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Applicant table 10-8

Table 10-8. Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Patients studied			
Total no. of patients	214	218	208
Serious or significant events			
Death*	31 (14.5)	48 (22.0)	35 (16.8)
SAEs	106 (49.5)	128 (58.7)	117 (56.3)
Clinically significant AEs	166 (77.6)	173 (79.4)	150 (72.1)
Discontinuation due to SAEs	21 (9.8)	27 (12.4)	21 (10.1)
Discontinuation due to other clinically significant AEs**	18 (8.4)	19 (8.7)	10 (4.8)

* Deaths are counted from study phase completion CRF or within 28 days of study drug discontinuation.

** Other clinically significant AEs, by definition, were not SAEs.

Source: Post-Text Table 10.2-5.

SAEs occurred in fewer of the zoledronate 4mg patients (49.5%), compared with 8/4 (58.7%) or placebo groups (56.3%). However, deaths were greatest in the zoledronate 8/4 mg group, followed by placebo. Similarly, discontinuation due to SAEs was greatest in the 8/4 mg group.

SAEs

Applicant's Table 10-9 shows the body systems most often involved in SAEs, with greater than 10% incidence in any treatment group.

Applicant table 10-9

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Table 10-9. Number (%) of patients with SAEs overall and by system/organ class (≥ 10% for any group) (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Patients studied			
Total no. of patients	214	218	208
Total no. with SAEs	108 (49.5)	128 (58.7)	117 (56.3)
System/organ class affected			
Blood and lymphatic system disorders	13 (6.1)	23 (10.6)	11 (5.3)
Gastrointestinal disorders	28 (13.1)	29 (13.3)	31 (14.9)
General disorders and administration site conditions	37 (17.3)	30 (13.8)	22 (10.6)
Infections and infestations	13 (6.1)	21 (9.6)	27 (13.0)
Metabolism and nutrition disorders	27 (12.6)	25 (11.5)	18 (8.7)
Musculoskeletal, connective tissue and bone disorders	21 (9.8)	27 (12.4)	29 (13.9)
Neoplasms benign and malignant	15 (7.0)	26 (11.9)	18 (8.7)
Nervous system disorders	13 (6.1)	12 (5.5)	21 (10.1)
Renal and urinary disorders	20 (9.3)	42 (19.3)	21 (10.1)
Respiratory, thoracic and mediastinal disorders	9 (4.2)	26 (11.9)	14 (6.7)

Source: Post-text table 10.2-1.

The incidence of SAEs for zoledronate 4 mg seems favorable when compared to placebo, except for the category of “metabolism and nutrition”. In contrast, the incidence of SAEs was higher for zoledronate 8/4 compared with both the 4 mg and placebo groups, for “blood and lymphatic” and “renal and urinary”. “Anemia NOS” occurred in 5.1% of the zoledronate 4 mg group, 8.3% of the 8/4 mg group, and 3.8% of placebo patients. It should be noted that skeletal related events (SRE) were not included as SAEs.

Applicant’s post-text table 10.2-1 (volume 109) summarizes SAEs, regardless of cause, by body system, preferred term and treatment group. Reviewer’s Table 4 is abstracted from this table, and shows SAEs occurring in at least 5% of patients in any treatment group. These events include anemia, nausea, vomiting, weakness, dehydration, bone pain, malignant neoplasm aggravated, acute renal failure, and urinary retention.

Table 66: SAE’s occurring in at least 5% of patients in any treatment group

Preferred term	Zol 4 mg N (%)	Zol 8/4 mg N (%)	Placebo N (%)
Anemia NOS	11 (5.1)	18 (8.3)	8 (3.8)
Nausea	13 (6.1)	13 (6.0)	7 (3.4)
Vomiting NOS	12 (5.6)	11 (5.0)	7 (3.4)
Weakness	14 (6.5)	7 (3.2)	7 (3.4)
Dehydration	16 (7.5)	9 (4.1)	7 (3.4)
Bone pain	11 (5.1)	21 (9.6)	25(12.0)
Malignant neopl. aggravated	13 (6.1)	20 (9.2)	13 (6.3)
Acute renal failure	10 (4.7)	12 (5.5)	3 (1.4)
Urinary retention	3 (1.4)	14 (6.4)	9 (4.3)

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Reviewer comment: The incidence of anemia in the zoledronate 8/4 population seems significant compared with the placebo population, although unexplained. The distribution of bone pain for the 3 treatment groups does *not* suggest a dose-dependant benefit of the study drug for this parameter. Acute renal failure is comparably increased in both zoledronate groups compared with placebo.

Deaths

One hundred fourteen patients died during the study or within 28 days of the last dose of study drug. The incidence of deaths was similar for placebo (16.8%) and zoledronate 4 mg (14.5%), but there was a higher per cent deaths in the zoledronate 8/4 mg group (22%). The most frequent cause of death was "aggravated malignant neoplasm."

Post-text table 10.2-3 lists the cause of death in the 97 patients who died before completing the study, who discontinued because of death. Of these patients, there were 10 (4.7%) in the 4 mg group, 16 (7.3%) in the 8/4 mg group and 11 (5.3%) in the placebo group. Of the 4 patients (1.8%) who died during the study due to urinary or renal disorders, all were in the zoledronate 8/4 mg group, with 2 deaths due to acute renal failure, 1 death due to "renal failure NOS" and 1 death due to hematuria.

When deaths were analyzed by stratum (patients without or with metastases), those with metastases at diagnosis had a shorter time to death if they were in the zoledronate 8/4 mg group compared with zoledronate 4 mg. In patients with no metastases at diagnosis, the time to death was similar in the 3 treatment groups. This data appears in post-text table 10.2-7. For the overall group, the median survival in days was 464 for placebo, 546 for the 4 mg group, and 407 for the 8/4 mg group.

Treatment discontinuations

Applicant table 10-11 lists the number of patients discontinued for adverse events by body system.

Applicant table 10-11

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Table 10-11. Number (%) of patients discontinued for adverse events by body system (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Patients studied			
Total number of patients	214	218	208
Number discontinued due to AE	39 (18.2)	46 (21.1)	31 (14.9)
Body system:			
Blood and lymphatic system disorders	3 (1.4)	2 (0.9)	1 (0.5)
Cardiac disorders	3 (1.4)	4 (1.8)	1 (0.5)
Gastrointestinal disorders	5 (2.3)	7 (3.2)	2 (1.0)
General disorders and administration site conditions	13 (6.1)	9 (4.1)	4 (1.9)
Hepato-biliary disorders	0 (0.0)	0 (0.0)	1 (0.5)
Infections and infestations	3 (1.4)	0 (0.0)	3 (1.4)
Injury and poisoning	0 (0.0)	1 (0.5)	0 (0.0)
Investigations	2 (0.9)	4 (1.8)	2 (1.0)
Metabolism and nutrition disorders	7 (3.3)	4 (1.8)	3 (1.4)
Musculoskeletal / connective tissue / bone disorders	5 (2.3)	8 (3.7)	7 (3.4)
Neoplasms benign and malignant	2 (0.9)	6 (2.8)	3 (1.4)
Nervous system disorders	1 (0.5)	6 (2.8)	4 (1.9)
Psychiatric disorders	2 (0.9)	1 (0.5)	0 (0.0)
Renal and urinary disorders	11 (5.1)	12 (5.5)	4 (1.9)
Respiratory, thoracic and mediastinal disorders	1 (0.5)	2 (0.9)	0 (0.0)
Skin & subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (0.5)
Social circumstances	0 (0.0)	0 (0.0)	1 (0.5)
Vascular disorders	2 (0.9)	0 (0.0)	0 (0.0)

Source: Post-text table 10.2-4.

The discontinuations for "General disorders" were predominantly for nonspecific symptoms such as weakness and fatigue and seem unlikely to be study-drug related. The discontinuations for "Renal and urinary disorders" are of concern. Reviewer's Table 5 (from post-text table 10.2-4) shows selected renal AEs associated with discontinuation.

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Table 67: Number (%) of patients discontinued for (selected) renal AEs by preferred terms and treatment group.

Preferred term	Zol 4mg, N=214 N (%)	Zol 8/4mg, N=218, N (%)	Placebo N=208, N (%)
<i>Total renal and urinary</i>	11 (5.1)	12 (5.5)	4 (1.9)
Renal impairment NOS	6 (2.8)	4 (1.8)	0
Renal failure acute	3 (1.4)	5 (2.3)	1 (0.5)
Oliguria	1 (0.5)	0	0
Urinary retention	1 (0.5)	2 (0.9)	2 (1.0)

Laboratory parameters

The treatment groups were similar when hematology tests were analyzed by number of patients reaching selected "notable" values of neutrophil count $< 0.5 \times 10^9$, platelets $< 25 \times 10^9$, and hemoglobin < 6.5 g/dL (applicant's table 10-13). However, applicant's table 10-14 demonstrates that more patients in the zoledronate arms had a greater than 25% decrease in hemoglobin, compared with placebo, possible in a dose-dependant fashion.

Applicant table 10-14

Table 10-14. Number (%) of patients with a > 25% decrease from baseline in hemoglobin (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Total number of patients	197 (100.0)	208 (100.0)	195 (100.0)
Number with a > 25% decrease	33 (16.8)	42 (20.4)	20 (10.3)

Source: Post-test table 10.3-1.

The following table shows grade 3 or 4 hematologic toxicity for the treatment groups.

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Applicant table 10-15

Table 10-15. Grade 3 or 4 hematology abnormalities post-baseline by treatment group (Safety evaluable patients)

	Zol 4 mg	Zol 8/4 mg	Placebo
Absolute lymphocyte count			
Total no. of patients*	195	203	193
Grade 3 (< 0.9 10 ⁹ /L)	25 (12.8)	29 (14.3)	29 (15.0)
Grade 4 (< 0.5 10 ⁹ /L)	0.0	0.0	0.0
Absolute neutrophil count			
Total no. of patients*	194	202	192
Grade 3 (< 1 10 ⁹ /L)	7 (3.6)	4 (2.0)	10 (5.2)
Grade 4 (< 0.5 10 ⁹ /L)	2 (1.0)	2 (1.0)	4 (2.1)
Platelet count			
Total no. of patients*	196	202	195
Grade 3 (< 50 10 ⁹ /L)	3 (1.5)	3 (1.5)	2 (1.0)
Grade 4 (< 25 10 ⁹ /L)	1 (0.5)	1 (0.5)	0.0
Hemoglobin			
Total no. of patients*	197	206	195
Grade 3 (< 8 g/dL)	7 (3.6)	17 (8.3)	8 (4.1)
Grade 4 (< 6.5 g/dL)	2 (1.0)	3 (1.5)	1 (0.5)
White blood cell count			
Total no. of patients*	196	203	195
Grade 3 (< 2 10 ⁹ /L)	7 (3.6)	4 (2.0)	10 (5.1)
Grade 4 (< 1 10 ⁹ /L)	0.0	0.0	0.0

* Number of patients with an in-range baseline value and at least one post-baseline measurement. Patients in high-range category and low-range category are exclusive.
Source: Post-text table 10.3-3.

Grade 3 hemoglobin values were more than twice as common in the zoledronate 8/4 mg group than either the 4 mg or placebo groups. The significance of this is uncertain, but it could relate to the higher incidence of renal dysfunction in the higher dose zoledronate group.

When patients were analyzed for notable biochemistry values (other than creatinine), there was almost twice the incidence in the zoledronate groups of hypermagnesemia > 3.0 (4 mg =6.4 %; 4/8 mg = 5.8%) compared with placebo (3%). In the zoledronate groups, there was more hypophosphatemia, and only a slight increase in hypokalemia and hyponatremia compared with placebo. Applicant table 10-19 shows grade 3 or 4 chemistry abnormalities by treatment group, demonstrating excess grade 3 hypermagnesemia, hypophosphatemia, and hypokalemia for the zoledronate groups compared with placebo.

