	--	13/179 (7.3%)	21/176 (11.9%)	10/181 (5.5%)
Protocol 010 Myeloma Pts	--	9/91 (9.9%)	27/66 (31.4%)	10/82 (12.2%)
Protocol 011	10/163 (6.1%)	17/164 (10.4%)	21/176 (11.6%)	--
Protocol 039	9/78 (11.5%)	13/92 (14.1%)	19/87 (21.8%)	--

a. Data from Feb. 2001 datasets faxed to reviewer.
b. Shows post-amendment data only.

The sponsor also performed a time-to-event analysis on these data, deriving hazard ratios for risk of renal deterioration events. In the post-amendment analysis, the risk of renal injury was similar for zoledronate and pamidronate in the one trial comparing the two agents (010, myeloma or breast ca). Similar to the result above, the two populations in the trial (breast cancer, myeloma) had differing rates. There was a consistent trend towards excess risk of renal injury in the zoledronate 8 mg group relative to both zoledronate 4 mg and placebo. Zoledronate 4 mg was associated with a higher risk of renal injury than placebo in both 011 and 039.

Cox Model Analysis of Risk of Renal Deterioration in Protocols 010, 011, and 039[a].

Trials and Comparison	Hazard Ratio (95% C.I.)	p-Value
Protocol 010		
Zoledronate 4 vs. Pamidronate	0.94 (0.51, 1.79)	0.85
Zoledronate 4 vs. Zoledronate 8	2.61 (1.57, 4.33)	<0.001
Zoledronate 4 vs. Pamidronate: Breast Cancer	1.13 (0.50, 2.59)	0.766
Zoledronate 4 vs. Pamidronate: Myeloma	0.77 (0.31, 1.90)	0.57
Protocol 011		
Zoledronate 4 vs. Placebo	1.77 (0.81, 3.87)	0.153
Zoledronate 4 vs. Zoledronate 8	1.23 (0.64, 2.33)	0.536
Protocol 039		
Zoledronate 4 vs. Placebo	1.38 (0.58, 3.39)	0.483
Zoledronate 4 vs. Zoledronate 8	1.82 (0.90, 3.70)	0.098

a. Data from Feb. 2001 datasets faxed to reviewer.

2. Incidence of Grade3 or 4 Renal Toxicity

The sponsor performed a similar analysis looking only at the incidence of Grade 3/ 4 renal toxicity. With few events, the same trends seen in the analyses above were seen.

Grade 3/ 4 Renal Toxicity in Protocols 010, 011, and 039[a].

Trials	Placebo	Zoledronate 4 mg	Zoledronate 8 mg	Pamidronate
Protocol 010	--	1/270 (0.4%)	7/262 (2.7%)	13/795 (1.6%)
Protocol 011	2/163 (1.2%)	3/164 (1.8%)	2/178 (1.1%)	--
Protocol 039	0/78 (0.0%)	5/92 (5.4%)	2/87 (2.3%)	--

a. Data from Feb. 2001 datasets faxed to reviewer.
b. Shows post-amendment data only.

3. Renal Adverse Events, Serious Adverse Events, and Discontinuations for Renal Adverse Events

As these trials are ongoing, information is not available on the incidence of reported renal adverse events, serious adverse events, and discontinuations for renal adverse events. The number of patients in each treatment group requiring dialysis per the sponsor is summarized in the table below.

Need for Dialysis in Studies 010, 011, and 039 as of 2.2001[a].

Treatment	Required Dialysis
Placebo	0/239 (0%)
Pamidronate	0/263 (0%)
Zoledronate 4	1/526 (0.2%)
Zoledronate 8	5/527 (0.9%)

a. Data from Feb. 2001 datasets faxed to reviewer.

4. Reversibility of Renal Deterioration Events in Protocols 010, 011, and 039.

The sponsor has collected follow-up information on the patients who developed abnormal creatininesSCr following treatment in the three trials. Patient summaries, including serum creatinines SCR and treatments, were submitted to the FDA in the form of line listings. Below is a summary of my review of those line listings, focusing on the last available data for each patient and whether that value suggests improving renal function. Only those patients who had at least 2 creatinine values after discontinuation of study drug were included. There are several important caveats to the data as it is shown. First, because only those patients where adequate follow-up exists are included in the table, the relative incidence of abnormal creatinines cannot be inferred from these data; see previous sections of this consult for that analysis. Second, the data on the pamidronate and placebo are shown only to give a crude estimate of the background variability of the changes in serum creatinine in this population. Finally, for many of the patients counted as 'improving', only two values are present to assess this (limiting the strength of the conclusion). In total, the most reasonable interpretation is that a substantial fraction of patients who develop elevated serum creatinines while taking zoledronate will have some improvement in renal function following drug discontinuation.

