

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-817

MEDICAL REVIEW

MEDICAL TEAM LEADER MEMO

NDA: 21-817

DRUG: Zoledronic acid, proposed name Reclast, 5 mg for intravenous injection

INDICATION: Treatment of Paget's disease of bone

COMPANY: Novartis, Inc

DATE: April 16, 2007

The Division of Medication Errors and Technical Support has raised a new concern regarding the trade name Reclast for this zoledronic acid application for the treatment of Paget's disease of bone. The initial consult, conducted in October 2005, found the proprietary name Reclast acceptable and there were no agents identified for sound-alike or look-alike confusion. On a follow-up review, the biologic agent Neulasta has been identified as a potential look-alike which may cause confusion.

Neulasta (pegfilgrastim), a colony stimulating factor, received marketing approval in 2002 for the treatment of myelosuppression from chemotherapy. The usual dose is 6 mg administered subcutaneously once every chemotherapy cycle. Neulasta is available as a 6 mg/mL syringe and must be refrigerated.

Reclast (zoledronic acid) is a bisphosphonate agent administered as a 5 mg dose by intravenous infusion over 15 minutes for a single dose. The intended population is patients with Paget's disease of bone. Zoledronic acid is currently approved as a 4 mg dose for use in the oncology population under the proprietary name Zometa.

The DMETS staff believes that there is a potential for confusion with these two agents. While there is a similarity in the proprietary names, the routes of administration are different and the approved patient populations do not significantly overlap. Zoledronic acid is used in the oncology population under a different proprietary name, Zometa, which is well recognized.

Therefore, in the opinion of this reviewer, the potential for confusion between Reclast and Neulasta is not sufficient to warrant not approving the proposed proprietary name of Reclast for zoledronic acid in the treatment of Paget's disease of bone. The Sponsor has proposed a program of education and surveillance of medication errors because of the dual trade names. The Division will continue to monitor for reports of medication errors and initiate corrective action if needed.

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/s/

Theresa Kehoe
4/16/2007 09:02:25 PM
MEDICAL OFFICER

Eric Colman
4/16/2007 10:10:42 PM
MEDICAL OFFICER
Agree

FDA Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products

MEMORANDUM

DATE: April 11, 2007

FROM: Eric Colman, MD
Deputy Director
Division of Metabolism and Endocrinology Products

TO: NDA 21-817

RE: Paget's disease of bone indication for zoledronic acid 5 mg injection

Background

Zoledronic acid 4 mg injection (Zometa) is currently approved for the treatment of hypercalcemia of malignancy (HCM) and for the treatment of multiple myeloma and bone metastases in patients with solid malignant tumors. If clinically indicated and renal function is acceptable, patients with HCM may be retreated with 4 mg zoledronic acid 7 or more days after the initial dose. Patients with multiple myeloma or with bone metastases from solid tumors may receive repeat doses of zoledronic acid 4 mg every 3 to 4 weeks, if renal function is acceptable.

This is the third and final review cycle for the zoledronic acid – Paget's disease of bone new drug application (NDA). The original NDA was submitted in September 2004. Two identical 6-month trials demonstrated that a single intravenous 5 mg dose of zoledronic acid was statistically and most likely clinically superior to 30 mg once-daily x 2 months risedronate in reducing serum alkaline phosphatase levels in nearly 400 patients with Paget's disease of bone. But because 21% of zoledronic acid patients compared with 3% of risedronate patients developed asymptomatic serum calcium levels < 8.4 mg/dl at Day 10 post-dosing, the Division issued an approvable letter on March 18, 2005, requesting that Novartis provide evidence that calcium (and vitamin D) supplementation can adequately attenuate the risk for hypocalcemia. (A lesser concern was also cited regarding hypophosphatemia).