Applicant table 10-19

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Table 10-19. Grade 3 or 4 electrolytes/serum chemistry abnormalities post baseline by treatment group (Safety evaluable patients)

	Zol 4 mg N (%)	Zol 8/4 mg N (%)	Placebo N (%)
Hypocalcemia			
Total no. of patients*	204	208	199
Grade 3 (< 7 mg/dL)	3 (1.5)	4 (1.9)	0
Grade 4 (< 6 mg/dL)	1 (0.5)	0	0
Hypercalcemia			
Total no. of patients*	204	208	199
Grade 3 (> 12.5 mg/dL)	1 (0.5)	0	2 (1.0)
Grade 4 (> 13.5 mg/dL)	0	0	0
Hypermagnesemia			
Total no. of patients*	204	208	199
Grade 3 (> 3 mEq/L)	13 (6.4)	10 (4.8)	4 (2.0)
Grade 4 (> 8 mEq/L)	0	1 (0.5)	2 (1.0)
Hypophosphatemia			
Total no. of patients*	204	208	199
Grade 3 (< 2 mg/dL)	19 (9.3)	42 (20.2)	10 (5.0)
Grade 4 (< 1 mg/dL)	3 (1.5)	1 (0.5)	0
Hyperphosphatemia			
Total no. of patients*	204	208	199
Grade 3 (> 6 mg/dL)	1 (0.5)	0	0
Grade 4 (> 7 mg/dL)	0	0	0
Hypokalemia			
Total no. of patients*	203	207	199
Grade 3 (< 3 mEq/L)	6 (3.0)	7 (3.4)	1 (0.5)
Grade 4 (< 2.5 mEq/L)	0	1 (0.5)	0
Hyperkalemia			
Total no. of patients*	203	207	199
Grade 3 (> 6 mEq/L)	10 (4.9)	5 (2.4)	3 (1.5)
Grade 4 (> 7 mEq/L)	4 (2.0)	3 (1.5)	5 (2.5)
Hyponatremia			
Total no. of patients*	203	207	199
Grade 3 (< 130 mEq/L)	11 (5.4)	10 (4.8)	8 (4.0)
Grade 4 (< 120 mEq/L)	1 (0.5)	1 (0.5)	0
Alkaline phosphatase			
Total no. of patients*	203	208	199
Grade 3 (> 5 x N)	42 (20.7)	57 (27.4)	53 (26.6)
Grade 4 (> 20 x N)	3 (1.5)	3 (1.4)	6 (3.0)
AST (SGOT)			
Total no. of patients*	203	207	199
Grade 3 (> 5 x N)	6 (3.0)	12 (5.8)	7 (3.5)
Grade 4 (> 20 x N)	0	1 (0.5)	2 (1.0)
ALT (SGPT)			
Total no. of patients*	203	207	199
Grade 3 (> 5 x N)	1 (0.5)	2 (1.0)	2 (1.0)
Grade 4 (> 20 x N)	0	0	1 (0.5)
Total bilirubin			
Total no. of patients*	202	207	199
Grade 3 (> 3 x N)	0	0	2 (1.0)
Grade 4 (> 10 x N)	0	0	2 (1.0)

*Number of patients who had a baseline value and at least one post-baseline values of laboratory measurements. Patients in grade 3 and grade 4 are exclusive
Source: Post-test table 10.3-3.

Serum creatinine and renal function deterioration

Baseline serum creatinine was considered normal if <1.4 mg/dL and abnormal if ≥ 1.4 mg/dL. Renal function deterioration was defined as any of the following:

- Normal baseline with change from baseline ≥ 0.5 mg/dL
- Abnormal baseline with change from baseline ≥ 1.0 mg/dL
- Post-baseline value ≥ 2 time the baseline value.

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Subsequent to amendment 3 (15 minute infusion), renal function deterioration as defined in applicant table 10-16, was 17.4% for zoledronate 4 mg, 25.3 % for zoledronate 25.3% and 11.5 % for placebo.

Applicant table 10-16

Table 10-16. Frequency distribution for post baseline notable creatinine by criteria and treatment group for pre 15-minute infusion amendment patients and post 15-minute infusion amendment patients (Safety evaluable patients)

	Zol 4 mg N (%)	Zol 8/4 mg N (%)	Placebo N (%)
Pre 15-minute infusion amendment patients			
In-range	80 (72.1)	77 (64.2)	106 (87.6)
≥4.5 mg/dL*	0.0	0.0	0.0
Increase from baseline ≥0.5 mg/dL*	31 (27.9)	42 (35.0)	14 (11.6)
Both*	0.0	1 (0.8)	1 (0.8)
Total	111	120	121
Post 15-minute infusion amendment patients			
In-range	76 (82.6)	65 (74.7)	69 (88.5)
≥4.5 mg/dL*	0.0	0.0	0.0
Increase from baseline ≥0.5 mg/dL*	12 (13.0)	21 (24.1)	9 (11.5)
Both*	4 (4.4)	1 (1.2)	0.0
Total	92	87	78

* Categories are mutually exclusive. If a patient met both criteria, then that patient is counted under the category "Both", but not in the other two categories.

Source: Post-text tables 10.3-2A, 10.3-2B.

No patient experienced grade 4 creatinine elevation (> 6xULN). Grade 3 (>3xULN) creatinine values occurred in 5 zoledronate 4 mg patients and in 2 of the 8/4 mg group following amendment 3, but none in the placebo group. (Prior to amendment 3, 2 placebo patients had grade 3 elevation of creatinine).

The incidence of renal function deterioration was increased in the zoledronate treatment groups for patients with a baseline serum creatinine of ≥ 1.4 , compared with those with a normal baseline creatinine. The incidence of deterioration decreased after amendment 3, but still was higher in the zoledronate groups. The following table is abstracted from applicant table 10-21.

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Table 68: Patients who experienced renal function deterioration by baseline serum creatinine (15-minute infusion)

	Zol 4 mg N (%)	Zol 8/4 mg N (%)	Placebo N (%)
Patients with normal baseline creatinine	82	68	68
- - - with deterioration	10 (12.2)	14 (20.6)	7 (10.3)
Patients with abnormal baseline creatinine	10	19	20
- - - with deterioration	4 (40.0)	4 (21.1)	2 (10.0)
Total # patients at baseline	92	87	78
- - - with deterioration	14 (15.2)	18 (20.7)	9 (11.5)

When time to renal function deterioration was analyzed by Cox regression for patients treated post amendment 3, there were no statistically significant differences in pairwise comparisons between any treatment groups. The Kaplan-Meier curves of first renal function deterioration by treatment group are similar for patients treated by 15-minute infusion (Applicant's figure 10.2). The risk ratio between zoledronate 4 mg and placebo was 1.066 for patients randomized after amendment 3. (The risk ratio between zoledronate 8/4 mg and placebo was 1.764.) The differences were not statistically significant.

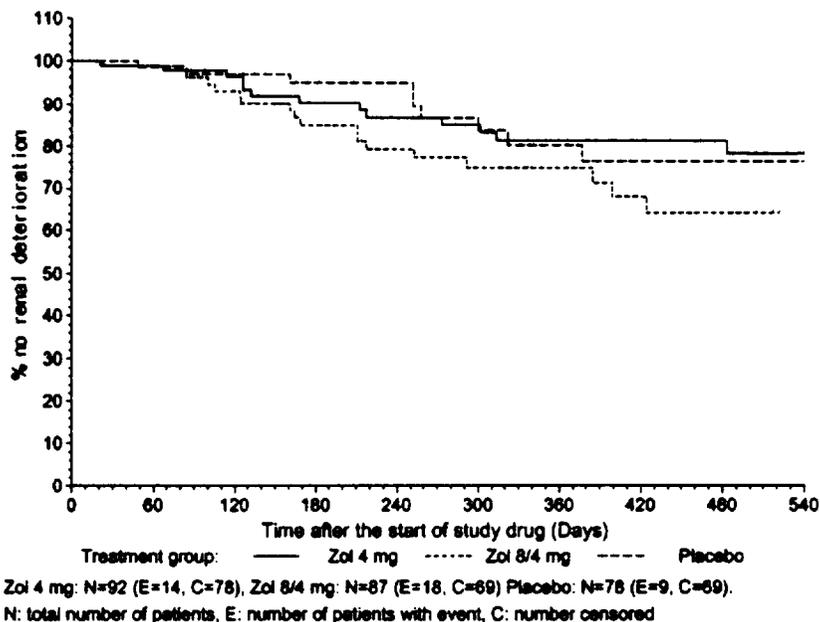
Applicant figure 10.2

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Figure 10.2. Kaplan-Meier curve for time to the first renal function deterioration by treatment group for the post 15-minute infusion amendment patients (Safety evaluable patients)



Urinalysis

The percentage of patients with elevated urine protein ($\geq 2+$) post-baseline was greater in the zoledronate treatment groups than in the placebo group (Post-text table 10.3-2).

Vital signs

More patients in the zoledronate groups had $\geq 10\%$ weight decrease. In the 4mg group, the incidence was 30.5 %. 32.7 in the 8/4 mg group, and 19.4% in the placebo group.

ECGs

For those patients who had follow-up ECGs, there were more abnormalities compared with baseline in all study groups

Special safety topics-PSA

For patients who had serum PSA measured within 30 days of disease progression, changes in PSA were similar for the zoledronate 4 mg and placebo groups. The applicant suggests that zoledronate 4 mg has “no effect on the secretion, clearance, or measurement of PSA”. This seems a reasonable interpretation of the data.

Reviewer comment and conclusions

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Increased risk of renal function deterioration is the only significant safety issue for zoledronate in this and related clinical trials of long-term treatment for patients with metastatic malignancy to bone. This toxicity was dose and time-related.

Adverse events, seen with other bisphosphonates, and possibly class effects of bisphosphonates, were reported more frequently with zoledronate than placebo. These include fever, arthralgias/myalgias, and electrolyte abnormalities, but do not present a safety issue.

Anemia was slightly more common in the zoledronate groups (approximately 27%) compared with placebo (17.8%). This is of uncertain, if any, significance. In the zoledronate groups, there was an excess of hypermagnesemia and hypophosphatemia compared with placebo.

Subsequent to the occurrence of acute renal failure in a total of 3 patients receiving zoledronate 8 mg in this and related trials for disease metastatic to bone, a renal advisory board (RAB) of nephrologists was convened and several amendments to the protocol were made. The incidence of renal function deterioration was decreased by prolonging the infusion time from 5 to 15 minutes (amendment 3). Amendment 4 further improved the safety profile by eliminating the 8 mg dose. The safety of the 4 mg dose was improved by requiring assessment of serum creatinine before each dose. Zoledronate was held for renal deterioration, as defined in the amended protocol. Therapy was not reinstated until creatinine returned to within 10% of the baseline value.

Following amendment 3, the overall incidence of renal related AEs was comparable for zoledronate 4 mg (30.9%) and placebo (31.0%). However, the incidence of "renal impairment NOS" was 7.2% for zoledronate 4 mg, 3.2% for zoledronate 8/4 mg and 3.6% for placebo. The incidence of renal failure acute" was 5.2% for zoledronate 4 mg, 4.3% for zoledronate 8/4 mg, and 0 for placebo. "Blood creatinine increased was reported at 0 for zoledronate 4 mg and 3.6% for placebo (4.3% for zoledronate 8/4 mg).

The incidence of renal function deterioration was higher in the zoledronate 4 mg group (15.2%) and zoledronate 8m (20.7%) compared with placebo (11.5%), even following amendment 3.

Cox regression analysis of time to renal function deterioration showed no difference between the groups. Kaplan-Meier curves of first renal function deterioration by treatment group showed no difference for patients treated by 15-minute infusion. The risk ratio between zoledronate 4 mg and placebo was 1.066 for these patients, but the difference was not statistically significant.

***Reviewer conclusion:** Zoledronate 4 mg i.v. over 15 minutes every 3 weeks has an acceptable risk profile. The risk of renal deterioration with zoledronate is greater than placebo, but acceptable with clinical monitoring of renal function before each dose. The*

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risk of renal toxicity increases with duration of therapy. Caution is indicated for patients with elevated baseline creatinine, particularly since the study population excluded patients with creatinine > 3 and the drug is excreted unchanged by the kidneys. This study population (prostate cancer) did not have extensive concomitant exposure to other potentially renal toxic drugs. As the treatment population is expanded, it will be necessary to monitor for possible enhancement of renal toxicity in patients who are treated concomitantly with drugs of known nephrotoxic potential.