Changes in SCr Following Renal Injury in Studies 010, 011 and 039[a].

Drug	Improving	Worsening	Unchanged
Zoledronate 4 mg	19/25 (76%)	5/25 (20%)	1/25 (4%)
Pamidronate	2/7 (28%)	2/7 (28%)	3/7 (42%)
Placebo	1/6 (16%)	4/6 (66%)	1/6 (16%)

a. Data from individual line listings from submission dated 2.19.01.

5. Risk of Renal Toxicity Following Single- Versus Multiple-Dose Therapy with Zoledronate

The final question to address from the data is the number of cycles needed before renal toxicity was evident. Using the line listings for the patients with identified renal adverse events from the 010, 011 and 039 trials, I identified the first time an evident trend upwards in serum creatinine first occurred, and counted the number of cycles given prior to that point. Patients who received 5 minute infusions at any time during their treatment were excluded from the analysis. The number of treatments for patients with missing labs is derived using the last available normal creatinine. The table below summarizes the results of this analysis. The rate of renal injury following one cycle is low in all groups, and the rate of injury following zoledronate is not obviously different from that following pamidronate and placebo.

Review of Individual Line Listings from 010, 011 and 039[a].

Treatment Group	Average # of Cycles Before Rise in Serum Creatinine (mean±sd)	Number of Patients with Increased Serum Creatinine After One Cycle
Zoledronate	6.6±5	4/48[c] (8.3%)
Pamidronate	7.8±4	1/20[b] (5.0%)
Placebo	4.6±3	2/18[d] (11.1%)

a. Data from line listings of individual patients submitted by sponsor, Response to Approvable Letter vol. 1.
b. Patient 33100.
c. Patients: 11704, 22941, 12311, 10865, and 10585.
d. Patient 10889 and 20434.

2.2 COMPLETED TRIALS IN TUMOR-INDUCED HYPERCALCEMIA (036, 037)

The first table summarizes the incidence of renal injury in the two pivotal trials in patients with tumor-induced hypercalcemia. The first row of data represents a pooling of the occurrence of three significant clinical renal events.

Change in Serum Creatinine in Protocols 036 and 037 (Tumor-induced Hypercalcemia)[a]

	Zoledronate 4 mg N=86	Zoledronate 8 mg N=98	Pamidronate N=103
Incidence of renal AEs: acute renal failure, renal function abnormal, uremia	6 (7.0%)	8 (8.2%)	1 (1.0%)
Serum creatinine >4.5 mg/dl or increase of 0.5 mg/dl from baseline	7 (8.1%)	1 (5.9%)	9 (9.0%)
Serum creatinine elevation, grade 3 or 4[b]	0 (0%)	0 (0%)	2 (2.0%)

a. Data from original zoledronate NDA submission, ISS table 5-6, 6-1 and 6-2.
b. Corresponds to a serum creatinine of >3.0 mg/dl.

The sponsor has provided more complete details of the 15 patients in the first row. Review of these 15 case reports was performed with two goals. First, the simple observation that the incidence of these events was higher in the zoledronate groups than in pamidronate requires that they be reviewed for possible, common patterns. Recognizing that these patients all received drug in the form of the short infusion, the second goal in reviewing these data was in whether they could provide additional information on the severity and reversibility of renal injury following a single dose of zoledronate.

A review of these cases suggests a temporal association between zoledronate infusion and renal injury shortly (<1 week) thereafter, but in all cases the association is complicated by other risk factors for renal injury also present in the patient. Illustrative of this pattern (as well as the difficulty interpreting their cases) is patient —1941— He entered with chronic renal insufficiency (serum creatinine, SCr, 2.3 mg/dl, with peak level of 2.7 prior to event). Following zoledronate 8 mg, his creatinine rose by the end of the first week, reaching 3.2 mg/dl within 10 days. After a peak value of 4.5 mg/dl, his SCr fell to 3.0. Complicating this interpretation is his disease state (myeloma) and the concomitant use of aminoglycosides. Overall, then, these cases add little to our understanding of the renal effects of zoledronate. While some patients clearly developed clinically significant renal injury that was temporally associated with zoledronate infusion, this does not tell us whether similar effects would be seen in patients using the longer infusion protocol.

