Cross-Discipline Team Leader Review Memo

Date	May 3, 2008
From	Theresa Kehoe, M.D. Clinical Team Leader, DMEP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supp #**	NDA 21-817 S-001
Proprietary / Established (USAN) names	Reclast (zoledronic acid)
Dosage forms / strength	5 mg for intravenous infusion once yearly
Proposed Indication(s)	Prevention of clinical fractures after hip fracture in men and women
Recommended	Approve, with agreed upon labeling changes

1. Introduction to Review

Novartis Pharmaceuticals, Inc. has submitted this supplemental new drug application for zoledronic acid (Reclast) 5 mg for infusion, seeking approval for the prevention of clinical fracture following hip fracture in men and women. The basis for approval is CZOL446L2310 (study 2310), a multinational, multicenter, double-blind, randomized, placebo-controlled, 3-year study evaluating the safety and efficacy of intravenous zoledronic acid in preventing subsequent osteoporotic fractures after hip fracture.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Zoledronic acid is currently approved in the United States as Zometa (4 mg for intravenous infusion) for treatment of hypercalcemia of malignancy, treatment of patients with multiple myeloma, and patients with documented bone metastases from solid tumors; and Reclast (5 mg for intravenous infusion) for treatment of Paget's disease of bone, and treatment of postmenopausal osteoporosis. [redacted]

Zoledronic acid is a bisphosphonate agent for intravenous use whose specificity for bone allows dosing once yearly for the treatment of osteoporosis. In addition to zoledronic acid, other currently approved and marketed bisphosphonate agents include etidronate (Didronel and generics - oral dosage form, intravenous product discontinued), pamidronate (Aredia and generics - intravenous administration), alendronate (Fosamax, Fosamax Plus D - oral administration), risedronate (Actonel, Actonel with Calcium (copackaged), oral administration), tiludronate (Skelid, oral administration), and ibandronate (Boniva, oral and intravenous administration).

Important safety signals associated with bisphosphonates include gastrointestinal adverse events, predominantly associated with orally administered bisphosphonates; acute phase reaction; hypocalcemia; inflammatory eye events; risk of renal insufficiency, primarily associated with intravenous bisphosphonates; osteonecrosis of the jaw; and musculoskeletal pain. An imbalance in the reporting of atrial fibrillations serious adverse events with zoledronic acid was noted in the postmenopausal osteoporosis trial 2301. These findings, combined with data from the alendronate fracture intervention trial raised concerns that bisphosphonate use may be associated with an increased risk of atrial fibrillation. Currently, the division is working with the Quantitative Safety and Pharmacoepidemiology (QASP) staff to further evaluate the atrial fibrillation safety signals in all bisphosphonate trials of at least one year duration.

3. CMC/Microbiology/Device

This NDA submission did not contain any CMC information.

4. Nonclinical Pharmacology/Toxicology

This NDA submission did not contain any nonclinical pharmacology / toxicology information.

5. Clinical Pharmacology/Biopharmaceutics

This NDA submission did not contain any new clinical pharmacology information.

6. Clinical Microbiology

No microbiology issues are relevant to this NDA.

7. Clinical/Statistical

7.1. Efficacy

7.1.1.1. Dose identification/selection and limitations

No new dose findings studies have been conducted in support of the proposed indication. The Sponsor is proposing a 5 mg once yearly dose of zoledronic acid, which is the dose currently approved for the treatment of postmenopausal osteoporosis.

7.1.1.2. Phase 3/ clinical studies essential to regulatory decision, including design, analytic features, and results

The pivotal trial supporting this application is study CZOL446L2310 (study 2310), a multinational, multicenter, double-blind, randomized, placebo-controlled, 3-year study evaluating the safety and efficacy of intravenous zoledronic acid in preventing subsequent clinical osteoporotic fractures after hip fracture. Subjects enrolled in the study were men and women age 50 years or older who suffered a low trauma hip fracture requiring surgical repair. Bone mineral density was not an inclusion criterion. Subjects were randomized 1:1 to receive either zoledronic acid 5 mg or placebo by intravenous infusion over 15 minutes every 12 months. All subjects received a loading dose of 75,000 – 125,000 units of vitamin D2 once or 50,000–75,000 units of vitamin D3 as well as a maintenance dose of 800–1200 IU of vitamin

D daily and elemental calcium (1000–1500 mg p.o. daily in a divided dose). Study drug was administered within 90 days of the surgery. Patients who were receiving the following osteoporosis therapy at randomization (calcitonin; SERMs [e.g., raloxifene]; hormone replacement therapy [HRT]; tibolone, DHEA[s]; and testosterone, in the case of hormone replacement therapy in hypogonadal men) could continue with these treatments during the trial

The primary efficacy endpoint is incidence of all clinical fractures, defined as all subsequent osteoporotic fractures, excluding fractures of the face, skull or digits. Radiographs for all fractures were obtained and adjudicated by the Clinical Endpoint Committee. Secondary efficacy endpoints include incidence of clinical vertebral fracture, hip fracture and non-vertebral clinical fracture; and change in total hip and femoral neck bone mineral density. As the primary efficacy endpoint of the study was event-driven, each patient was followed until at least 211 patients experienced at least one adjudicated clinical fracture or until the patient's Month 36 visit had occurred.