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15 Appendix 2 Review of Zoledronate Safety in Solid Tumors, Study 011

Study # CGP 42446-03-011: "A randomized, double-blind, placebo-controlled, multicenter trial to evaluate the safety and efficacy of zoledronate (4 and 8 mg) administered intravenously as an adjuvant to anticancer therapy to patients with any cancer with bone metastases other than breast cancer, multiple myeloma or prostate cancer."

This is a multicenter, international study (141 sites, in US 72, others in Europe, Australia/New Zealand). The first patient enrolled 27 August 1998 and the last patient completed therapy 30 January 2001. The study population consisted of adults with solid tumors other than breast or prostate cancer. Patients could receive antineoplastic chemotherapy. Patients were to have objective evidence of at least 1 site of metastatic disease to bone. ECOG performance status was to be 0.1, or 2. If ECOG 2, patients needed to have been diagnosed within 6 weeks of the screening visit.

Criteria for exclusion included creatinine >3 . Corrected calcium < 8 or ≥ 12 at visit 1 was an indication for exclusion.

From December 1998 to May 1999 there were 3 renal failure SAEs in patients receiving zoledronate 8mg, manifested by progressively rising serum creatinine. "These 3 cases represent approximately 1% of the patients who have been exposed to the 8 mg dose in the zoledronate program." This occurred in 1 patient each of a Phase II myeloma study (cycle #11), protocol 010 (diagnosis breast cancer, cycle #1), and protocol 039 (prostate cancer, after cycle #7). The patients were, respectively, ages 75, 80, and 71, with baseline creatinines of 1.6, 1.9, and 1.4. These events led to Amendment 3 on 25 June 1999 and Amendment 5 on 7 June 2000.

The duration of therapy was 9 months (36 weeks). Patients were randomized to receive zoledronate 4 mg or 8 mg or placebo i.v. over 5 minutes q 3 weeks. After amendment 3, the infusion duration was prolonged to 15 minutes. After amendment 5, all zoledronate patients received 4 mg per dose. Serum creatinine was to be evaluated before each dose, and treatment held for deterioration of creatinine, as defined in the amendment, until the level was within 10% of the baseline creatinine.

Applicant assessment and analysis of safety

Adverse events, serious adverse events, laboratory studies, and survival data were the main safety variables. Baseline and end of study (week 36) physical examination, EKG, and laboratory evaluations were done, including hematology, blood chemistries, urine chemistries and urinalysis. Interim physical examination, vital signs, assessment for adverse events, and laboratory studies were repeated every 3 weeks, except urine studies were approximately every 3 months. After amendment 5, the results of creatinine levels were required prior to each dose of zoledronate, so that the drug could be held for renal deterioration.

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Safety analysis was based on the type and frequency of adverse events and the laboratory values outside of pre-determined ranges. The data were tabulated.

The effect on renal function was analyzed according to the number of patients who experienced renal adverse events using selected terms suggested by the renal advisory board (RAB) and the number of patients who met pre-defined criteria of renal deterioration. Kaplan-Meier curves were used to describe the time course of renal function deterioration.

“For laboratory and adverse event analysis, data were cut at the end of the study drug period,” either at the end of the core study phase or the last date of study medication plus 28 days. For time to death and renal deterioration analysis, all available data was included, up to the date of the data base lock. For other safety parameters, the last visit date was used.

Study population

Seven hundred seventy-three patients with osteolytic bone metastases from solid tumors other than breast and prostate cancer were randomized to the following groups:

Zoledronate 4 mg	#257
Zoledronate 8 mg	#266
Placebo	#250

Patients were stratified into two groups, patients with non-small cell lung cancer (NSCLC) and patients with all other types of solid tumors (except breast and prostate).

The safety population consisted of all randomized patients who received study medication, and had documented evidence of at least one post-baseline safety evaluation. Seven randomized patients were not included in the safety analysis because they failed to receive any study treatment. The number of patients in each arm is shown in applicant's table 7-2.

Applicant Table 7-2

Table 7-2. Number (%) of patients in analysis populations by treatment group

	Zol 4 mg	Zol 8/4 mg	Placebo
Populations			
All randomized	257 (100.0%)	266 (100.0%)	250 (100.0%)
ITT population	257 (100.0%)	266 (100.0%)	250 (100.0%)
Safety evaluable population	254 (98.8%)	265 (99.6%)	247 (98.8%)

Source: Post-text table 7.1-1.

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Reviewer's Note: Analysis of data provided by the applicant, demonstrates that for patients assigned to the 8/4 mg group, 391 of 1809 zoledronate doses administered were actually 4mg rather than 8 mg, or approximately 22%.

Thirty-eight patients were randomized to the incorrect stratum.

- 3 patients with NSCLC were randomized into the other solid tumors stratum, one in each of the 3 treatment groups.
- 35 patients with small cell lung cancer were randomized in the NSCL cancer stratum with 12 in the 4 mg group, 10 in the 8/4 mg group and 13 in the placebo group.

For the efficacy analysis, the patients were not reassigned, but for the safety analysis, "such patients were reassigned to the correct stratum."

Reviewer comment: The protocol (section 3.4.1) describes stratification for "patients with lung cancer" and "patients with all other cancers". NSCLC and SCLC are not distinguished in the protocol or its amendments and, it seems there was no clear distinction between NSCLC and SCLC until the study report.

The following table abstracts data from applicant's tables 7-3 and 7-4, to illustrate baseline age and serum creatinine. These are patient factors which might increase the susceptibility to the renal toxic effects of zoledronate.

Applicant Tables 7.3 / 7.4. Baseline patient age and serum creatinine by treatment group. (excerpted)

	Zol 4 mg N=254	Zol 8/4 mg N=265	Placebo N=247
Age (years)			
n	254	265	247
Mean ± SD	62.3± 10.60	60.8± 10.46	62.3± 10.87
Median	63.5	62.0	64.0
Age			
≤ 60	106(41.7%)	124(46.8%)	98(39.7%)
> 60	148(58.3%)	141(53.2%)	149(60.3%)
Serum creatinine			
Normal (< 1.4 mg/dL)	233 (91.7%)	232 (87.5%)	220 (89.1%)
Abnormal (≥ 1.4 mg/dL)	18 (7.1%)	33 (12.5%)	25 (10.1%)
Missing	3 (1.2%)	0 (0.0%)	2 (0.8%)

This data shows similar age for treatment groups whether viewed as median age or % older than 60 years of age. The baseline serum creatinine values are similar, particularly for the zoledronate 4 mg and placebo groups.

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Reviewer's comment: The treatment related factors that might predict for renal toxicity of zoledronate include dose, duration of infusion, exposure over time (# of months of treatment), and concomitant exposure to renal toxic drugs.

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Overall exposure

The duration of exposure to the study drug was similar for all treatment groups (applicant's table 8-1). The mean duration of exposure was 4.51 months for zoledronate 4 mg, 4.45 months for the 8/4 mg group and 4.62 months for placebo. The median duration of exposure was 4.04 months for zoledronate 4mg, 3.21 months for zoledronate 8/4 mg, and 3.79 months for placebo.

Most patients in all groups were treated following amendment 3 and, therefore, were treated by infusion over 15 (rather than 5) minutes. This was 73% of the zoledronate 4 mg patients, 76% of the 8/4 mg group and 74.5% of the placebo group. Many patients were treated fewer than 3 months. For the 15 minute infusion patients, this includes 37.1% of the 4mg group, 40.8% of the 8/4 mg group, and 41.8% of the placebo patients.

Concomitant medication

"Approximately 80% in each group were receiving antineoplastic therapy at study entry and during the study with the most common agents being carboplatin, cisplatin, paclitaxel, gemcitabine, fluorouracil, etoposide, folinic acid, vinorelbine and doxorubicin." Post-text table 8.2-4 shows that the incidence of treatment with the nephrotoxic drug, cisplatin, concomitant with study medication was similar among the treatment groups. The incidence of cisplatin therapy was 14.6% for the zoledronate 4mg group, 17.4% for the 8/4 mg group, and 16.6% for placebo.

Overall incidence and severity of adverse events:

Clinical study reports used the IMN dictionary to code adverse events (AEs.) The data is summarized in the study report using MedDRA preferred terms. Adverse events were mapped from the IMN preferred terms to the corresponding MedDRA terms. The number of patients with AEs is provided by body system, preferred term, and treatment group. If a patient had more than one type of event within a body system, the patient was counted only once.

"Almost all patients in all treatment groups experienced at least one adverse event." There was a slightly higher incidence among the zoledronate 4 mg patients of AEs affecting gastrointestinal, nervous, and respiratory systems, and the eye, compared with the other 2 groups. Applicant table 10-1 shows the % of patients with adverse events overall and by system, for events occurring $\geq 15\%$ in any group.

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Applicant Table 10-1

Table 10-1. Number (%) of patients with AEs overall and by system organ class (≥ 15% for any group)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Patients studied			
Total no. of patients	254	265	247
Total no. with AEs	251 (98.8)	261 (98.5)	245 (99.2)
System organ class affected			
Gastrointestinal disorders	199 (78.3)	193 (72.8)	178 (72.1)
General disorders and administration site conditions	189 (74.4)	199 (75.1)	175 (70.9)
Musculoskeletal, connective tissue and bone disorders	160 (63.0)	175 (66.0)	178 (72.1)
Nervous system disorders	156 (61.4)	144 (54.3)	120 (48.6)
Respiratory, thoracic and mediastinal disorders	156 (61.4)	157 (59.2)	130 (52.8)
Metabolism and nutrition disorders	136 (53.5)	141 (53.2)	126 (51.0)
Blood and lymphatic system disorders	124 (48.8)	106 (40.0)	107 (43.3)
Infections and infestations	103 (40.6)	114 (43.0)	112 (45.3)
Psychiatric disorders	85 (33.5)	84 (31.7)	71 (28.7)
Vascular disorders	72 (28.3)	53 (20.0)	60 (24.3)
Neoplasms benign and malignant (including cysts and polyps)	71 (28.0)	81 (30.6)	77 (31.2)
Investigations	54 (21.3)	72 (27.2)	50 (20.2)
Renal and urinary disorders*	53 (20.9)	61 (23.0)	48 (19.4)
Cardiac disorders	42 (16.5)	47 (17.7)	38 (15.4)
Eye disorders	34 (13.4)	28 (10.6)	18 (7.3)

Body systems are sorted in descending frequency, as reported in the Zol 4 mg column

The patients with renal and urinary disorders include all patients, regardless of whether they were treated by 5- or 15-minute infusion. The incidence is similar for zoledronate 4 mg and placebo, slightly higher for the 8/4 mg group.

The most frequent adverse events were bone pain, nausea, anemia, vomiting, constipation, dyspnea, fatigue, pyrexia, weakness, anorexia, lower extremity edema, and malignant neoplasm aggravated. Nausea, vomiting, and dyspnea were higher in the zoledronate 4 mg group than in the placebo group. There was no clear dose relationship. This data appears in applicant table 10-2.