3.0 ISSUES AND COMMENTS

The first issue to be addressed is what new information is included in the current submission. The new patient material comes from the three ongoing long-term trials (010, 011, and 039), consisting of substantial new data on additional cycles given to patients already enrolled in the trials (as opposed to new patients). This is seen in the table below, which compares the numbers of patients in the three trials as of 10.18.00 with the numbers in the current submission.

Patients in Data Submissions.

Trial	Zoledronate 4 mg, 2.19.01 Submission	Zoledronate 4 mg, 10.18.00 submission
Study 010	270	255
Study 011	164	142
Study 039	92	84

a. Shown is the zoledronate 4 mg, post-amendment, population.

In addition, the sponsor has provided additional data on these same patients: line listings of all treatments and changes in serum creatinine. Finally, narratives have been submitted for patients who had renal adverse events in two of the pivotal trials in tumor-induced hypercalcemia (036, 037).

What have we learned from these new data? For zoledronate, use as short-term treatment of tumor-induced hypercalcemia, the questions related to the renal injury have not changed:

1) How does the incidence of renal injury following zoledronate 4 mg administered over 15 minutes compare to pamidronate and to placebo?

Based on the data reviewed above, there is no clear signal for excess renal toxicity of zoledronate 4 mg given over 15 minutes, when compared with pamidronate. This conclusion is based primarily on the most recent data from the long-term, multiple-dose studies provide longer-term follow-up from patients receiving multiple cycles of therapy. In these trials, the renal injury following the use of the two drugs was similar in incidence, and that the majority of the renal toxicity is seen following multiple doses of zoledronate. While there were clearly patients whose serum creatinine started rising after the first dose administered in all three treatment groups, the incidence of this rise was not clearly higher in the zoledronate group. The data comparing short-term use of zoledraonte and pamidronate in TIH is limited. In the early trials in TIH there was a disproportionate incidence of severe clinical adverse renal events in the zoledronate arms, but details of those cases preclude concluding they were related to the zoledronate.

By contrast, the latest data continue to support the conclusion that zoledronate 4 mg is more nephrotoxic than placebo.

What information is lacking? The data show that prolonging the time of infusion and alerting physicians to the careful monitoring of renal function can decrease the renal toxicity of zoledronate, but we don't know if the toxicity of zoledronate may vary among cancers. This concern is based on the observed differences in the rates of renal adverse events in the breast and myeloma patients in trial 010, but the data are simply insufficient to explore it further. We also don't know if patients who are severely ill (*i.e.*, TIH) are at higher risk for severe renal injury.

Additionally, the conclusion that the renal toxicity of zoledronate 4 mg is similar to that of pamidronate is based on relatively small numbers of patients. As a result, while I'm comfortable that there is no evidence of a large excess toxicity of zoledronate relative pamidronate, additional exposure will be needed to furthre define the relative risk of the two products.

2) How does the severity and rapidity of renal injury following zoledronate 4 mg administered over 15 minutes compare to placebo and to pamidronate?

The data comparing the severity of the injury with zoledronate with pamidronate is limited: the experience from the pivotal TIH trials is worrisome (more clinically-severe injury with zoledronate), but a review of those case narratives finds them to be quite conflicted and difficult to interpret. There is no clear pattern of excess, clinically-severe injury with zoledronate.

Similarly, the data on the rapidity of the injury is incomplete, but they do more suggest that an effect of both pamidronate and zoledronate on renal function can be seen after as little as one cycle. Zoledronate was not clearly worse than pamidronate or placebo with regard to the rapidity of onset, but the database for this conclusion was quite small, especially for pamidronate and placebo. In studies 010, 011 and 039, the injury is slow to develop in most patients (that is, it progresses from mild to moderate to severe as the number of cycles of therapy increases), rather than becoming severe with a single dose.

3) How reversible is the renal injury associated with the use of zoledronate 4 mg?

For this question there are new relevant data in the form of serial creatinines for patients who experienced renal injury. These data suggest that some recovery of renal function follows the discontinuation of zoledronate in the majority of patients who have an increased serum creatinine following zoledronate use. Again, in this regard, there are no data to differentiate pamidronate from zoledronate as regards to recovery of renal function. Having said this, it is also clear that some patients are left with residual renal injury that is substantial (marked by persistent elevations in serum creatinine) which have adverse consequences for them in the future.

What information is lacking? We don't have good long-term data following patients after discontinuation of zoledronate for renal toxicity. Instead, these conclusions about reversibility are based on as few as two follow-up creatinine values. This is not a critical issue for the current consult, given the patient population, but will be highly relevant for the long-term use of zoledronate.