Disposition: A total of 2127 subjects were randomized and included in the ITT efficacy population. A total of 2111 subjects received at least one dose of study medication and were included in the safety population. The primary efficacy endpoint was event-driven. Overall, the mean duration of follow-up was 706 days for the zoledronic acid group and 711 days for the placebo group. As outlined in the table below, of the 611 (29%) subjects who withdrew from the study, 244 (12%) died, 46 (2%) withdrew due to adverse events, and 229 (11%) withdrew due to patient request. It is not clear why so many subjects withdrew consent.

Study 2310: Patient Disposition

	zole	**placebo**	**Total**
N, randomized	1065	1062	2127
Discontinued*	295 (27.7)	316 (29.8)	611 (28.7)
Death	102 (9.6)	142 (13.4)	244 (11.5)
Withdrew Consent	120 (11.3)	109 (10.3)	229 (10.8)
Lost to follow-up	35 (3.3)	28 (2.6)	63 (3.0)
Adverse Event**	25 (2.3)	21 (2.0)	46 (2.2)
All Other***	13 (1.2)	15 (1.4)	28 (1.3)
Unsatisfactory response	0 (0)	1 (0.09)	1 (0.05)
N, treated	1054 (98.8)	1057 (99.5)	2111 (99.2)
Completed	770 (72.3)	746 (70.3)	1516 (71.3)

*including deaths
**including abnormal laboratory values
***including administrative problems, protocol violations

Demographics: As outlined in the table below, baseline subject demographics were generally well balanced across the treatment groups. The study population is comprised of 24% men and 75% women. The average age of enrollees was 74 years, with a range of 50 to 98 years. Most subjects were Caucasian. Bone mineral density was not an enrollment criterion. Overall, approximately 46% of the enrolled population met the BMD criteria for osteoporosis. However, all subjects met the diagnostic criteria for osteoporosis based on having sustained a low trauma hip fracture.

Study 2310: Patient Demographics			
	zole	**placebo**	**Total**
N, randomized	1065	1062	2127
Age (yrs, mean ± SD)	74 ± 9.5	75 ± 9.9	74 ± 9.7
Age range	50 - 95	50 - 98	50 - 98
Sex, n (%)			
Male	248 (23)	260 (24)	508 (24)
Female	817 (77)	802 (76)	1619 (76)
Race, n (%)			
White	973 (91)	965 (91)	1938 (91)
Asian	2 (0.2)	1 (0.1)	3 (0.1)
Black	6 (0.6)	12 (1)	18 (0.8)
Hispanic	70 (7)	70 (7)	140 (7)
Other	14 (1)	14 (1)	28 (1)
Weight (kg, mean ± SD)	65 ± 13.7	66 ± 14.0	65 ± 13.8
Height (cm, mean ± SD)	162 ± 9.7	162 ± 10.0	162 ± 9.8
Femoral neck BMD, n	934	933	1867
FN BMD (gm/cm^2)	0.653	0.646	0.649
FN BMD T score (mean)	-2.36	-2.42	-2.39
FN BMD T score range	-5.0 , 10.8	-5.7 , 3.4	-5.7 , 10.8
> -1.5, n (%)	123 (12)	121 (11)	244 (12)
-2.4 to -1.5, n (%)	360 (34)	375 (35)	735 (35)
≤ -2.5, n (%)	451 (42)	437 (41)	888 (42)
Missing	131 (12)	129 (12)	260 (12)

Data Reliability Issues: During monitoring visits and data review, the Sponsor identified data irregularities for DXA scans at site 0829. Specifically, follow-up bone mineral density scans were noted to be duplicates of patients' baseline scans. The duplicated scans were all photocopied records - either a baseline scan with a new hand written date entered, or data cut and pasted together with new header information. The problem was further isolated to a single DXA technician, whose employment was terminated. Irregularities were noted in ten patients. A total of 95 patients (48 patients in the zoledronic acid group and 47 in the placebo group) were enrolled at this site. The suspected BMD data was removed from the database. Additional quality control review of all BMD, bone scans and x-ray data was conducted by the Sponsor and similar problems were not identified. In addition, a DSI audit was performed at site 0829.