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Applicant Table 10-2

Table 10-2. Number (%) of patients with most frequent AEs (≥ 10% for any group)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Patients studied			
Total no. of patients	254	265	247
Total no. with an AE	251 (98.8)	261 (98.5)	245 (99.2)
Bone pain	129 (50.8)	130 (49.1)	145 (58.7)
Nausea	116 (45.7)	106 (40.0)	83 (33.6)
Anemia NOS	94 (37.0)	82 (30.9)	82 (33.2)
Vomiting NOS	91 (35.8)	83 (31.3)	71 (28.7)
Constipation	85 (33.5)	76 (28.7)	89 (36.0)
Dyspnoea NOS	83 (32.7)	90 (34.0)	65 (26.3)
Fatigue	79 (31.1)	78 (29.4)	72 (29.1)
Pyrexia	67 (26.4)	70 (26.4)	56 (22.7)
Weakness	66 (26.0)	67 (25.3)	65 (26.3)
Anorexia	58 (22.8)	60 (22.6)	62 (25.1)
Oedema lower limb	56 (22.0)	53 (20.0)	49 (19.8)
Malignant neoplasm aggravated	54 (21.3)	67 (25.3)	56 (22.7)
Cough	47 (18.5)	44 (16.6)	38 (15.4)
Diarrhoea NOS	43 (16.9)	48 (18.1)	44 (17.8)
Headache NOS	42 (16.5)	36 (13.6)	26 (10.5)
Insomnia NEC	42 (16.5)	38 (14.3)	30 (12.1)
Dehydration	40 (15.7)	48 (18.1)	41 (16.6)
Appetite decreased NOS	34 (13.4)	29 (10.9)	18 (7.3)
Dizziness (exc vertigo)	34 (13.4)	26 (9.8)	28 (11.3)
Weight decreased	33 (13.0)	49 (18.5)	31 (12.6)
Abdominal pain NOS	31 (12.2)	34 (12.8)	24 (9.7)
Depression NEC	31 (12.2)	31 (11.7)	20 (8.1)
Thrombocytopenia	30 (11.8)	23 (8.7)	16 (6.5)
Paraesthesia NEC	29 (11.4)	14 (5.3)	17 (6.9)
Confusion	28 (11.0)	27 (10.2)	32 (13.0)
Arthralgia	27 (10.6)	43 (16.2)	34 (13.8)
Myalgia	26 (10.2)	38 (14.3)	31 (12.6)
Neutropenia	26 (10.2)	33 (12.5)	32 (13.0)
Anxiety NEC	24 (9.4)	31 (11.7)	23 (9.3)
Alopecia	21 (8.3)	25 (9.4)	28 (11.3)

Source: Post-text table 10.1-1 and 10.1-2.

Reviewer comment: The applicant also presented the number of patients with the most common AEs by stratum (NSCLC or not) and treatment group (table 10.3) but this did not seem to add significantly to the analysis.

The overall incidence of grade 3 and 4 adverse events, regardless of cause, is similar for the treatment groups. (Post text table 10.1-4, volume 95.) The incidence of grade 3 AEs

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for the zoledronate 4 mg group was 33.5% and 38.9% for the placebo group. The incidence of grade 4 AEs was 43.3% and 39.8%, respectively.

Renal adverse events

A Renal Advisory Board (RAB) was established in November 1999 to monitor the renal safety of zoledronate, due to concerns about renal toxicity. Three patients in other studies had renal failure after receiving zoledronate 8 mg. Applicant table 10-4 shows renal AEs using the preferred terms specified by the RAB for patients randomized before the 15-minute infusion amendment and in table 10-5 for patients randomized after the 15-minute infusion amendment. For the pre-amendment patients, the incidence of renal AEs was 16.2 % in the zoledronate 4 mg group, 20.3% in the 8/4 mg group and 12.7% in the placebo group. The incidence of acute renal failure was 5.9% (4 patients) and 6.3% for zoledronate 4 mg and 8/4 mg, respectively, and 0 for placebo. The incidence of "renal impairment NOS" was 2.9% (2 patients) and 3.1% in the zoledronate groups, and 0 in the placebo group.

Renal AEs decreased in the zoledronate arms after extending the infusion time to 15 minutes, and was stable for the placebo patients. Applicant table 5 shows the renal AEs by preferred term and treatment group for the patients randomized after the 15-minute infusion amendment.

Applicant Table 10.5

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Table 10.5. Renal related adverse events by preferred term and treatment group for post 15-minute infusion amendment patients (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Total no. of patients	186	201	184
Total no. of patients with a renal related adverse event	22(11.8)	30(14.9)	23(12.5)
Blood creatinine increased	5(2.7)	8(4.0)	1(0.5)
Haematuria	4(2.2)	6(3.0)	7(3.8)
Renal failure acute	4(2.2)	7(3.5)	1(0.5)
Urinary retention	4(2.2)	2(1.0)	5(2.7)
Renal impairment NOS	2(1.1)	4(2.0)	1(0.5)
Urinary tract disorder NOS	2(1.1)	2(1.0)	0(0.0)
Haematuria present	1(0.5)	2(1.0)	0(0.0)
Hydronephrosis	1(0.5)	1(0.5)	1(0.5)
Hyperuricaemia	1(0.5)	0(0.0)	2(1.1)
Nephritis NOS	1(0.5)	0(0.0)	0(0.0)
Oliguria	1(0.5)	3(1.5)	2(1.1)
Renal failure NOS	1(0.5)	1(0.5)	2(1.1)
Urethral obstruction	1(0.5)	0(0.0)	0(0.0)
Urinary frequency	1(0.5)	1(0.5)	2(1.1)
Anuria	0(0.0)	1(0.5)	1(0.5)
Difficulty in micturition	0(0.0)	0(0.0)	1(0.5)
Micturition urgency	0(0.0)	0(0.0)	2(1.1)
Obstructive uropathy	0(0.0)	3(1.5)	0(0.0)
Renal failure chronic	0(0.0)	1(0.5)	0(0.0)

Source: Post-text table 10.1-7B.

Even after institution of the 15-minute amendment, the incidence of “renal failure acute” is higher for zoledronate (4mg, 2.2) compared with placebo (0.5), but particularly for the 8/4 mg group (3.5). The category of “blood creatinine increased” is higher in the post 15-minute group, 5% for 4 mg, 8% for 8/4 mg, and 1% for placebo, compared with the pre 15-minute incidence of 0, 1.6% and 0 respectively.

Reviewer comment: The higher incidence of elevated creatinine post- compared with pre-amendment 3 may actually be a higher incidence of discovery, relating to the requirement to assess creatinine prior to each treatment, following amendment 5 in June 2000.

In table 10-6 of the study report, the applicant reviews chemotherapy-associated AEs to determine if these were increased by the addition of zoledronate. The most common AEs were nausea, vomiting, anorexia and appetite decrease. Each of these, except anorexia, was more frequent in the zoledronate groups than in the placebo group.

Reviewer comment: Since the incidence of these AEs was higher for zoledronate 4 mg than 8/4 mg, makes it less likely that zoledronate caused the symptoms. Of interest, but

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probably not of causal significance, is the fact that stomatitis is present at higher incidence in the zoledronate 4 mg (5.9%) and 8/4 mg (6.4%) groups than for placebo (3.6%).

AEs (other than renal) tabulated as "most clinically relevant for bisphosphonates" showed no overall increased incidence for zoledronate patients when "any body system" was specified. However, the zoledronate 4 mg group did have excess AEs compared to placebo for "electrolytes" (20.1% vs. 12.1%) and "eye abnormalities" (12.6% vs. 6.9%). There was no dose-related increase for the zoledronate 8/4 mg group, which was similar to the 4 mg group for these AEs (19.2% "electrolytes" and 11.3% "eye abnormalities."

Deaths, SAEs and other "significant adverse events"

In section 3.5.3.2 of the protocol, the applicant defines a serious adverse event (SAE) as an event which:

1. Is fatal or life threatening
2. Requires or prolongs hospitalization
3. Is significantly or persistently disabling or incapacitating
4. Constitutes a congenital anomaly or a birth defect
5. Encompasses any other clinically significant event

Item 5 is not clearly explained. "Clinically significant AEs" are defined as events which were no SAEs, but "resulted in withdrawal of study drug or were considered to be clinically important and required concomitant therapy.

The applicant's table 10.8 lists "patients who died (up to the end of the core study phase or within 28 days following last treatment), had other serious or clinically significant AEs or discontinued because of them".

Applicant table 10-8

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Table 10-8. Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Patients studied			
Total no. of patients	254 (100.0)	265 (100.0)	247 (100.0)
Serious or significant events			
Death	89 (35.0)	89 (33.6)	83 (33.6)
SAEs	170 (66.9)	179 (67.5)	152 (61.5)
Other significant AEs	188 (78.0)	199 (75.1)	202 (81.8)
Discont. due to SAEs	32 (12.6)	37 (14.0)	25 (10.1)
Discont. due to clin sig AEs *	15 (5.9)	25 (9.4)	25 (10.1)

* excluding discontinuations due to SAEs

Deaths are counted from study phase completion CRF or within 28 days of study drug discontinuation.

Source: Post-text table 10.2-5.

There is a slight excess of SAEs for zoledronate 4mg compared with placebo, but not for the other events. There were 261 deaths, with a similar incidence in each treatment group. The most frequent cause of death was progression of cancer.

Post-text table 10.2-3 summarizes number of patients who discontinued due to death by body system, preferred term and treatment group. This shows 10.6% of the zoledronate 4 mg group and 17.4% of the placebo group dying from "malignant neoplasm aggravated". Death was attributed to "renal and urinary disorders" for only 1 patient in the zoledronate 4 mg group, and no patients in the placebo group.

Reviewer note: There is a discrepancy between the per cent of patients in each treatment group for table 10-8 and post-text-table 10.2-3. The latter cites 26.0%, 28.3% and 26.7% incidence of deaths in the zoledronate 4 and 8/4 mg groups, compared with 35.0%, 33.6%, and 33.6% deaths in table 10-8.

The most frequent SAEs, regardless of study drug relationship, were anemia, dehydration, malignant neoplasm aggravated and dyspnea. Anemia occurred in 7.9% of the zoledronate 4 mg group and in 3.6% of the placebo group. Dyspnea was present in 10.2% and 7.7%, respectively. The incidence of "renal and urinary disorders" was 5.1% in zoledronate 4mg, 7.2% in 8/4 mg, and 3.6% in placebo. For acute renal failure, the incidence was 3.1%, 4.2%, and 0.4%, respectively.

Note that the efficacy endpoint of SREs (skeletal related events) was not to be included in the SAE tabulation.

Applicant's table 10-9 summarizes the number of patients discontinued from study for an adverse event.

Applicant table 10-9

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Table 10-9. Number (%) of patients discontinued for adverse events, by body system

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Placebo n (%)
Patients studied			
Total number of patients	254	265	247
Number discontinued due to AE	47 (18.5)	62 (23.4)	50 (20.2)
Body system			
Neoplasms benign and malignant (including cysts and polyps)	10 (3.9)	17 (6.4)	18 (7.3)
Respiratory, thoracic and mediastinal disorders	10 (3.9)	5 (1.9)	9 (3.6)
Gastrointestinal disorders	8 (3.1)	7 (2.6)	4 (1.6)
General disorders and administration site conditions	8 (3.1)	22 (8.3)	9 (3.6)
Infections and infestations	4 (1.6)	3 (1.1)	1 (0.4)
Metabolism and nutrition disorders	4 (1.6)	5 (1.9)	4 (1.6)
Renal and urinary disorders	4 (1.6)	9 (3.4)	3 (1.2)
Musculoskeletal, connective tissue and bone disorders	3 (1.2)	4 (1.5)	6 (2.4)
Investigations	2 (0.8)	3 (1.1)	1 (0.4)
Blood and lymphatic system disorders	1 (0.4)	0 (0.0)	1 (0.4)
Cardiac disorders	1 (0.4)	1 (0.4)	0 (0.0)
<hr/>			
Injury and poisoning	1 (0.4)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (0.4)	6 (2.3)	6 (2.4)
Psychiatric disorders	1 (0.4)	5 (1.9)	5 (2.0)
Endocrine disorders	0 (0.0)	0 (0.0)	1 (0.4)
Eye disorders	0 (0.0)	1 (0.4)	0 (0.0)
Hepato-biliary disorders	0 (0.0)	1 (0.4)	2 (0.8)
Immune system disorders	0 (0.0)	1 (0.4)	0 (0.0)
Skin & subcutaneous tissue disorders	0 (0.0)	1 (0.4)	0 (0.0)
Vascular disorders	0 (0.0)	2 (0.8)	2 (0.8)

Source: Post-text table 10.2-4.

There is no increase in discontinuations for zoledronate 4 mg compared with placebo. Discontinuation for renal and urinary disorders is similar for the 2 groups, but slightly higher for the zoledronate 8/4 mg group.

Laboratory parameters

Hematology

The treatment groups were similar when hematology tests were analyzed by number of patients reaching selected "notable" values of neutrophil count $<0.5 \times 10^9$, platelets $< 25 \times 10^9$ and hemoglobin < 6.5 G/dL (applicant's table 10-12). The percentage of patients with $>25\%$ decrease in hemoglobin is also similar for the groups.