4.0 CONSULTANT RECOMMENDATIONS

For patients with tumor-induced hypercalcemia, there is no evidence that the renal toxicity of zoledronate, 4 mg, when administered over 15 minutes, is substantially more nephrotoxic than pamidronate. Further, the renal toxicity is usually associated with repeated doses of zoledronate and is at least partially reversible in the majority of patients who experience it. Some individuals are left with significant renal impairment following multiple doses of zoledronate. These individuals may be at increased risk of future renal injury.

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/s/

Doug Throckmorton
4/18/01 10:49:36 AM
MEDICAL OFFICER
Cardio-Renal Consult for Zoledronate

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Memorandum

DATE: 7.25.00 /S/ 7.25.00

FROM: Douglas C. Throckmorton, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Ray Lipicky, M.D., Ph.D., Division Director
Division of Cardio-Renal Drug Products, HFD-110 /S/

TO: Randy Hedin, Project Manager
Eric Colman, M.D., Medical Officer
David Orloff, M.D., Division Director
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Renal toxicity of zoledronic acid
NAME OF DRUG: Zoledronic acid/ zoledronate
TRADE NAME: Zometa
FORMULATION: IV

RELATED APPLICATIONS: N/A
APPROVED INDICATIONS: N/A
SPONSOR: Novartis Pharmaceutical Corporation

DOCUMENTS USED FOR REVIEW:
1. IND —— General Correspondence, Serial #150.
2. NDA 21-223, Integrated Safety Summary, dated 12.3.99.

DATE CONSULT ASSIGNED: 6.29.00
DATE CONSULT COMPLETED: 7.20.00

1.0 BACKGROUND

Zoledronate is under development for the treatment of hypercalcemia of malignancy ——— It is a bisphosphonate, similar to other drugs approved for these indications (*e.g.*, pamidronate). Zoledronate is administered by IV infusion and its primary route of elimination is renal. In two trials in malignant hypercalcemia the incidence of renal adverse events was higher in the two zoledronate arms (4 and 8 mg) when compared with pamidronate. Similar data were later seen in trials in metastatic bone disease, leading to the discontinuation of the higher dose (8 mg) in those trials.

Because of the concerns about the renal effects of zoledronate, HFD-510 has extended the review for the NDA to September 2000, and has asked that the following questions be addressed by HFD-110:

1. The Division would appreciate your interpretation of the significance of the data related to renal safety/toxicity of zoledronate as used in the treatment of hypercalcemia of malignancy.

2. What additional information do you believe should be obtained to better characterize the safety profile of zoledronate?

2.0 AVAILABLE DATA ON THE RENAL EFFECTS OF ZOLEDRONATE

What follows is a summary of the pertinent information regarding renal adverse events reported in the Integrated Summary of Safety. The reader is referred to the primary medical review for additional details, including patient demographics and extent of exposure.

2.1 TUMOR-INDUCED HYPERCALCEMIA (PROTOCOLS CJ/HC1, 036, 037)

Included in this group (320 total patients) are one Phase I trial (Cj/HC1) two pivotal, randomized, double-blind, placebo-controlled trials (036, 037) in patients with tumor-induced hypercalcemia. These last two trials compared zoledronate (4 and 8 mg) with pamidronate (a previously approved bisphosphonate). There were 320 patients enrolled in these trials.

1. Renal Adverse Events

The table below summarizes selected renal adverse events reported by the investigators. Metabolic and obstructive AEs are not included.

Renal Adverse Events from Protocols CJ/HC1, 036 and 037 (Tumor-induced Hypercalcemia)[a]

	Zoledronate <4 mg N=33	Zoledronate 4 mg N=86	Zoledronate 8 mg N=98	Zoledronate 8 mg ReTx N=70	Pamidronate N=103
Anuria	0	0	1 (1.0%)	0	0
Renal Failure, Acute	0	1 (1.2%)	1 (1.0%)	2 (2.9%)	0
Renal Function, Abnormal	0	4 (4.7%)	3 (3.1%)	1 (1.4%)	1 (1.0%)
Uremia	0	2 (2.3%)	4 (4.1%)	0	0
Renal Injury, Combined[b]	0	7 (8.2%)	9 (10.5%)	3 (4.3%)	1 (1.0%)

a. Data from ISS, table 5-6.
b. Represents combined incidence of any of the four severe renal AEs presented above.

2. Discontinuations Due to Renal Adverse Events

Information on discontinuations due to renal adverse events is not available and has been requested from the sponsor.

3. Serious Adverse Events

Renal SAEs are summarized in the table below. SAEs related to urinary obstruction are not included.