Given the findings, the Sponsor conducted analyses of fracture endpoints, both primary and secondary, both with and without data from site 0829. BMD endpoints were analyzed with and without data from site 0829. Similar results were noted in these analyses, minimizing concerns over the impact of site 0829 on the overall study findings.

Efficacy Measures: The primary efficacy endpoint is incidence of clinical fractures, including clinical vertebral fracture. Secondary efficacy endpoints, in prespecified order, include percent change from baseline in total hip BMD at Month 12; percent change from baseline in total hip BMD at Month 24; percent change from baseline in total hip BMD at Month 12 in patients who received study medication within 6 weeks of hip fracture surgery; percent change from baseline in total hip BMD at Month 12 in patients who received study medication after 6

weeks of hip fracture surgery; time to first clinical vertebral fracture; time to first hip fracture; time to first non-vertebral fracture; percentage of patients with any hospitalization post-baseline; and time to first clinical fracture in men.

Incidence of clinical fractures: The primary efficacy endpoint is incidence of clinical fracture. This was an event-driven study and 211 fractures were required to meet the endpoint, assuming a 14.4% 2-year fracture rate in the placebo arm. Subjects were not stratified based on gender. Two interim analyses were planned after approximately 1/3 and 2/3 of the goal number of patients with at least one confirmed clinical event (i.e., 211 patients) had occurred. After reviewing the 2nd interim results, the DSMB requested a third interim analysis and the results were presented to them on November 2006 with 185 patients having confirmed clinical fractures. After review of the third analysis, the DSMB recommended to stop the study and begin closeout procedures over a 90-day period. At study close-out, 231 subjects had confirmed fractures (109.5% of goal) with a significance level of 0.0351. Therefore, the superiority of zoledronic acid over placebo could be concluded for the final analysis if the statistical significance was achieved at $p \leq 0.0351$ level.

As outlined in the table below, in the ITT population, 8.6% (= 92/1065) of the zoledronic acid-treated patients and 13.1% (= 139/1062) of the placebo-treated patients had at least 1 adjudicated clinical fracture over the duration of the study, resulting in a hazard ratio of 0.65 (95% CI 0.50 , 0.84) and p=0.0012. The p-value of 0.0012 is less than the required significance level of ≤ 0.0351, therefore it can be concluded that zoledronic acid is superior to placebo in reducing the incidence of clinical fractures.

Study 2310: Clinical Fractures		
	zoledronate	**placebo**
N, ITT	1065	1062
completed study		
actual event rate	92 (8.6%)	139 (13.1%)
Hazard ratio (95% CI)	0.65 (0.50 , 0.84)	
p-value	0.0012	
KM estimate	22.1%	24.2%
at Month 24		
actual event rate	77 (7.2%)	120 (11.3%)
Hazard ratio (95% CI)	0.63 (0.47 , 0.84)	
p-value	0.0014	
KM estimate	8.6%	13.9%
at Month 36		
actual event rate	89 (8.4%)	135 (12.7%)
Hazard ratio (95% CI)	0.64 (0.49 , 0.84)	
p-value	0.0011	
KM estimate	12.1%	18.6%

An analysis excluding data from study site 0829 was performed and the results were similar to those achieved with the overall population: hazard ratio of 0.64 (95% CI: 0.49 to 0.84) for the zoledronic acid group vs. the placebo group (p = 0.0014).

Change in BMD: Bone mineral density secondary endpoints evaluated using closed testing procedures include (in specified order): 1) percent change from baseline in total hip BMD at Month 12; 2) percent change from baseline in total hip BMD at Month 24; 3) percent change from baseline in total hip BMD at Month 12 in patients who received study medication within 6 weeks of hip fracture surgery; 4) percent change from baseline in total hip BMD at Month 12 in patients who received study medication after 6 weeks of hip fracture surgery; and 5) percent change from baseline in total hip BMD at Month 24 in male patients.

As outlined in the table below, zoledronic acid 5 mg once yearly increased BMD at the hip significantly at Months 12 and 24 when compared to placebo.