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There was a slightly increased incidence of grade 3, but not grade 4, post-baseline hemoglobin (<8 g/dL) for the zoledronate 4 mg group compared with 8/4 mg and placebo. These percentages were 3.6%, 2.2%, and 1.4% respectively.

Serum chemistry

The tests performed include sodium, potassium, SGOT, SGPT, alkaline phosphatase, LDH, creatinine, BUN, calcium, phosphorus and magnesium. When patients were analyzed for notable biochemistry values (other than creatinine), there were no major differences between the zoledronate 4 mg and placebo groups. The incidence of phosphorus < 1.5 mg/dL was 2.7% for zoledronate 4 mg and 0.9% for placebo (applicant table 10-15). Grade 3 and 4 abnormalities are shown in table 10-17 and reveal little difference between zoledronate groups and control for chemistry abnormalities post baseline, except for more hypophosphatemia with zoledronate. Phosphorus <2 (grade 3 hypophosphatemia) was present 8.9%, 12.0% and 1.4%, respectively for zoledronate 4 mg, 8/4 mg and placebo. Grade 3 hypokalemia was slightly higher (4.9%) in the zoledronate 4 mg group compared with placebo (3.2%).

Serum creatinine and renal function deterioration

Baseline serum creatinine was considered normal if <1.4 mg/dL and abnormal if ≥ 1.4 mg/dL. Renal function deterioration was defined as any of the following:

- Normal baseline with change from baseline ≥ 0.5 mg/dL
- Abnormal baseline with change from baseline ≥ 1.0 mg/dL
- Post-baseline value ≥ 2 time the baseline value.

Applicant table 10-14 shows the incidence of post-baseline notable serum creatinine. Subsequent to amendment 3 (15 minute infusion), 2 patients (1.2%) in the zoledronate 4 mg group developed creatinine ≥ 4.5 , 2 patients in the 8/4 mg group, and 0 in the placebo group. Excluding these patients, the incidence of creatinine increase ≥ 0.5 was 10.3% for zoledronate 4 mg, 11.6% for zoledronate 8/4 mg and 7.4 % for placebo. This represents an improvement for the zoledronate groups, compared with pre 15-minute infusion amendment.

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Applicant table 10-14

Table 10-14. Frequency distribution for post-baseline notable serum creatinine by criteria and treatment group for pre 15-minute infusion amendment patients and post 15-minute infusion amendment patients (Safety evaluable patients)

	Zol 4 mg N (%)	Zol 8/4 mg N (%)	Placebo N (%)
Pre 15-minute infusion amendment patients			
Total no. of patients*	61	55	54
In-range	51 (83.6)	46 (83.6)	51 (94.4)
>= 4.5 mg/dL**	0 (0.0)	0 (0.0)	0 (0.0)
Increase from baseline >= 0.5 mg/dL**	11 (16.4)	7 (12.7)	3 (5.6)
Both**	0 (0.0)	2 (3.6)	0 (0.0)
Post 15-minute infusion amendment patients			
Total no. of patients*	165	181	163
In-range	146 (88.5)	158 (87.3)	151 (92.6)
>= 4.5 mg/dL**	0 (0.0)	0 (0.0)	0 (0.0)
Increase from baseline >= 0.5 mg/dL**	17 (10.3)	21 (11.6)	12 (7.4)
Both**	2 (1.2)	2 (1.1)	0 (0.0)

*Number patients who had a baseline value and at least one post-baseline value of serum creatinine

** Categories are mutually exclusive

Source: Post-text table 10.3-2A, 10.3-2B.

Applicant table 10-16 shows the distribution of grade 3 or 4 creatinine elevations.

Applicant table 10-16

Table 10-16. Frequency distribution for post-baseline grade 3 or 4 serum creatinine by treatment group for pre 15-minute infusion amendment patients and post 15-minute infusion amendment patients (Safety evaluable patients)

	Zol 4 mg N (%)	Zol 8/4 mg N (%)	Placebo N (%)
Pre 15-minute infusion amendment patients			
Total no. of patients	61	55	54
Grade 3 (> 3 x ULN)	0 (0.0)	1 (1.8)	0 (0.0)
Grade 4 (> 6 x ULN)	0 (0.0)	1 (1.8)	0 (0.0)
Post 15-minute infusion amendment patients			
Total no. of patients	165	181	163
Grade 3 (> 3 x ULN)	1 (0.6)	2 (1.1)	2 (1.2)
Grade 4 (> 6 x ULN)	2 (1.2)	0 (0.0)	0 (0.0)

* Number of patients who had a baseline value and at least one post-baseline value of serum creatinine

Patients in grade 3 and grade 4 are exclusive.

ULN: Upper limit of normal value

Source: Post-text table 10.3-3A and 10.3-3B.

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For the post amendment patients, the incidence of grade 3 and 4 creatinine elevations was similar across the 3 treatment groups, representing an increase in incidence for zoledronate 4 mg and placebo groups compared with pre amendment.

The incidence of renal function deterioration was increased in the zoledronate treatment groups for patients with normal baseline creatinine and creatinine ≥ 1.4 compared with placebo pre and post amendment.

Reviewer comment: There were too few patients with abnormal creatinine in the pre amendment group to make quantitative comparisons with the post amendment group. In the 5-minute infusion group, 3 of 6 patients with abnormal baseline serum creatinine experienced renal function deterioration after zoledronate 4 mg, compared with 2 of 8 in the 8/4 mg group and 0 of 4 in the placebo group. The following table is abstracted from applicant's table 10-19, demonstrating renal deterioration in the patients randomized following amendment 3.

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Table 69: Patients who experienced renal function deterioration by baseline serum creatinine (15- minute infusion)

	Zol 4 mg N (%)	Zol 8/4 mg N (%)	Placebo N (%)
Patients with normal baseline creatinine	154	160	143
---with deterioration	17 (11.0%)	19 (11.9%)	10 (7.0%)
Patients with abnormal baseline creatinine	11	21	20
---with deterioration	1 (9.1%)	2 (9.5%)	1 (5.0%)
TOTAL # patients at baseline	165	181	163
---with deterioration	18 (10.9%)	21 (11.6%)	11 (6.7%)

When time to renal function deterioration was analyzed by Cox regression for patients treated post amendment 3, there was no statistically significant difference between zoledronate and placebo groups. The risk ratio was 1.571 between zoledronate 4 mg and placebo, indicating a higher risk of renal function deterioration for zoledronate 4 mg compared with placebo. However, the p-value was not statistically significant.

Applicant's figure 10-2 is the Kaplan-Meier curve for time to first renal function deterioration by treatment group for patients randomized after the 15-minute infusion amendment.

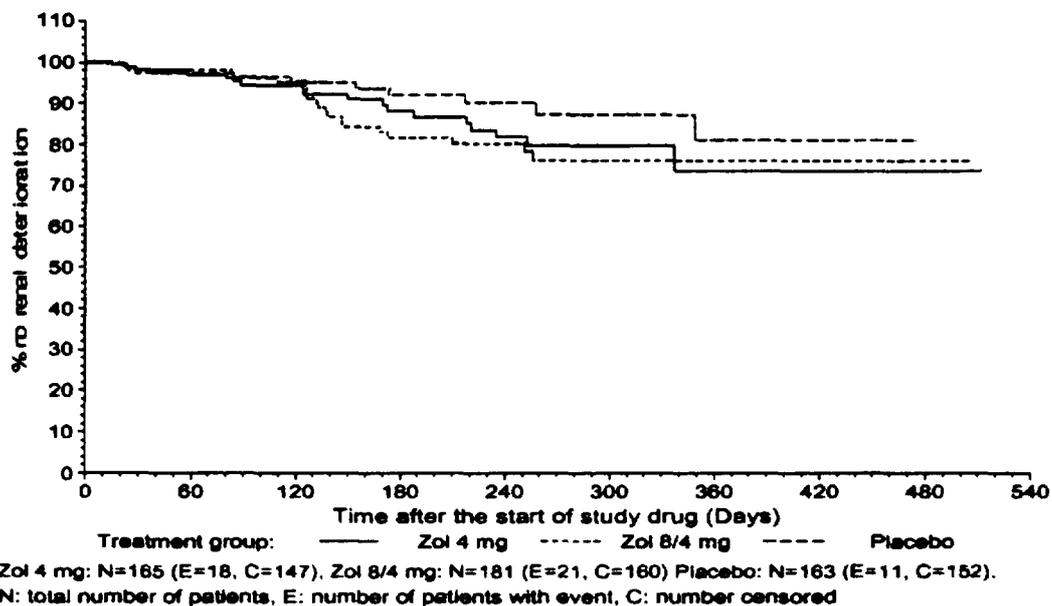
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Applicant figure 10-2

Figure 10-2. Kaplan-Meier curve for time to the first renal function deterioration by treatment group for the post 15-minute infusion amendment patients (Safety evaluable patients)



Urinalysis

The percentage of patients with elevated urine protein (≥ 2) post-baseline was similar in all groups (6-8%). Post-text table 10.3-2.

Vital signs

Systolic and diastolic blood pressure

The incidence of patients with notably high or low systolic or diastolic blood pressures is similar in all groups.

Weight

The incidence of patients with $\geq 10\%$ change in weight was similar for zoledronate 4 mg and placebo groups.

ECGs

“The proportion of evaluated patients who had an abnormality was similar at baseline and end of study, but most patients were not evaluated at the end of the study.”

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Special safety topics

The zoledronate 4 mg treatment group had the longest median time to death (203 days), compared to the 8/4 mg (189 days) and placebo (183) groups. This date is from post-text table 10.2-7.

Reviewer comment and conclusions

Increased risk of renal function deterioration is the only significant safety issue for zoledronate in this and related clinical trials of long-term treatment for patients with metastatic malignancy to bone. This toxicity was dose and time-related.

Of the more common adverse events, nausea, vomiting, and dyspnea were higher in the zoledronate 4 mg group than in the placebo group. There was no clear dose relationship. The overall incidence of grade 3 and 4 adverse events, regardless of cause, is similar for all the treatment groups. The most frequent SAEs, regardless of study drug relationship, were anemia, dehydration, malignant neoplasm aggravated and dyspnea. Anemia occurred in 7.9% of the zoledronate 4 mg group and in 3.6% of the placebo group. Dyspnea was present in 10.2% and 7.7%, respectively.

Hypophosphatemia was more common with zoledronate than placebo. The incidence of grade 3 hypophosphatemia was 8.9%, 12.0% and 1.4%, respectively for zoledronate 4 mg, 8/4 mg and placebo. Grade 3 hypokalemia was slightly higher (4.9%) in the zoledronate 4 mg group compared with placebo (3.2%).

Subsequent to the occurrence of acute renal failure in 3 patients receiving zoledronate 8 mg in related trials for disease metastatic to bone, several amendments were made to the protocol and a renal advisory board (RAB) of nephrologists was convened. Prolonging the infusion time from 5 to 15 minutes (amendment 3), decreased the incidence of renal function deterioration. Amendment 5 further improved the safety profile by eliminating the 8 mg dose. The safety of the 4 mg dose was improved by requiring assessment of serum creatinine before each dose. Zoledronate was held for renal deterioration, as defined in the amended protocol, and therapy was not reinstated until creatinine returned to within 10% of the baseline value.

Following amendment 3, the overall incidence of renal related AEs was comparable for zoledronate 4 mg (11.8%) and placebo (12.5%). However, the incidence of "blood creatinine increased" was 2.7% for zoledronate 4mg and 0.5 for placebo. "Renal failure acute" was 2.2% and 0.5%, respectively.

The incidence of renal function deterioration was increased in the zoledronate treatment groups for patients with normal baseline creatinine and creatinine ≥ 1.4 compared with placebo pre and post amendment. For patients randomized following amendment 3, the overall incidence of renal deterioration was 10.9% for zoledronate 4 mg, 11.6% for 4/8 mg and 6.7% for placebo. (From applicant table 10-19)

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When time to renal function deterioration was analyzed by Cox regression for patients treated post amendment 3, there was no statistically significant difference between zoledronate and placebo groups. The risk ratio was 1.571 between zoledronate 4 mg and placebo, indicating a higher risk of renal function deterioration for zoledronate 4 mg compared with placebo. However, the *p-value* was not statistically significant.