Renal Serious Adverse Events from Protocols CJ/HC1, 036 and 037 (Tumor-induced Hypercalcemia)[a]

Treatment Grp/ Pt #	SAE	Start Day	Concomitant Meds & PMHx
Zoledronate 4 mg			
AUS/11/101	Acute Renal Failure	57	Gentamicin, Ketoprofen
D/97/230	Renal Insufficiency	4	Ciprofloxacin, Renal Insufficiency, Cystitis
AUS/3/1092	Renal Failure, Uremia	25	Diabetes, HTN, Renal Insufficiency (Baseline Crt 1.8)
Zoledronate 8 mg			
CDN/34/1322	Renal Failure, Uremia	4	Gentamicin, Ciprofloxacin, Pneumonia, Sepsis
Zoledronate 8 mg ReTx			
USA/7/1158	Acute Renal Failure	5	Prior Acute Renal Failure, Hydronephrosis, Ciprofloxacin
S/81/317	Acute Renal Failure	7	Diabetes, HTN
Pamidronate			
USA/7/1158	Decreased Renal Function	5	Gentamicin, Renal Insufficiency (Baseline Crt. 5.9)

2.1 TUMOR-INDUCED HYPERCALCEMIA (PROTOCOLS CJ/HC1, 036, 037) (cont)

4. Change in Serum Creatinine

The incidence of renal injury measured by change in serum creatinine is summarized below. It is not clear from the available data how the sponsor handled patients such as USA/7/1158 in the table above, who started with a creatinine of 5.9 mg/dl.

Change in Serum Creatinine in Protocols CJ/HC1, 036 and 037 (Tumor-induced Hypercalcemia)[a]

	Zoledronate <4 mg N=33	Zoledronate 4 mg N=86	Zoledronate 8 mg N=98	Zoledronate 8 mg ReTx N=70	Pamidronate N=103
Serum creatinine >4.5 mg/dl or increase of 0.5 mg/dl from baseline	2 (6.1%)	7 (8.1%)	12 (12.5%)	4 (5.9%)	9 (9.0%)
Serum creatinine elevation, grade 3 or 4[b]	0 (0%)	2 (2.3%)	5 (5.2%)	4 (4.0%)	2 (3.0%)

a. Data from ISS table 6-1 and 6-2.

b. Corresponds to a serum creatinine of >3.0 mg/dl.

2.2 COMPLETED BONE METASTASIS TRIALS (PROTOCOLS 003, 007, 035)

Included in this group are two phase dose-ranging trials (003 and 035) and a phase II trial (007). These trials enrolled 383 patients with bone metastases from various malignancies. The largest of these was 007, which enrolled 280 subjects with either myeloma or breast cancer.

1. Renal Adverse Events

The table below summarizes selected renal adverse events reported by the investigators. Metabolic and obstructive AEs are not included.

Renal Adverse Events from Protocols 003, 007, and 035 (Completed Bone Metastases Trials)[a]

	Zoledronate <4 mg N=168	Zoledronate 4 mg N=65	Zoledronate 8 mg N=17	Zoledronate 8 mg ReTx N=50	Pamidronate N=73
Nephritis	0	1 (1.5%)	0	0	0
Toxic Nephropathy	1 (0.6%)	0	0	0	0
Oliguria	0	0	0	0	1 (1.4%)
Renal Failure, Acute	3 (1.8%)	0	0	2 (4.0%)	2 (2.7%)
Renal Function, Abnormal	2 (1.2%)	3 (4.6%)	0	0	2 (2.7%)
Renal Tubular Disorder	0	1 (1.5%)	0	0	0
Uremia	2 (1.2%)	3 (4.6%)	0	2 (4.0%)	3 (4.1%)
Combined Renal AEs[b]	8 (4.8%)	7 (10.8%)	0	4 (8.0%)	8 (11.0%)

a. Data from ISS, table 5-22.

b. Represents combined incidence of any of the renal AEs presented above, excluding Renal Tubular Disorder.

2. Discontinuations Due to Renal Adverse Events

Uremia led to the discontinuation of one patient in the zoledronate 8 mg re-treatment arm. Additional details about subject discontinuations due to renal adverse events have been requested from the sponsor.

3. Serious Adverse Events

Information on renal SAEs in protocols 003, 007, and 035 has been requested from the sponsor.

2.2 COMPLETED BONE METASTASIS TRIALS (PROTOCOLS 003, 007, 035) (cont)

4. Change in Serum Creatinine

The incidence of renal injury measured by change in serum creatinine is summarized below.