Following review of data submitted in a August 23, 2005 complete response, the Division determined that calcium supplementation of \geq ~~—~~ mg per day satisfactorily reduced the risk for developing hypocalcemia. The Division concluded that the benefits of the 5 mg dose of zoledronic acid outweighed the risks and was moving towards approving the

Paget's NDA when Novartis notified us in January 2006 about imbalances, based on an August 5, 2005 cutoff date, in atrial fibrillation in nearly 8000 postmenopausal women treated with annual 5 mg doses of zoledronic acid vs. placebo in an ongoing 3-year osteoporosis fracture trial (Study 2301). A second approvable letter was issued for the Paget's application on February 22, 2006, to allow Novartis, their consultants, and the Division to explore the clinical significance of these safety signals. The company submitted their response to the second approvable letter on October 13, 2006. This information is discussed in the Clinical Safety Data section below.

Clinical Safety Data

With a March 31, 2006 cutoff date (by which time the majority of patients had completed Study 2301), the incidence of death was 2.8% in the placebo group and 3.3% in the zoledronic acid group in Study 2301. The incidence of death due to a cardiovascular event was 0.8% in the placebo group and 1.0% in the zoledronic acid group. The incidence of atrial fibrillation coded as serious by the investigators was 0.4% (n=17) in the placebo group and 1.2% (n=48) in the zoledronic acid group. A group of consultants external to Novartis reviewed the data and confirmed that all but one event in the placebo group were in fact atrial fibrillation. The majority of the atrial fibrillation events occurred more than 30 days post-dosing, suggesting that the arrhythmias were not drug related.

It should be noted that the incidence of atrial fibrillation coded as serious from a second large osteoporosis trial of 5-mg annual zoledronic acid was 1.1% in the placebo group and 0.3% in the zoledronic acid group. Further support for the lack of a causal association between zoledronic acid and atrial fibrillation comes from large trials of oral alendronate, oral risedronate, and intravenous ibandronate, where no meaningful increase in the incidence of atrial fibrillation has been noted between active drug and placebo. Query of the AERS database likewise failed to reveal an increased reporting rate for atrial fibrillation with the marketed bisphosphonates.

Dr. Kehoe discusses additional safety information, including ocular events, in her review. At this point there are no safety signals that preclude approval of zoledronic acid for Paget's disease.

Pharmacology/Toxicology

There are no outstanding pharmacology/toxicology issues and this discipline recommends approval of the NDA.

Clinical Pharmacology

The Office of Clinical Pharmacology is recommending that zoledronic acid dosing for Paget's patients be adjusted based on creatinine clearance – as is currently recommended for the bone metastases indication – rather than administered as a 5 mg infusion to all patients regardless of renal function. The dosing regimen for oncology patients was changed to take into account creatine clearance following post-approval spontaneously-

reported cases of acute renal failure in patients with cancer, primarily multiple myeloma, treated with 4 mg zoledronic acid.¹ Multiple myeloma itself increases the risk for renal insufficiency and failure.²

Based on a study in patients with cancer, mild renal impairment increased the plasma AUC of zoledronic acid by 15%, while moderate renal insufficiency increased the ACU by 43%. The creatinine-clearance based dosing regimen was derived from population PK/PD modeling and recommends that patients with baseline creatinine clearance values of 30 to 39 ml/min receive 3.0 mg zoledronic acid, those with clearance values of 40 to 50 ml/min receive 3.3 mg, those with clearance values of 50 to 60 ml/min receive 3.5 mg, and those with values above 60 ml/min receive 4 mg. It is believed that the potential for renal injury with zoledronic acid is directly related to drug AUC and C_{max} levels.

In a large subset of women from the osteoporosis fracture trial (2301), of whom many had creatinine clearance values in the 30 to 60 ml/min range, the incidence of an increase in serum creatinine > 0.5 mg/dl measured 9 to 11 days post-dose was 1.8% in the zoledronic acid group and 0.8% in the placebo group. When assessed at the end of the trial, 0.8% of zoledronic acid vs. 0.7% of placebo subjects had an increase in serum creatinine > 0.5 mg/dl. While 12/3862 patients in the zoledronic acid group reportedly developed acute renal failure, as defined by the investigator, compared with 6/3852 patients in the placebo group, many of the cases occurred well after study drug was administered, reducing the likelihood that the event was causally related to zoledronic acid.