Study 2310: Secondary BMD Endpoints		
	zoledronate	**placebo**
N, ITT	1065	1062
Change in Total Hip BMD at Month 12		
n	681	683
LS mean % change	2.59	-1.04
LS mean difference (95% CI)	3.64 (2.98 , 4.29)	
p-value	<0.0001*	
Change in Total Hip BMD at Month 24		
n	405	400
LS mean % change	4.68	-0.74
LS mean difference (95% CI)	5.42 (4.26 , 6.57)	
p-value	<0.0001*	
Change in Total Hip BMD at Month 12, Dosed Within 6 Weeks		
n	295	309
LS mean % change	1.73	-1.18
LS mean difference (95% CI)	2.92 (1.94 , 3.89)	
p-value	<0.0001*	
Change in Total Hip BMD at Month 12, , Dosed After 6 Weeks		
n	385	375
LS mean % change	3.28	-0.91
LS mean difference (95% CI)	4.19 (3.32 , 5.06)	
p-value	<0.0001*	
Change in Total Hip BMD at Month 24 in Male Patients		
n	85	100
LS mean % change	3.59	-0.22
LS mean difference (95% CI)	3.81 (1.38 , 6.23)	
p-value	<0.0021*	
*statistically significant under closed testing procedure		

Secondary fracture endpoints: Fracture secondary endpoints evaluated using closed testing procedures include (in specified order): 6) time to first clinical vertebral fracture; 7) time to first hip fracture; 8) time to first non-vertebral fracture and 10) time to first clinical fracture in male patients. As outlined in the table below, treatment with zoledronic acid resulted in a significant reduction in the rate of clinical vertebral fractures. There was no significant difference in the rate of hip fracture.

Study 2310: Secondary Fracture Endpoints		
	zoledronate	**placebo**
N, ITT	1065	1062
Time to First Clinical Vertebral Fracture		
actual event rate (%*)	21 (1.7%)	39 (3.8%)
Hazard ratio (95% CI)	0.54 (0.32 , 0.92)	
p-value	0.0210**	
Time to First Hip Fracture		
actual event rate (%*)	23 (2.0%)	33 (3.5%)
Hazard ratio (95% CI)	0.70 (0.41 , 1.19)	
p-value	0.1815	
Time to First Non-Vertebral Fracture		
actual event rate (%*)	79 (7.6%)	107 (10.7%)
Hazard ratio (95% CI)	0.73 (0.55 , 0.98)	
p-value	0.0338	
Time to First Clinical Vertebral Fracture in Male Patients		
actual event rate (%*)	16 (7.4%)	20 (8.7%)
Hazard ratio (95% CI)	0.85 (0.44 , 1.65)	
p-value	0.6374	
*based on KM estimate at 24 months **statistically significant under closed testing procedure		

An analysis excluding data from study site 0829 was performed and the results were similar to those achieved with the overall population.

Resource Utilization: The percentage of patients with any hospitalization post baseline was the ninth secondary endpoint evaluated using closed testing procedures. Overall, 381 (36%) patients in the zoledronic acid group and 390 (37%) patients in the placebo group required hospitalization at some point during the study (p=0.65).

7.1.2. Other efficacy studies

No other efficacy studies were submitted with this supplemental NDA.

7.1.3. Discussion of primary and secondary reviewers' comments and conclusions

I agree with Dr. Lubas's and Ms. Liu's conclusions that study 2310 has demonstrated adequate evidence of reduction in clinical fracture following hip fracture. Because of the hierarchy of the closed testing procedure used, the clinical vertebral fracture reduction efficacy is also acceptable for labeling.

7.1.4. Pediatric use/PREA waivers/deferrals

A request for a full waiver of pediatric studies (i.e. for all pediatric age groups) was submitted with this supplemental NDA. The rationale for the waiver is that zoledronic acid "does not represent a meaningful therapeutic benefit as the pediatric population does not typically experience recurrent clinical fractures post hip fractures as in the adult population which is at a relatively higher risk of subsequent fractures". The waiver request was presented to the Pediatric Review Committee on May 14, 2008 and was approved.

7.1.4.1.Discussion of notable efficacy issues

With this supplemental NDA, the Sponsor is seeking approval of a new indication for zoledronic acid – prevention of clinical fracture following hip fracture in men and women. It is this reviewer's belief that the proposed indication is subsumed in the current indication treatment of osteoporosis. Although the diagnosis of osteoporosis by BMD criteria was not required for study enrollment, all subjects did meet the diagnostic criteria for osteoporosis based on the occurrence of a low trauma hip fracture. After having already sustained a low trauma hip fracture, the enrolled study population would be considered a group at high-risk for subsequent fracture. These high-risk patients are ones in need of treatment for their osteoporosis. They are not a "prevention" population, which is what the proposed indication suggests. Therefore, rather than a new indication, it would be more appropriate to include specific language regarding these patients at high-risk of fracture in the current treatment of osteoporosis indication.

7.2. Safety

7.2.1. General safety considerations

Known safety signals associated with bisphosphonate medications include renal insufficiency, hypocalcemia, acute phase reaction, osteonecrosis of the jaw, inflammatory eye events, and musculoskeletal pain. Concerns regarding atrial fibrillation associated with bisphosphonate use have also been raised.