Change in Serum Creatinine in Protocols CJ/HC1, 036 and 037 (Completed Bone Metastasis Trials)[a]

	Zoledronate <4 mg N=168	Zoledronate 4 mg N=65	Zoledronate 8 mg N=17	Zoledronate 8 mg ReTx N=50	Pamidronate N=73
Serum creatinine >4.5 mg/dl or increase of 0.5 mg/dl from baseline	14 (8.4%)	6 (9.2%)	1 (5.9%)	15 (30%)	7 (9.6%)
Serum creatinine elevation, grade 3 or 4[b]	2 (1.2%)	0 (0%)	0 (0%)	3 (6.0%)	2 (2.8%)

a. Data from ISS table 6-5, 6-6.

b. Corresponds to a serum creatinine of >3.0 mg/dl.

2.3 ONGOING BONE METASTASIS TRIALS (PROTOCOLS 010, 011, 039)

This group includes 1648 patients with either myeloma or breast cancer (protocol 010), 639 patients with prostate cancer (protocol 039) and 761 patients with other malignancies (protocol 011). Patients were randomized to receive zoledronate (4 or 8 mg), placebo (protocols 011 and 039), or pamidronate (protocol 010).

An external safety monitoring board was established by the sponsor to periodically review the safety data. During 1999, a concern about the increased number of serious renal adverse events prompted the review board to increase the time of infusion from 5 to 15 minutes and to convene a 'Renal Safety Advisory Board' (RAB). The board later recommended evaluation of additional renal safety data as it emerged.

In May 2000, the RAB reviewed the analyses of the data through April 2000, and recommended several changes, most critically the discontinuation of the 8 mg dose to any patients in the ongoing trials. The RAB also provided guidelines for the future dosing of patients, based on the patient's baseline serum creatinine. The analyses through April 2000 were then submitted to the FDA, and form the basis of the summary below. Within each of the three trials, the treatment groups were well-balanced with regard to age and serum creatinine. No unblinded clinical adverse events are available, as these trials are ongoing.

1. Incidence of Renal Deterioration Events

The RAB defined renal deterioration as follows:

1) In patient with normal renal function (baseline serum Crt <1.4 mg/dl), any increase in serum Crt ≥0.5 mg/dl.

2) In patients with abnormal renal function (baseline serum Crt ≥1.4 mg/dl), any increase of ≥1.0 mg/dl.

The incidence of these events is summarized in the table below. The incidence of renal adverse events was higher for both doses of zoledronate, when compared with either the active control (Pamidronate) or placebo.

Renal Adverse Events from Protocols 010, 011, and 039 (Ongoing Bone Metastasis Trials)[a]

Trials	Placebo	Zoledronate 4 mg	Zoledronate 8 mg	Pamidronate
Protocol 010		27/491 (5.5%)	47/454 (10.4%)	13/482 (2.7%)
Protocol 011	2/168 (1.2%)	13/181 (7.2%)	14/184 (7.6%)	
Protocol 039	13/172 (7.6%)	20/178 (11.2%)	39/173 (22.5%)	
Protocol 010 Breast Ca Pts		15/328 (4.6%)	30/316 (9.5%)	7/338 (5.3%)
Protocol 010 Myeloma Pts		12/163 (7.4%)	17/138 (12.3%)	6/144 (4.3%)

a. Data from [redacted] 2.

2. Renal Adverse Events, Serious Adverse Events, and Discontinuations for Renal Adverse Events

As these trials are ongoing, information is not available on the incidence of reported renal adverse events, serious adverse events, and discontinuations for renal adverse events.

3.0 ISSUES AND COMMENTS

The trials reviewed for this consultation enrolled patients with a variety of malignancies who received zoledronate as the following:

1) Single dose (Tumor-induced Hypercalcemia Trials, protocols CJ/HC1, 036 and 037)

2) Repeated doses every 4 weeks for 3 months (completed Bone Metastases Trials , protocols 003, 007, and 035), or

3) Repeated doses every 4 weeks for 9 to 24 months (ongoing Bone Metastases Trials , protocols 010, 011, and 039).

Based on my review of the available data, patients who received zoledronate as part of these nine clinical trials had a higher incidence on intrinsic renal injury when compared with patients who received either pamidronate or placebo. While there is evidence associating both doses of zoledronate with renal injury, the evidence is particularly strong for the highest dose studied (8 mg). These conclusions are based on two lines of data.