Reviewer Conclusion: Zoledronate 4 mg i.v. over 15 minutes every 3 weeks has an acceptable risk profile. The risk of renal deterioration with zoledronate is greater than placebo, but acceptable with clinical monitoring of renal function before each dose. Risk of renal toxicity increases with cumulative time under therapy. Caution is indicated for patients with elevated baseline creatinine, particularly since the study population excluded patients with creatinine > 3.0 and the drug is excreted by the kidneys.

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16 Appendix 3 Review of Zoledronate Safety in Breast Cancer and Myeloma, Study 010

Study # ZOL42446-03-010: "A randomized, double-blind, multi-center, comparative trial of i.v. zoledronic acid (4 mg or 8 mg) versus i.v. Aredia (90 mg), as an adjunct to standard therapies, in the treatment of multiple myeloma and breast cancer patients with cancer-related bone lesions."

This is a multi-center, international study (248 centers in 20 countries). The first patient was enrolled 16 October 1998 and the last patient completed therapy 12 January 2001. The study duration was 13 months (12 months treatment, 1 month observation), with an optional 12 month extension period.

The study population consisted of adults with Stage III multiple myeloma or stage IV breast cancer. Patients were to be receiving anti-cancer therapy at the time of randomization. Breast cancer patients could be receiving chemotherapy and/or first or second line hormonal therapy. Myeloma patients were required to have at least one osteolytic bone lesion on conventional (plain film) radiograph. Breast cancer patients were required to have a lytic, sclerotic or mixed lesion on plain film. Patients were to be performance status ≤ 2 .

Exclusions included serum creatinine > 3 , bilirubin > 2.5 , and corrected serum calcium < 8 mg/dL or ≥ 12 mg/dL.

Patients were stratified according to the diagnosis of multiple myeloma or breast cancer on chemotherapy or breast cancer on hormonal therapy.

Patients were randomized to receive zoledronate 4 mg or 8 mg or Aredia 90 mg i.v. every 3 or 4 weeks for 12 months. Initially, zoledronate was to be infused over 5 minutes. Aredia was infused over 2 hours. Patients were not taken off study for progressive disease.

From December 1998 to May 1999 there were 3 renal failure SAEs in patients receiving zoledronate 8mg, manifested by progressively rising serum creatinine. This occurred in 1 patient each of a Phase II myeloma study (cycle #11), protocol 010 (diagnosis breast cancer, cycle #1), and protocol 039 (prostate cancer, after cycle #7). The patients were, respectively, ages 75, 80, and 71, with baseline creatinines of 1.6, 1.9, and 1.4. These events led to Amendment 2 on 25 June 1999 and Amendment 5 on 7 June 2000 and the formation of a Renal Advisory Board (RAB) in November 1999.

After amendment 2, the infusion duration was prolonged to 15 minutes for zoledronate. After amendment 5, all zoledronate patients received 4 mg per dose. Serum creatinine was to be evaluated before each dose, and treatment held for deterioration of creatinine, as defined in the amendment, until the level was within 10% of the baseline creatinine.

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Applicant assessment and analysis of safety

Adverse events, serious adverse events, laboratory studies, and survival data were the main safety variables. Physical examination, assessment for adverse events and laboratory studies were done at baseline and then every 3-4 weeks, and at the end of study. Chemistries were repeated every 3-4 weeks. Hematology and urine chemistries and urinalyses were repeated at 3-4 weeks, then at month 3, then every 3 months. Serum creatinine was measured prior to each dose of study drug following amendment 5, so that treatment could be held for renal deterioration. The time to discontinuation of study and duration of survival were assessed.

Safety analysis was based on the type and frequency of adverse events and laboratory values outside of pre-determined ranges. The data were tabulated. Data were cut at the end of the study drug period for laboratory and adverse event analysis. This was the later of the end of the core study phase or the last date of study medication plus 28 days. All data was included up to the date of the data base lock for time to death and renal deterioration. The last visit date was used for other safety parameters.

The effect on renal function was analyzed according to the number of patients who experienced renal adverse events using selected terms suggested by the renal advisory board (RAB) and the number of patients who met pre-defined criteria of renal deterioration. Kaplan-Meier curves were used to describe the time course of renal function deterioration.

Study population

There were 1648 patients randomized to the following treatment groups:

Zoledronate 4 mg	#564
Zoledronate 8/4 mg	#526
Aredia 90 mg	#558

Five patients were not included in the safety analysis because they did not receive study drug. The safety population includes all patents that were randomized and received study drug. "There were 9, 9, and 10 patients who were randomized to the incorrect stratum" for zoledronate 4 mg, 8/4 mg, and Aredia, respectively. They were re-assigned for safety analysis.

A similar % of patients did not complete the study for all treatment groups: 37.3% for zoledronate 4 mg, 40.3% for 8/4 mg and 39.2% for Aredia 90 mg. Discontinuation was most frequently due to adverse events and death. The % of discontinuation for death in each group was 10.8%, 10.7% and 11.5%, respectively.

The number of patients in each arm is shown in applicant's table 7-2.

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Applicant table 7-2

Table 7-2. Number (%) of patients in analysis populations by treatment group (All randomized patients)

	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg
Populations			
ITT population	561 (99.5%)	524 (99.6%)	555 (99.5%)
Per Protocol population	453 (80.3%)	435 (82.7%)	448 (79.9%)
Safety evaluable population	563 (99.8%)	524 (99.6%)	556 (99.6%)

Source: Post-text tables 7.1-1 and 7.1-2. Post-text listing 7.1-2.

Reviewer Note: Analysis of data provided by the applicant demonstrates that for patients assigned to the 8/4 mg group, 1394 of 7072 zoledronate doses delivered were actually 4 mg rather than 8 mg doses, or approximately 20% were 4 mg doses.

The following table is an abbreviated, composite version of applicant's table 7-3 and 7-4, to illustrate baseline age and serum creatinine. These are some of the patient factors that might affect susceptibility to the renal toxic effects of treatment.

Table 70: Baseline patient age and serum creatinine by treatment group

	Zol 4 mg	Zol 8/4 mg	Aredia 90 mg
Age (years)			
n	563	524	556
mean ± SD	59.7 ± 12.00	58.9 ± 12.33	58.8 ± 12.65
median	60.0	59.0	58.5
Age - n (%)			
≤ 60	301 (53.5)	290 (55.3)	307 (55.2)
> 60	262 (46.5)	234 (44.7)	249 (44.8)
Baseline serum creatinine			
Normal (<1.4 mg/dL)	147 (79.0%)	127 (79.4%)	145 (86.8%)
Abnormal (≥1.4 mg/dL)	36 (19.4%)	32 (20.0%)	22 (13.2%)
Missing	3 (1.6%)	1 (0.6%)	0 (0.0%)

This data shows similar age for treatment groups whether viewed as median age or % older than 60 years of age. The baseline serum creatinine values are similar for the zoledronate groups, but less favorable compared with the Aredia patients, of whom only 13.2% had abnormal creatinine ≥ 1.4.

Reviewer comment: The treatment related factors that might predict for renal toxicity include dose, duration of infusion, exposure over time (# of months of treatment), and concomitant exposure to renal toxic drugs.

Overall exposure

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The duration of exposure to study drug was similar for the treatment groups. The mean duration of exposure for the multiple myeloma patients and hormonal breast cancer patients was 10 months. The mean for chemotherapy breast cancer patients was 9 months. For the overall group, the mean was approximately 10 months and the median exposure approximately 12 months for each of the 3 treatment groups. (This information is found in applicant's table 8-1).

Concomitant medication

Most patients received antineoplastic therapy during the study. The most common chemotherapy drugs were cyclophosphamide and doxorubicin. Post-text table 8.2-2 and 8.2-3 show # of patients who received antineoplastic therapy prior to and after the start of the study respectively. The incidence of prior therapy with cisplatin was 2%, 1.0% and 0.9% for zoledronate 4, 8/4 and Aredia. The incidence of therapy with cisplatin after the start of the study was 2.0%, 1.0%, and 0.7%, respectively.

Overall incidence and severity of adverse events:

Clinical study reports used the IMN dictionary to code adverse events (AEs). The data is summarized in the study report using MedDRA preferred terms. Adverse events were mapped from the IMN preferred terms to the corresponding MedDRA terms. The number of patients with AEs is provided by body system, preferred term, and treatment group. If a patient had more than one type of event within a body system, the patient was counted only once.

Most patients experienced at least one adverse event.

Applicant table 10-1 shows the % patients with adverse events overall and by system for events occurring $\geq 15\%$ in any group.

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Applicant table 10-1

Table 10-1. Number (%) of patients with AEs overall and by system organ class (≥ 15% for any group) (Safety evaluable patients)

	Zol4 mg n (%)	Zol8/4 mg n (%)	Aredia 90 mg n (%)
Patients studied			
Total no. of patients	563	524	556
Total no. with AEs	556 (98.8)	521 (99.4)	547(98.4)
System organ class affected			
General disorders and administration site conditions	459 (81.5)	432 (82.4)	445 (80.0)
Gastrointestinal disorders	435 (77.3)	404 (77.1)	418 (75.2)
Musculoskeletal, connective tissue and bone disorders	434 (77.1)	408 (77.9)	420 (75.5)
Infections and infestations	349 (62.0)	312 (59.5)	327 (58.8)
Nervous system disorders	325 (57.7)	312 (59.5)	340 (61.2)
Respiratory, thoracic, mediastinal disorders	311 (55.2)	261 (49.8)	292 (52.5)
Skin, subcutaneous tissue disorders	265 (47.1)	231 (44.1)	250 (45.0)
Metabolism and nutrition disorders	240 (42.6)	245 (46.8)	209 (37.6)
Blood and lymphatic system disorders	236 (41.9)	231 (44.1)	226 (40.6)
Vascular disorders	170 (30.2)	153 (29.2)	186 (33.5)
Psychiatric disorders	164 (29.1)	156 (29.8)	173 (31.1)
Neoplasms benign and malignant	144 (25.6)	103 (19.7)	114 (20.5)
Investigations	135 (24.0)	124 (23.7)	114 (20.5)
Renal and urinary disorders*	106 (18.8)	106 (20.2)	102 (18.3)
Eye disorders	92 (16.3)	100 (19.1)	105 (18.9)
Cardiac disorders	88 (15.6)	82 (15.6)	86 (15.5)
Injury and poisoning	80 (14.2)	82 (15.6)	82 (14.7)

Body systems are sorted in descending frequency, as reported in the Zol 4 mg treatment group

* The number of patients and percent of renal and urinary disorders includes all patients, regardless whether the patient was randomized before or after the date of 15-minute infusion Amendment.

Source: Post-text table 10.1-1.

There is no major imbalance in AEs by system, although the incidence of “metabolism and nutrition disorders” and “neoplasms benign and malignant” is slightly higher for zoledronate 4 than Aredia. The incidence of renal AEs is similar for these treatment groups, including for patients treated with 5 minute and 15 minute infusion.

The most frequent adverse events were bone pain, nausea, fatigue, pyrexia, and vomiting. Of these, only pyrexia was present more frequently in the zoledronate 4 mg and 8/4 mg groups than in the Aredia group. There was a slight increase in the zoledronate 4 mg group compared with the Aredia group of cough, arthralgia, weakness and anorexia. This information is summarized in applicant table 10-2.