7.2.2. Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

The pivotal study 2310 provides the basis for this safety review.

Safety events and exposure: The overall safety event rates are listed in the table below. Overall, 82% of the safety population experienced at least one adverse event during the trial. The rate of discontinuation, including death, and serious adverse events were slightly higher in the placebo group.

Study 2310: Safety Events		
	zoledronate	**placebo**
N, Safety	1054	1057
Discontinued	295 (27.7)	316 (29.8)
Death, untreated*	1 (0.1)	1 (0.1)
Death, untreated	101 (9.6)	141 (13.3)
Serious Adverse Event	404 (38.3)	436 (41.2)
Adverse Event, Withdrawal from Study**	24 (2.3)	21 (2.0)
Adverse Event, Discontinuation of Study Drug	56 (5.3)	50 (4.7)
Adverse Event, Treatment Emergent	867 (82.3)	852 (80.6)
*patients who died prior to receiving any dose of study drug **including laboratory abnormalities		

As noted previously, study 2310 is an event-driven trial and the duration of follow-up is highly variable. The mean duration of follow-up was 706 day for the zoledronic acid group and 711

days for the placebo group. Enrolled subjects received one to five yearly infusions of study drug. As outlined in the table below, approximately 70% of both groups received at least two yearly doses of study medication. The total number of doses a patient was to receive was limited to three in Amendment 6. However, by the time this amendment was approved, 77 patients had already received four doses, and one patient had received five. In addition, one patient in each treatment group did not receive the Year 2 infusion (skipped the dose).

Study 2310: Exposure		
	zoledronate	**Placebo**
N, ITT	1065	1062
n (%), untreated	12 (1.1)	5 (0.5)
N, Safety	1054	1057
n (%), Year 1 infusion	1054 (100)	1057 (100)
n (%), Year 2 infusion	738 (70.0)	752 (71.1)
n (%), Year 3 infusion	325 (30.9)	322 (30.5)
n (%), Year 4 infusion	43 (4.1)	34 (3.2)
n (%), Year 5 infusion	1 (0.1)	0 (0.0)

Deaths: A total of 244 patients died during the study. The total number of deaths was significantly lower in the zoledronic acid group (9.6%) compared to the placebo group (13.3%), p=0.0117. The lower death rate in the zoledronic acid group was due primarily to a decrease in Cardiac disorders (3.4% zoledronic acid group vs. 4.9% placebo group), Respiratory disorders (1.2% zoledronic acid group vs. 2.1% placebo group), General disorders (0.9% zoledronic acid group vs. 1.4% placebo group) and Neoplasms (0.7% zoledronic acid group vs. 1.2% placebo group). This finding was not expected and has not been noted with other bisphosphonates. As outlined in Dr. Lubas's review, the difference in mortality seen between zoledronic acid and placebo was not attributable to recurrent fracture.

Dr. Lubas has outlined the similarities and discrepancies between the subjects enrolled in the osteoporosis fracture trial, study 2301, where the mean age of enrollees was 73 years with an age range of 64 – 89 years and no evidence of improved mortality with zoledronic acid use; and the current study 2310, where the mean age of enrollees was 74 years with an age range of 50 – 98 years and improved mortality with zoledronic acid use. The one major difference between these two study populations is the presence of a low trauma hip fracture in all subjects enrolled in study 2310. Increased mortality following hip fracture is well described. Risk factors for morbidity and mortality following hip fracture include increasing age, male sex, co-existing illness and poor pre-fracture functional status. In his evaluation of the pre-existing conditions of subjects enrolled in study 2310, Dr. Lubas has outlined that although this was a randomized trial, it appears that subjects in the placebo group could be considered generally sicker, as evidenced by higher baseline rates of underlying diseases. Ms. Liu also pointed out in her review that the median age among the patients who died in this current study (80 and 79 years for zoledronic and placebo, respectively) was higher than the overall mean age of the study cohort (73 years). Furthermore, no significant association was noted between fracture and death (Fisher's Exact p=0.0792). I agree with Dr. Lubas in that this study was not designed to evaluate mortality and given the differences noted in the baseline disease state, it is not possible to place clinical significance on the mortality findings.

Serious adverse events: A total of 840 subjects (404 (38%) in the zoledronic acid group and 436 (41%) in the placebo group) experienced a serious adverse event during the trial. The most frequently reported SAEs were pneumonia (3.1% zoledronic acid group vs. 3.4% placebo group), post procedural complication (2.8% in both treatment groups), arthralgia (2.4% zoledronic acid group vs. 2.3% placebo group), cerebrovascular accident (2.0% zoledronic acid group vs. 1.9% placebo group), and congestive heart failure (1.7% zoledronic acid group vs. 1.9% placebo group). Anemia SAEs were more common in the zoledronic acid group (1.2%) compared to placebo (0.7%). SAEs related to fractures were more common in the placebo group. There was no increase in the number of atrial fibrillations SAEs with zoledronic acid use in this trial. These findings are more thoroughly discussed below.