Changes serum creatinine

Changes in serum creatinine are frequently used as a surrogate for renal injury, and large changes (roughly, doubling over baseline or increases to >2.0-3.0 mg/dl) are almost certainly associated with permanent damage to the kidney. Changes in serum creatinine were not analyzed uniformly across the three sets of trials. In particular, the analysis done by the Renal Advisory Board in the ongoing Bone Metastasis Trials has not been conducted on the other six trials. Similarly, the incidence of Grade 3 and 4 changes in serum creatinine (to >3.0 mg/dl) were tabulated for the completed studies but no the ongoing Bone Metastasis Trials. The available data do suggest that zoledronate use is associated with a greater frequency of creatinine elevations.

First, in the completed Tumor-induced Hypercalcemia trials (Protocols CJ/HC1, 036 and 037) the incidence of significant elevation of serum creatinine was higher in the zoledronate 8 mg group when compared with pamidronate and lower doses of zoledronate. Similarly, the highest dose of zoledronate used in significant numbers of patients in the completed Bone Metastases Trials (Protocols 003, 007, and 035) had a higher frequency of elevated creatinines relative to pamidronate. No placebo group was included in these studies for comparison.

In the ongoing Bone Metastasis trials, changes in serum creatinine were analyzed by the use of 'Renal Deterioration Events'. These events were more common in both of the zoledronate dose groups compared with either placebo (protocols 011, 039) or pamidronate (protocol 010). This pattern was regardless of whether the patients had breast cancer or multiple myeloma (protocol 010). It is also important to note that the incidence of these events was higher in the 8 mg dose of zoledronate in all cases than in the 4 mg group, suggesting a dose-dependent association with renal toxicity. The decision to stop the 8 mg dose would seem to reflect a similar conclusion by the sponsor's Renal Advisory Board.

The definitions used by the Renal Advisory Board were fairly liberal; *i.e.* detecting changes that included mild increases in serum creatinine. It would be of interest to know how many patients in the ongoing trials had large increases in serum creatinine (say, doubling of baseline or grade 3/ 4 changes), where the link to irreversible damage to the kidney is unquestioned.

Incidence of Renal Adverse Events

In the patients who received a single dose of zoledronate (Tumor-Induced Hypercalcemia (Protocols CJ/HC1, 036, 037) the incidence of both renal adverse events and serious renal adverse events was higher in the zoledronate groups, when compared with placebo and pamidronate. While we lack clinical details regarding several key aspects of these events (*i.e.*, need for dialysis, resolution), it seems clear that some of the events were clinically significant (including two cases of uremia in zoledronate-treated patients).

In the patients who received multiple doses of zoledronate with available data (Completed Bone Metastasis Trials, protocols 003, 007, 035), the data are less clear, and illustrate the need for additional data from patients receiving chronic zoledronate treatment. For this group, there was no significant difference between the 4 mg and 8 mg re-treatment groups of zoledronate and the pamidronate group. These trials enrolled a similar patient population as the ongoing bony metastasis group (Protocols 010, 011, 039), where zoledronate use was associated with more renal injury as defined by increases in serum creatinine. A comparison of the reported renal adverse events and serious renal adverse events between these six trials would be quite helpful in defining the renal effects of zoledronate during chronic administration.

3.0 ISSUES AND COMMENTS (cont)

While there is an association between zoledronate administration and an increased incidence of renal adverse events, there are important pieces of data missing that would better allow us to define, and perhaps limit, the renal toxicity.

1) A full discussion of the consequences of renal toxicity associated with zoledronate in all nine trials (including the ongoing trials). For example, in the completed Tumor-Induced Hypercalcemia trials (Protocols CJ/HC1, 036, 037) two patients who received zoledronate developed 'uremia.' If these patients required dialysis this is extremely serious: dialysis in this population would be more than ordinarily dangerous and unpleasant for the patient. This discussion would include not only the adverse events reported, but the serious adverse events and discontinuations for adverse events, similar to what is summarized in section 2.1 above for the completed Tumor-Induced Hypercalcemia trials (Protocols CJ/HC1, 036, 037).

2) Follow-up for patients who experience renal adverse events in the trials. While acute renal toxicity is obviously significant in these patients, we also need to know if the injury resolves with sufficient follow-up, or whether some patients experience long-term renal damage. As discussed above, the need for dialysis in this population would be an extremely serious outcome.

3) Additional exposure data to examine whether the lower dose of zoledronate (4 mg) and/or the longer period of infusion are associated with a lower level of renal toxicity. The available data is uneven, but suggest that this dose may still be associated with a higher incidence of renal toxicity compared with pamidronate.