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Applicant table 10-2

**Table 10-2. Number (%) of patients with most frequent AEs ($\geq 15\%$ for any group)
(Safety evaluable patients)**

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Aredia 90 mg n (%)
Patients studied			
Total no. of patients	563	524	556
Total no. with an AE	556 (98.8)	521 (99.4)	547 (98.4)
Bone pain	312 (55.4)	276 (52.7)	303 (54.5)
Nausea	250 (44.4)	240 (45.8)	245 (44.1)
Fatigue	217 (38.5)	192 (36.6)	212 (38.1)
Pyrexia	200 (35.5)	180 (34.4)	160 (28.8)
Vomiting NOS	166 (29.5)	158 (30.2)	164 (29.5)
Anemia NOS	153 (27.2)	155 (29.6)	155 (27.9)
Myalgia	144 (25.6)	119 (22.7)	130 (23.4)
Diarrhea NOS	141 (25.0)	138 (26.3)	139 (25.0)
Dyspnea NOS	138 (24.5)	110 (21.0)	134 (24.1)
Cough	135 (24.0)	101 (19.3)	114 (20.5)
Constipation	134 (23.8)	130 (24.8)	132 (23.7)
Arthralgia	125 (22.2)	98 (18.7)	95 (17.1)
Weakness	113 (20.1)	93 (17.7)	91 (16.4)
Headache NOS	106 (18.8)	113 (21.6)	131 (23.6)
Anorexia	105 (18.7)	83 (15.8)	70 (12.6)
Edema lower limb	92 (16.3)	83 (15.8)	108 (19.4)
Alopecia	89 (15.8)	73 (13.9)	72 (12.9)
Neutropenia	84 (14.9)	80 (15.3)	77 (13.8)
Insomnia NEC	80 (14.2)	78 (14.9)	94 (16.9)
Back pain	60 (10.7)	82 (15.6)	72 (12.9)

Source: Post-text table 10.1-2

The overall incidence of grade 3 and 4 AEs was similar for the treatment groups. Post-text table 10.1-4 was reviewed.

Renal adverse events

A Renal Advisory Board (RAB) was established in November 1999 to monitor the renal safety of zoledronate, due to concerns about renal toxicity when a total of 3 patients in this and other studies developed renal failure following treatment with zoledronate 8 mg. Renal adverse events with preferred terms specified by the RAB are presented in applicant table 10-3 for patients randomized prior to the 15-minute infusion amendment and table 10-4 for patients randomized following the amendment. The overall incidence of renal adverse events is similar for zoledronate 4 mg and Aredia 90 mg both pre and post amendment. The incidence for zoledronate 8/4 mg is approximately 30% higher than the other treatment groups for the 5-minute and 15-minute infusions. For the post amendment patients, the incidence of "blood creatinine increased" is 2.8% for zoledronate 4 mg, 4.3% for zoledronate 8/4 mg and 1.8% for

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Aredia 90 mg. The incidence of "renal impairment NOS is identical for the zoledronate 4 mg and Aredia groups, as it for renal failure acute. The incidence for both events is higher for zoledronate 8/4 mg. The incidence of 4.7% "renal failure acute" is significantly higher for the 8/4 mg dose zoledronate, than for the lower dose zoledronate or Aredia, which are both 0.7%.

Applicant table 10.4

Table 10.4. Renal related adverse events by preferred term and treatment group for post 15-minute infusion Amendment patients (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Aredia 90 mg n (%)
Total no. of patients	281	276	273
Total no. of patients with a renal related adverse event	34 (12.1)	48 (17.4)	35 (12.8)
Blood creatinine increased	8 (2.8)	12 (4.3)	5 (1.8)
Urinary frequency	7 (2.5)	5 (1.8)	3 (1.1)
Renal impairment NOS	5 (1.8)	9 (3.3)	5 (1.8)
Haematuria	3 (1.1)	6 (2.2)	6 (2.2)
Nephritis NOS	3 (1.1)	0 (0.0)	1 (0.4)
Urinary retention	3 (1.1)	5 (1.8)	2 (0.7)
Calculus renal NOS	2 (0.7)	1 (0.4)	1 (0.4)
Renal failure acute	2 (0.7)	13 (4.7)	2 (0.7)
Urinary tract disorder NOS	2 (0.7)	0 (0.0)	3 (1.1)
Haematuria present	1 (0.4)	1 (0.4)	0 (0.0)
Oliguria	1 (0.4)	3 (1.1)	1 (0.4)
Proteinuria present	1 (0.4)	0 (0.0)	0 (0.0)
Renal failure NOS	1 (0.4)	1 (0.4)	2 (0.7)
Renal failure chronic	1 (0.4)	1 (0.4)	0 (0.0)
Hydronephrosis	0 (0.0)	3 (1.1)	0 (0.0)
Hyperuricaemia	0 (0.0)	1 (0.4)	5 (1.8)
Micturition urgency	0 (0.0)	0 (0.0)	3 (1.1)
Nephrotic syndrome	0 (0.0)	0 (0.0)	0 (0.0)
Obstructive uropathy	0 (0.0)	0 (0.0)	1 (0.4)
Pyelonephritis NOS	0 (0.0)	0 (0.0)	1 (0.4)
Renal disorder NOS	0 (0.0)	0 (0.0)	0 (0.0)
Renal tubular acidosis	0 (0.0)	1 (0.4)	0 (0.0)
Renal vascular disorder NOS	0 (0.0)	0 (0.0)	1 (0.4)
Urethral disorder NOS	0 (0.0)	1 (0.4)	0 (0.0)
Urethral obstruction	0 (0.0)	0 (0.0)	0 (0.0)

Source: Post-text table 10.1-7B.

The sponsor selected and reviewed adverse events previously reported with bisphosphonates. These are reported in table 10-5. The incidence of arthralgias and fever was higher for zoledronate 4 mg than Aredia, but the incidence for zoledronate 8/4 mg was intermediate, suggesting that there is no causal relationship for these events. The incidence of electrolyte AEs

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was higher for both zoledronate groups (15.3% and 19.1%), possibly in a dose-dependant way, compared with Aredia (11.9%)

Applicant table 10-5

Table 10-5. Number of patients experiencing adverse events previously reported with bisphosphonate therapy by treatment (Safety evaluable patients)

	Zol 4 mg N=563	Zol 8/4 mg N=524	Aredia 90 mg N=556
Preferred grouping	n (%)	n (%)	n (%)
Any body system	499 (88.6)	446 (85.1)	475 (85.4)
Arthralgia/Myalgias	262 (46.5)	223 (42.6)	228 (41.0)
Cytopenias	230 (40.9)	220 (42.0)	228 (41.0)
Electrolytes	86 (15.3)	100 (19.1)	66 (11.9)
Eye abnormalities	94 (16.7)	95 (18.1)	110 (19.8)
Fever	203 (36.1)	180 (34.4)	162 (29.1)
Infections	354 (62.9)	318 (60.7)	332 (59.7)
Injection site reactions	42 (7.5)	36 (6.9)	50 (9.0)

Source: Post-text table 10.1-8.

Events believed to be chemotherapy-associated were not increased in incidence for zoledronate patients compared with those that received Aredia.

Deaths, SAEs and other significant adverse events

In Section 3.5.3 of the protocol, a serious adverse event (SAE) is defined as an untoward event which:

1. Is fatal or life-threatening,
2. Required or prolonged hospitalization,
3. Was significantly or permanently disabling or incapacitating,
4. Constitutes a congenital anomaly or a birth defect,
5. May jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Applicant table 10-7 lists patients who died, had other SAE or "clinically significant AEs" or discontinued because of them. Deaths are included if they occurred up to the end of the core study phase or within 28 day following the last treatment.

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Applicant table 10-7

Table 10-7. Number (%) of patients who died, had other serious or other clinically significant AEs or discontinued because of them (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Aredia 90 mg n (%)
Patients studied			
Total no. of patients	563 (100.0)	524 (100.0)	556 (100.0)
Serious or significant events			
Death	76 (13.5)	70 (13.4)	71 (12.8)
SAEs	275 (48.8)	253 (48.3)	277 (49.8)
Other significant AEs	454 (80.6)	428 (81.7)	438 (78.8)
Discont. due to SAEs	33 (5.9)	35 (6.7)	31 (5.6)
Discont. due to clin sig AEs *	24 (4.3)	29 (5.5)	18 (3.2)

* excluding discontinuations due to SAEs

deaths are counted from study phase completion CRF or within 28 days of study drug discontinuation.

Source: Post-text table 10.2-5

There were 217 deaths during the core study phase or within 28 days of last study medication. The percentage of deaths in each treatment arm was similar. The most frequent cause was progression of cancer. There were no deaths due to renal causes in the zoledronate 4 mg or Aredia 90 groups. There were 4 such deaths in zoledronate 8/4 mg.

SAEs occurred in a similar proportion of patients in each treatment group (from post-text table 10.2-1, 48.8%, 48.3% and 49.8%). The most frequent SAE was infection for all groups. The incidence of "renal and urinary" SAEs was 2.8% for zoledronate 4 mg, 5.7% for 8/4 mg and 2.9% for Aredia. The incidence for "renal failure acute" was 0.5%, 3.4% and 1.4%, respectively. The incidence for which "renal and urinary" SAEs were suspected to be treatment related were 0.5%, 1.9% and 0.2%, respectively.

The study report provides specific information about 27 SAEs that were not included in the database at the time of the lock, but the SAEs were not felt to be study drug related. Of these, one breast cancer patient was treated with Aredia and had unexplained sudden death. One additional breast patient (zoledronate 4 mg) had azotemia and hypercalcemia at study day 400, for which she was hospitalized. A myeloma patient (zoledronate 8/4 mg) had "renal impairment NOS" at study day 80.

In this study, skeletal related events (SRE) were reported as SAEs. The percentage was 5.0%, 3.8%, and 7.7%, respectively for zoledronate 4 and 8/4 mg and for Aredia.

The incidence of patients discontinuing therapy for adverse events was 10.1% for zoledronate 4 mg, 12.2% for 8/4 mg, and 8.8% for Aredia. Discontinuations for "renal and urinary disorders" was 0.5% for zoledronate 4 mg and Aredia 90 mg. It was 2.5% for zoledronate 8/4 mg.

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Laboratory parameters

Hematology

The treatment groups were similar when hematology tests were analyzed by number of patients reaching selected "notable" values of neutrophil count $< 0.5 \times 10^9$, platelets $< 25 \times 10^9$, and hemoglobin < 6.5 gm/dL. However, a greater percentage of patients in the zoledronate 4 mg (10.2%) and 8/4 mg (11.1%) had a decrease of $>25\%$ from baseline hemoglobin compared with the Aredia group (7.8%). The incidence of grade 3 and grade 4 hematologic toxicity is similar for the treatment groups.

Serum chemistry

The tests performed include sodium, potassium, SGOT, SGPT, alkaline phosphatase, LDH, creatinine, BUN, calcium, phosphorus and magnesium. When patients were analyzed for notable biochemistry values (other than creatinine), there were few differences between the treatment groups. There was a higher incidence of hypercalcemia > 12.0 mg/dL in the Aredia group (2.24%) than in the zoledronate 4 (0.37%) or 8/4 mg groups (0.60%). There was more hypokalemia < 3 mEq/L in the zoledronate 8/4 mg group (9.84%) and more hyperkalemia > 6 mEq/L (4.68%) in the zoledronate 4 mg group compared with the other 2 treatment groups. The incidence of grade 3 and grade 4 toxicity was similar for the treatment groups, except for excess grade 3 hypophosphatemia and grade 3 hypokalemia for zoledronate 8/4 mg. Zoledronate 4 mg patients had 3% grade 4 hyperkalemia, but only 0.8% for zoledronate 8/4 mg and 1.3% for Aredia. The following table shows notable chemistry abnormalities by treatment group.

Applicant table 10-15 (abbreviated)

Table 10-15. Number (%) of patients with an in-range baseline and a post-baseline notable abnormal biochemistry values by treatment group (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Aredia 90 mg n (%)
Total no. of patients *	543	503	536
Corrected calcium < 7.0 mg/dL	6 (1.10)	4 (0.80)	5 (0.93)
Corrected calcium > 12.0 mg/dL	2 (0.37)	3 (0.60)	12 (2.24)
Total no. of patients *	541	500	534
Magnesium < 0.9 mg/dL	1 (0.18)	1 (0.20)	1 (0.19)
Magnesium > 3.0 mg/dL	3 (0.55)	4 (0.80)	5 (0.94)
Total no. of patients *	536	498	525
Phosphorus < 1.5 mg/dL	10 (1.87)	16 (3.21)	7 (1.33)
Phosphorus > 5.5 mg/dL	21 (3.92)	10 (2.01)	28 (5.33)
Total no. of patients *	534	498	524
Potassium < 3.0 mEq/L	30 (5.62)	49 (9.84)	19 (3.63)
Potassium > 6 mEq/L	25 (4.68)	13 (2.61)	11 (2.10)

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Reviewer comment : *There were more electrolyte abnormalities for zoledronate 8/4 mg. However, comparing zoledronate 4 mg and Aredia, there are probably no significant differences. The lack of dose relationship for hyperkalemia in the zoledronate groups makes it unlikely to be a treatment-related occurrence.*

Serum creatinine and renal function deterioration

Baseline serum creatinine was considered normal if <1.4 mg/dL and abnormal if ≥ 1.4 mg/dL. Renal function deterioration was defined as any of the following:

- Normal baseline with change from baseline ≥ 0.5 mg/dL
- Abnormal baseline with change from baseline ≥ 1.0 mg/dL
- Post-baseline value ≥ 2 time the baseline value.