Adverse events leading to withdrawal from the study: A total of 46 subjects (24 (2%) in the zoledronic acid group and 21 (2%) in the placebo group) withdrew from the study because of adverse events, or abnormal laboratory value. The most common adverse events occurring in patients who withdrew from the study were pyrexia, back pain, pain in extremity, musculoskeletal pain, fall, cerebrovascular accident, and urinary tract infection.

Of note, a large number of subjects (229 = 120 (11%) in the zoledronic acid group and 109 (10%) in the placebo group) withdrew from the study and are listed as "withdrew consent". Query of the study 2310 adverse events database indicates that 152 (66%) of these subjects (77 (7%) in the zoledronic acid group and 75 (7%) in the placebo group) reported adverse events during participation in the trial. The most common adverse events occurring in this group of patients were: arthralgia, back pain, urinary tract infection, fall, diarrhea, pyrexia and anemia.

Adverse events leading to study drug discontinuation: A total of 106 subjects (56 (5%) in the zoledronic acid group and 50 (5%) in the placebo group) permanently discontinued study drug due to adverse events during the trial. Of these, 65 (33 (3%) in the zoledronic acid group and 32 (3%) in the placebo group) were classified as having a serious adverse event leading to study drug discontinuation. The most common adverse events leading to study drug administration were renal creatinine clearance decreased, renal failure, sepsis, cardiac failure, and general physical health deterioration.

Adverse events: Overall, 867 (82%) subjects in the zoledronic acid group and 852 (81%) subjects in the placebo group reported at least one adverse event during the trial. The most common adverse events (≥ 10% of the subjects in at least 1 treatment group) were arthralgia, urinary tract infection, back pain, and fall.

Adverse events of special interest

Renal Adverse Events: Intravenous zoledronic acid 4 mg has been associated with increased renal toxicity, most notably when comparing a 5 minute infusion to a 15 minute infusion. Zoledronic acid 8 mg was associated with increased renal toxicity regardless of infusion time and this dose has been discontinued from clinical development. In study 2310, subjects with a baseline calculated creatinine clearance < 30 mL/min were excluded from the study. Renal dysfunction was defined as:

1) an increase in serum creatinine > 0.5 mg/dL
2) a calculated creatinine clearance < 30 mL/min

3) a creatinine clearance ≤ 60 mL/min and a ≥ 30% decrease in creatinine clearance

Overall, 55/886 (6%) subjects in the zoledronic acid group and 50/900 (6%) in the placebo group developed an increase in creatinine > 0.5 mg/dL. A calculated creatinine clearance < 30 mL/min was reported in 72/882 (8%) subjects in the zoledronic acid group and 65/891 (7%) in the placebo group. A ≥ 30% decrease in creatinine clearance with a baseline creatinine clearance value ≤ 60 mL/min occurred in 72/339 (21%) subjects in the zoledronic acid group and 72/350 (21%) in the placebo group.

A total of 306 subjects (160 in the zoledronic acid group and 146 in the placebo group) had renal events that were sent to the adjudication committee for review. After review, the committee determined that 177 subjects (87 in the zoledronic acid group and 90 in the placebo group) had confirmed clinically significant renal events. The incidence is similar between the two groups.

Three subjects died due to renal failure during the trial, all were receiving placebo. Renal failure or decreased creatinine clearance adverse events led to study drug discontinuation in 10 (0.9%) zoledronic acid-treated subjects and six (0.6%) placebo-treated subjects.

As outlined in Dr. Lubas's review, risk factors associated with an increased likelihood of a change in renal function are mainly those that are well known including increasing age, use of anti-hypertensive medications and diabetes.

Hypocalcemia: Bisphosphonate use, most notably intravenous bisphosphonates, has been associated with hypocalcemia. Studies in Paget's disease of bone evidenced a concerning signal of hypocalcemia following zoledronic acid treatment in patients with Paget's disease.

Patients with a serum calcium level less than 8.0 mg/dL were excluded from enrollment in study 2310. Vitamin D levels were not required at baseline and there were no specific inclusion or exclusion criteria related to vitamin D levels. Study participants received a loading dose of 50,000 – 125,000 IU vitamin D and then were begun on 800 – 1200 IU vitamin D and 1000 – 1500 mg calcium daily. Subjects began the calcium and vitamin D supplementation at least 14 days prior to study drug and continued throughout the study duration.