4) Additional analyses of the data available to date, including the following:

a. Analysis of the completed trials for the incidence of Renal Deterioration Events as defined in the analyses performed for the ongoing trials (Protocols 010, 011, and 039).

b. Analysis of the Protocols 010, 011, 039 cohort for the incidence of Grade 3 and Grade 4 changes in serum creatinine, as performed for the completed trials.

4.0 CONSULTANT RECOMMENDATIONS

The available data support an association between zoledronate use and renal adverse events, including serious adverse events such as uremia. The rate of renal adverse events following single- and repeated-doses of zoledronate was higher than the control groups for the individual trials (pamidronate and placebo). The data on the incidence of significant changes in serum creatinine (from the 3 ongoing trials) suggests a dose-dependent effect of zoledronate to cause renal injury.

The available data are insufficient to answer key questions related to the toxicity of zoledronate, most especially the extent of renal injury and the resolution of the renal injury following discontinuation of therapy. Finally, while the 8 mg dose of zoledronate has been halted in the ongoing trials, the safety of the 4 mg dose has not yet been established. The ongoing trials should provide important information on the safety of zoledronate use in patients with cancer, and critical information in describing the course of the renal injury. The sponsor should be encouraged to collect all available data on these patients, including long-term follow-up for patients who develop renal toxicity during the trials.

5.0 APPENDIX ONE: ADDITIONAL MATERIALS AND ANALYSES REQUESTED OF THE SPONSOR

The following data tables from the full NDA have been requested from HFD-510 and/or the sponsor (arranged by type of trial).

TUMOR-INDUCED HYPERCALCEMIA (PROTOCOLS CJ/HC1, 036, 037)

NDA Enumeration	Description
Post-text Tables 4.1-1, 4.1-2, 4.1-3	Adverse Events leading to discontinuation
Post-text Supplement 2	Narratives for discontinuation
Post-text listing 5.1-11	Serious Adverse Events (SAEs)
Post-text supplement 3	Narratives for SAEs
Post-text table 6.1-1 through 6.1-3	Labs

COMPLETED BONE METASTASIS TRIALS (PROTOCOLS 003, 007, 035)

NDA Enumeration	Description
Post-text Tables 5.3-11	Adverse Events leading to discontinuation
Post-text Supplement 3	Narratives for discontinuation
Post-text listing 5.3-12, 5.3-2	Serious Adverse Events (SAEs)
Post-text supplement ??	Narratives for SAEs
Post-text table 6.6-1, 6.6-2	Labs

HYPERCALCEMIA OF MALIGNANCY (PROTOCOLS 010, 011, 039)

NDA Enumeration	Description
Post-text listing 5.4-1	Serious Adverse Events (SAEs)
Post-text supplement ??	Narratives for SAEs

In addition, the following data analyses, as described in the body of the consultation, are needed (pending the completion and unblinding of the ongoing Bone Metastasis Trials).

1) Follow-up data on all patients with renal injury during the trials to death or resolution of injury.

2) Analysis of the Protocols CJ/HC1, 036, 037 and Protocols 003, 007, 035 for the incidence of Renal Adverse Events as defined by the Renal Advisory Board.

3) Analysis of the Protocols 010, 011, 039 cohort for the incidence of Grade 3 and Grade 4 changes in serum creatinine.

cc:
ORIG: Division File

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Memo to the File

Re: Comments from Clinical Pharmacology and Biopharmaceutic, NDA 21-223

When the original NDA for Zometa was submitted, the following comments with respect to Clinical Pharmacology and Biopharmaceutics were made:

1) Although acceptable, the — assays have large precision and accuracy errors which you should minimize through further optimization of the assay.
2) The sponsor should re-format the pharmacokinetic section of the labeling into the following sections: Distribution, Metabolism, Excretion, Special Populations.
3) In a Phase 4 commitment the sponsor should pursue the development of rational dosing guidelines in renally impaired patients. The sponsor should pursue defining an exposure (probably AUC-related) that shows efficacy and develop a dosing regimen based on creatinine clearance that would result in that exposure at different creatinine clearances. All study designs should be submitted for review before the sponsor proceeds with these studies.

The sponsor submitted an amendment – response to review comments on August 22, 2000, which addressed comments 1 and 2 adequately, and included a protocol for comment 3. The protocol is adequate (signed off by Rob Shore on 9/28/00).

Therefore, the sponsor adequately addressed all the issues raised from the Office of Clinical Pharmacology and Biopharmaceutics.

Hae-Young Ahn, Ph.D.

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/s/

Hae-Young Ahn
6/22/01 10:55:38 AM
BIOPHARMACEUTICS

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