Applicant table 10-14 shows the incidence of post-baseline notable serum creatinine for patients randomized before and after the 15-minute infusion amendment. For post-amendment patients, 10.7%, 18.6% and 7.5% of zoledronate 4, 8/4 and Aredia patients, respectively, developed creatinine increase from baseline ≥ 0.5 . Patients in each group who developed creatinine ≥ 4.5 were 0 for zoledronate 4 mg, 1.1 % (3 patients) for 8/4 mg and 0.8% (2 patients) for Aredia.

Applicant table 10-14

Table 10-14. Frequency distribution for post-baseline notable serum creatinine by criteria and treatment group for pre 15-minute infusion Amendment patients and post 15-minute infusion Amendment patients (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Aredia 90 mg n (%)
Pre 15-minute infusion Amendment patients			
Total no. of patients *	272	240	270
In-range	229 (84.2)	187 (77.9)	249 (92.2)
≥ 4.5 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)
Increase from baseline ≥ 0.5 mg/dL	40 (14.7)	52 (21.7)	20 (7.4)
Both criteria	3 (1.1)	1 (0.4)	1 (0.4)
Post 15-minute infusion Amendment patients			
Total no. of patients *	272	263	268
In-range	243 (89.3)	211 (80.2)	246 (91.8)
≥ 4.5 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)
Increase from baseline ≥ 0.5 mg/dL	29 (10.7)	49 (18.6)	20 (7.5)
Both criteria	0 (0.0)	3 (1.1)	2 (0.8)

*Number patients who had a baseline value and at least one post-baseline value of serum creatinine.

Patients in each criteria are exclusive

Source: Post-text table 10.3-2A and Post-text table 10.3-2B.

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There was a decrease in the frequency of post-baseline notable serum creatinine for both zoledronate groups when the infusion time was prolonged from 5 minutes to 15 minutes. The incidence remains significantly elevated for zoledronate 8/4 mg compared with the two other treatment groups. The incidence of post-baseline notable serum creatinine elevation is 10.7% for zoledronate 4 mg and 8.3% for Aredia (7.5% + 0.8%). Applicant table 10-16 shows the distribution of post-baseline grade 3 or 4 creatinine by treatment group.

Applicant table 10-16

Table 10-16. Frequency distribution for post-baseline grade 3 or 4 serum creatinine by treatment group for pre 15-minute infusion Amendment patients and post 15-minute infusion Amendment patients (Safety evaluable patients)

	Zol 4 mg n (%)	Zol 8/4 mg n (%)	Aredia 90 mg n (%)
Pre 15-minute infusion Amendment patients			
Total no. of patients *	272	240	270
Grade 3 (> 3 x ULN)	6 (2.2)	1 (0.4)	2 (0.7)
Grade 4 (> 6 x ULN)	1 (0.4)	1 (0.4)	0 (0.0)
Post 15-minute infusion Amendment patients			
Total no. of patients *	272	263	268
Grade 3 (> 3 x ULN)	1 (0.4)	6 (2.3)	4 (1.5)
Grade 4 (> 6 x ULN)	0 (0.0)	1 (0.4)	1 (0.4)

* Number of patients with a baseline value and at least one post-baseline measurement

Patients in grade 3 and grade 4 are exclusive

ULN: Upper limit of normal value.

Source: Post-text table 10.3-3A and Post-text table 10.3-3B.

For the patients randomized post amendment, the incidence of grade 3 and 4 creatinine was least in the zoledronate 4 mg group. The incidence of grade 3 plus grade 4 creatinine is slightly higher for zoledronate 8/4 mg (2.7%) than Aredia (1.9%).

For the pre 15-minute infusion amendment patients, renal function deterioration was experienced by 13.2% of the zoledronate 4 mg patients, 20.4% of the zoledronate 8/4 mg patients, and by 6.7% of the Aredia patients. Extending the time of the infusion significantly decreased the incidence of creatinine deterioration for the zoledronate 4 mg patients. The following table is abstracted from applicant's table 10-19 and shows renal function deterioration by baseline creatinine for post 15-minute infusion amendment patients.

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Table 71: Patients who experienced renal function deterioration by baseline serum creatinine (15-minute infusion)

	Zol 4 mg N (%)	Zol 8/4 mg N (%)	Aredia 90 mg N (%)
Patients with normal baseline creatinine	246	242	246
---with deterioration	23 (9.3%)	43 (17.8%)	20 (8.1%)
Patients with abnormal baseline creatinine	26	21	22
---with deterioration	1 (3.8%)	6 (28.6%)	2 (9.1%)
TOTAL patients at baseline	272	263	268
---with deterioration	24 (8.8%)	49 (18.6%)	22 (8.2%)

Zoledronate 4 mg was comparable to Aredia 90 mg for the entire population and for patients with normal baseline creatinine. For the small number of patients with abnormal baseline creatinine, zoledronate 4 mg had a lower incidence of creatinine deterioration (3.8%) than Aredia 90 mg (9.1%). Zoledronate 8/4 mg was more renal toxic than either zoledronate 4 mg or Aredia 90 mg for patients with normal and abnormal baseline creatinine.

When time to renal function deterioration was analyzed by Cox regression for patients randomized after the 15-minute infusion amendment, there was no statistically significant difference between zoledronate 4 mg and Aredia 90 mg. The risk ratio was 0.984 between zoledronate 4 mg and Aredia 90 mg groups. However, there was a statistically significant difference in terms of time to renal function deterioration for each of zoledronate 4 mg and Aredia 90 mg compared with zoledronate 8/4 mg. The risk ratios were 2.372 and 2.379, respectively.

Applicant's figure 10-2 is the Kaplan-Meier curve for time to first renal function deterioration by treatment group for patients randomized after the 15-minute infusion amendment.

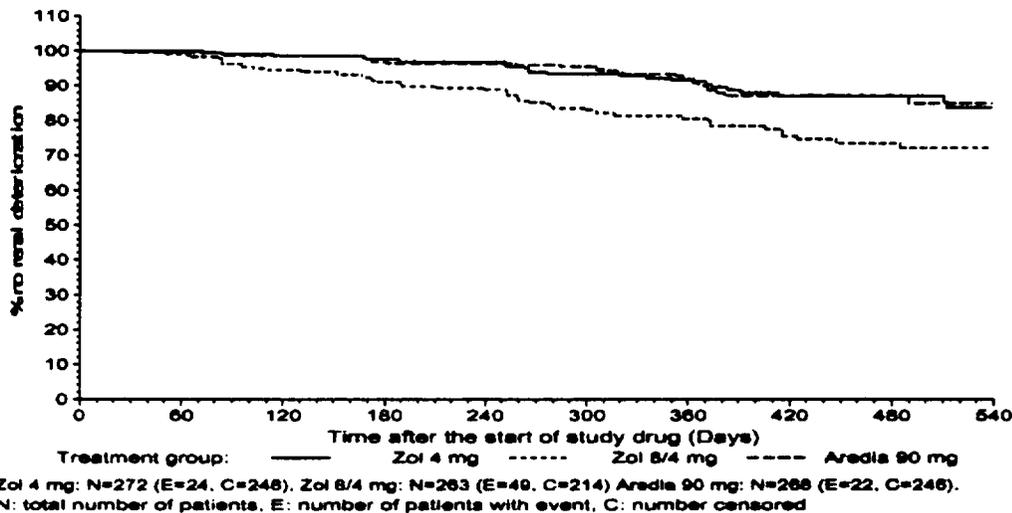
**APPEARS THIS WAY
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Applicant figure 10-2

Figure 10-2. Kaplan-Meier curve for time to the first renal function deterioration by treatment group for the post 15-minute infusion Amendment patients (Safety evaluable patients)



Urinalysis

The percentage of patients with elevated post-baseline urine protein was similar for zoledronate 4 mg and Aredia 90 mg.

Vital signs, other safety evaluations, special safety topics

Vital signs were not collected. There were no other clinically relevant findings.

Reviewer comment and conclusions

Increased risk of renal function deterioration is the only significant safety issue for zoledronate in this and related clinical trials of long-term treatment for patients with metastatic malignancy to bone. Toxicity was dose-related and exposure over time-related.

The more common adverse events were bone pain, nausea, fatigue, pyrexia, and vomiting. Pyrexia, cough, arthralgia, weakness and anorexia were slightly increased in the Zoledronate 4 mg group compared with the Aredia 90 mg group. The incidence of grade 3 and 4 AEs was similar.

More patients in the zoledronate 4 mg group had a decrease of > 25% from baseline hemoglobin compared with the Aredia patients, although there was no difference in notable hematology values or grade 3 and 4 hematologic toxicity.

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There were no major differences in blood chemistry abnormalities for zoledronate 4 mg, compared with Aredia.

Subsequent to the occurrence of acute renal failure in 3 patients receiving zoledronate 8 mg in trials for malignancy metastatic to bone, several amendments were made to the protocol, which improved safety. The infusion time of zoledronate was increased from 5 to 15 minutes (amendment 2), which decreased the incidence of renal function deterioration in the zoledronate groups. Amendment 5 further improved the safety profile by eliminating the 8 mg dose. The safety of the 4 mg dose was improved by requiring assessment of serum creatinine before each dose. Zoledronate was held for renal deterioration, as defined in the amended protocol, and therapy was not reinstated until creatinine returned to within 10% of the baseline value.

The overall incidence of renal adverse events was similar for zoledronate 4 mg and Aredia 90 mg both pre and post the amendment which prolonged the infusion time. The incidence of renal function deterioration with zoledronate 4 mg was higher than Aredia pre-amendment, but was similar (8.8% and 8.2%, respectively) when zoledronate was infused over 15 minutes. Zoledronate was comparable to Aredia for the entire population of patients and for patients with normal baseline creatinine. For the small number of patients with abnormal baseline creatinine, zoledronate 4 mg had a lower incidence of creatinine deterioration (3.8%) than Aredia 90 mg (9.1%). There was no statistically significant difference in time to first renal function deterioration for zoledronate 4 mg compared with Aredia 90 mg.

Reviewer conclusions: Zoledronate 4 mg i.v. over 15 minutes every 3-4 weeks has an acceptable risk profile that is comparable to Aredia. To minimize renal risk, zoledronate must be infused over 15 minutes and clinical monitoring of serum creatinine should be performed before each dose. Caution is indicated for patient with elevated serum creatinine, particularly since the study population excluded patients with creatinine > 3.0 and the drug is excreted unchanged by the kidneys.

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PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

v/BLA # 21-386

Supplement # 000 Circle one: SE1 SE2 SE3 SE4 SE5 **SE6**

Trade and generic names/dosage form: Zometa for injection Action: **AP** AE NA

Applicant Novartis Pharma Corp Therapeutic Class bisphosphonate

Indication(s) previously approved HCM

Pediatric information in labeling of approved indication(s) is adequate X inadequate

Proposed indication in this application Treatment of patients with multiple myeloma and documented bone metastases from solid tumors

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION. IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) X No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

 Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

- 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
- 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
- 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- X 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
- 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from MO see 2-13-02 Tcon Mtg Min #40, for ped. waiver
(e.g., medical review, medical officer, team leader)

Debra Vause, Regulatory Health Project Manager
Signature of Preparer and Title

February 14, 2002
Date

cc: **Orig NDA/BLA # 21-223 _____**
HF 540 _____ /Div File
NDA/BLA Action Package
HFD-960/ Peds Team
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

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