Overall, there were 10 (0.9%) subjects in the zoledronic acid group and 5 (0.5%) subjects in the placebo group who had an adverse event of hypocalcemia (defined as calcium < 8.3 mg/dL). Most cases of hypocalcemia were considered mild (serum calcium 7.0 – 8.3 mg/dL). One patients in the place group developed moderate hypocalcemia (serum calcium 6.1 – 7.0 mg/dL) and there were no cases of severe hypocalcemia.

Atrial fibrillation: In the postmenopausal osteoporosis study 2301, an imbalance in cardiac arrhythmias serious adverse events, driven mainly by an increase in atrial fibrillation SAEs in the zoledronic acid group, raised concerns regarding the effect of bisphosphonates on atrial fibrillation. However, the events did not appear to be related to the timing of the study drug infusion. In the current study 2310, the atrial fibrillation events do not show an imbalance with atrial fibrillations SAEs reported in 11 (1.0%) subjects in the zoledronic acid group and 13

(1.2%) subjects in the placebo group, and any atrial fibrillation event reported in 29 (2.8%) subjects in the zoledronic acid group and 27 (2.6%) subjects in the placebo group. As outlined in Dr. Lubas's review, it appears that the imbalance in SAE events in study 2301 may be due to an underestimation of the true placebo rate.

Acute Phase Reaction: Symptoms consistent with acute phase reaction have been reported with intravenous bisphosphonate use. Symptoms considered possibly related to an acute phase reaction include flu-like symptoms such as fatigue, fever, chills, myalgia, arthralgia, pain and generalized body aches, occurring within 3 days of i.v. dosing and lasting less than 7 days. The most common adverse events reported in patients receiving zoledronic acid were symptoms attributable to the acute phase reaction-like syndrome associated with intravenous bisphosphonate use including arthralgia (18% in both treatment groups), pyrexia (9% in the zoledronic acid group and 3% in the placebo group), myalgia (5% in the zoledronic acid group and 3% in the placebo group), headache (4% in the zoledronic acid group and 2% in the placebo group), nausea (4% in the zoledronic acid group and 5% in the placebo group), asthenia (3% in both treatment groups), and bone pain (3% in the zoledronic acid group and 1% in the placebo group). As outlined in Dr. Lubas's review, the event rates for acute phase reaction symptoms are lower than the rates seen in the postmenopausal osteoporosis study 2301. This is most likely due to pre-dose medication with acetaminophen required in the protocol.

Osteonecrosis of the Jaw: Both intravenous and oral bisphosphonates have been associated with osteonecrosis of the jaw (ONJ). In order to evaluate maxillofacial adverse events, a blinded adjudication committee comprised of 5 dental experts reviewed all adverse event reports pertaining to the jaw. A total of 60 preferred terms were predefined for selection of cases requiring adjudication. The predefined criteria for osteonecrosis of the jaw were an area of exposed bone for longer than 6 weeks with delayed healing despite adequate medical therapy. There were no spontaneous reports of ONJ in study 2310 and a total of 17 subjects (6 in the zoledronic acid group and 11 in the placebo group) reported events that were referred for adjudication. No cases of ONJ were determined. One placebo-treated subjects was listed as indeterminate.

Inflammatory Eye Disease: An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. In order to evaluate inflammatory ocular findings in study 2310, a blinded ophthalmologist predefined criteria for evaluation for defining pertinent ocular AEs. These criteria included the preferred terms blepharitis, conjunctivitis, diplopia, episcleritis, eye irritation, eye pain, iridocyclitis, iritis, lacrimation increased, ocular icterus, orbital edema, photophobia, scleritis, uveitis and vision blurred. Overall, 37 subjects (21 in the zoledronic acid group and 16 in the placebo group) met the predefined criteria for further ophthalmologic review. All cases were confirmed upon adjudication. The most common ocular adverse event reported was conjunctivitis. There was one case of iritis in a zoledronic acid-treated subject.

Musculoskeletal Pain: An increased incidence of muscular and bone pain has been reported with bisphosphonate use. Overall, musculoskeletal pain symptoms occurred in 456 (43%) subjects in the zoledronic acid group and 453 (43%) subjects in the placebo group. Bone pain

was reported in 34 (3%) subjects in the zoledronic acid group and 11 (1%) subjects in the placebo group. The bone pain was classified as severe in one patient in each treatment group. As outlined in Dr. Lubas's review, the rate of occurrence of bone pain is less than what was observed in the postmenopausal osteoporosis study 2301. One main difference in these two trails is the approach to vitamin D supplementation. In study 2301, patients received 400 – 1200 IU vitamin D daily while in study 2310, subjects received a loading dose of vitamin D, then 800 – 1200 IU daily. These findings suggest that the etiology of the bone pain with bisphosphonate use may be related to subtle changes in the calcium and vitamin D status of the patient.

Laboratory evaluations: Increased liver transaminase or liver function abnormal adverse events were reported in three subjects in each treatment group. As outlined in Dr. Lubas's review, increases in SGOT greater than 100 U/L were seen in four subjects in each treatment group, while increases in SGPT greater than 110 U/L were seen in five subjects in each treatment group.

Anemia adverse events were reported in 13 (1.2%) of zoledronic acid-treated subjects and 7 (0.7%) of placebo-treated subjects. The baseline hemoglobin levels were 121 g/L in the zoledronic acid group and 122 g/L in the placebo group, with hematocrit levels of 0.38 in the zoledronic acid group and 0.38 in the placebo group. Hematology parameters were not assessed in this study beyond baseline measurements.

7.2.3. Safety update

No new findings were revealed.

7.2.4. Special safety concerns

No new special safety concerns have arisen in the review of this application.

7.2.5. Discussion of primary reviewer's comments and conclusions

I agree with Dr. Lubas that study 2310 confirms the safety of zoledronic acid for the treatment of postmenopausal women and in men who sustain a low trauma hip fracture. The data from study 2310 do not confirm the finding that zoledronic acid use increases the risk of atrial fibrillation, as seen in study 2301.

7.2.6. Discussion of notable safety issues

Safety signals known to occur with bisphosphonate use were adequately evaluated in this trial and no new safety signals were noted.

8. Advisory Committee Meeting

This supplemental NDA was not presented to the Endocrine and Metabolism Drugs Advisory Committee.

9. Other Relevant Regulatory Issues

There are no other notable regulatory issues for this supplemental NDA.

10. Financial Disclosure

Dr. Lubas has reviewed the financial disclosure information and found them acceptable for Study 2310.

11. Labeling

Labeling negotiations are in process; please see the separate labeling document.

12. DSI Audits

The Division of Scientific Investigations conducted audits of two U.S. investigative sites for study 2310. As outlined in Dr. Lubas's review, the two sites were chosen because based on number of patients enrolled, number of adverse events and noted irregularities in some baseline DXA scans. Minor deficiencies were noted at both sites. However, overall the data was acceptable for use in evaluating the efficacy of the study medication.

13. Conclusions and Recommendations

The Sponsor has demonstrated adequate evidence that treatment with zoledronic acid reduces the incidence of clinical fractures in patients who have sustained a low trauma hip fracture efficacy. The patients in study 2310 represent a population at higher risk of fracture than those evaluated in study 2301. Therefore, we now have evidence that treatment with zoledronic acid is efficacious at reducing the risk of fracture in patients diagnosed with osteoporosis by BMD criteria only and well as those diagnosed with osteoporosis based on the occurrence of a low trauma fracture. However, these two studies and their findings do not warrant separate indications as they more likely represent overlapping populations. Indeed, a subgroup analysis of the patients with at least one prevalent vertebral fracture in the postmenopausal osteoporosis trial revealed a similar 36% risk reduction in clinical fractures. No new safety issues have been noted in this trial. Results of study 2310 in comparison with results from study 2301 would suggest that the prophylactic use of acetaminophen is beneficial in decreasing the symptoms of acute phase reaction that occur with zoledronic acid dosing.

13.1. Recommended regulatory action

Approve

13.2. Safety concerns to be followed postmarketing

We will continue to follow the adverse events known to occur with bisphosphonate use including deterioration in renal function, acute phase reaction symptoms, hypocalcemia, osteonecrosis of the jaw, inflammatory eye changes, and musculoskeletal and bone pain. An in-depth analysis of atrial fibrillation events in all of the bisphosphonate trials of at least one year duration is currently ongoing to evaluate if further study is needed to assess the questions of an increased risk of atrial fibrillation with bisphosphonate use.

13.3. Risk Minimization Action Plan

13.3.1. General considerations on the need for, and goals of, any RiskMAP beyond standard labeling and pharmacovigilance

None needed beyond standard labeling and pharmacovigilance

13.4. Postmarketing studies, voluntary or required

None

13.5. Comments to be conveyed to the applicant in the regulatory action letter (e.g., deficiencies and information needed to resolve each deficiency)

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Theresa Kehoe
5/28/2008 08:38:59 AM
MEDICAL OFFICER

Mary Parks
5/28/2008 09:17:06 AM
MEDICAL OFFICER
I concur with Dr. Kehoe's recommendations and her CDTL memo will serve as the division's decisional memo for this supplement.