The Division discussed the appropriate dosing regimen for the Paget's population with the Office of Clinical Pharmacology. At this time we do not believe that the available data support adjusting the dose based on creatinine clearance. In contrast to patients with cancer who often have comorbid conditions, are taking concomitant medications that increase the risk for renal failure, and receive zoledronic acid as often as every 3-4 weeks, patients with Paget's disease are in general a "cleaner" population and will receive zoledronic acid at widely-spaced intervals (e.g., > 6 months), if more than one dose is required at all. Trial data suggest that many patients have appropriate suppression of serum alkaline phosphatase for years following a single 5-mg dose.

We will closely monitor post-approval data and if credible reports of renal failure are received in patients with Paget's we will consider changing the labeling to recommend creatinine clearance-based dosing (\downarrow AUC and C_{max}) or an increased infusion time ($\downarrow C_{max}$) or both.

1 Chang, JT, et al. Renal failure with the use of Zoledronic Acid. *New Engl. J Med* 2003;349:1676-1678.
2 Eleutherakis, V, et al. Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. *Leuk Lymphoma* 2007;48:337-41.

Chemistry/Manufacturing/Controls

There are no outstanding pharmacology/toxicology issues and this discipline recommends approval of the NDA.

Division of Scientific Investigation

The Division of Scientific Investigation conducted a routine inspection of three clinical investigative sites and concluded that no violations occurred.

Tradename Review

Novartis is proposing the tradename Reclast for the Paget's indication and for the postmenopausal osteoporosis indication, which is currently under review.

The Division of Drug Marketing, Advertising, and Communication has no objection to the tradename Reclast.

The Division of Medication Errors and Technical Staff (DMETS) recommends against the approval of Reclast because this would introduce a second tradename for zoledronic acid into the marketplace. If Reclast is approved, however, DMETS in their December 1, 2005, consult recommends that several measures be taken to reduce the risk of patients receiving both Zometa and Reclast. Novartis has committed to implement many of these recommendations.

I believe there is good reason to believe that medication errors will occur if: 1) all of the zoledronic acid indications and their individual dosing regimens are marketed under the tradename Zometa, or 2) the oncology indications are marketed under the tradename Zometa while the non-oncology indications are marketed as Reclast. Whether a single or dual tradename will result in fewer medication errors is unknown and very difficult to accurately assess pre-approval.

I think it is reasonable to accept the dual tradename approach. We will closely monitor for post-approval medication errors attributable to dual tradenames.

Post-Approval Commitment

In a letter dated April 13, 2007, Novartis commits to perform a post-approval registry study to determine the incidence of hypocalcemia in 300 Paget's disease patients after they've received information on calcium and vitamin D supplementation, as recommended in the Reclast labeling. This study will begin in March 2008, and submission of the final report is estimated to occur in September 2010. An interim analysis will be submitted after the first 50 patients are evaluated.

Summary

- A single 5-mg infusion of zoledronic acid is more effective than two months of 30 mg daily risedronate in the treatment of Paget's disease of the bone.
- The incidence of hypocalcemia (and hypophosphatemia) is higher with zoledronic acid than with risedronate and presumably alendronate or any other oral bisphosphonate.
 - The zoledronic acid labeling strongly recommends that all patients receive 500 mg three times daily supplemental calcium and 800 IU of daily vitamin D.
 - Novartis has committed to conducting a post-approval registry study of at least 300 patients to examine the effectiveness of calcium and vitamin D supplementation in the real-world setting.
- Adverse renal events, including acute renal failure, have been reported in patients with cancer receiving 4 mg zoledronic acid q 3-4 weeks.
- Data from Paget's and osteoporosis clinical trials do not indicate that single or annual 5-mg doses of zoledronic acid increase the risk for clinically significant renal injury.
- Interim data from a large osteoporosis trial suggested that the risk for atrial fibrillation was higher in women treated with annual 5-mg doses of zoledronic acid vs. placebo: In addition to lacking biological plausibility, data from AERS and from clinical trials of risedronate, alendronate, and ibandronate do not support a causal relationship between bisphosphonates and increased risks for atrial fibrillation.
- Post-approval safety items that the Division needs to closely track include hypocalcaemia, renal injury, and medication errors due to dual tradenames.

Regulatory Recommendation

Approve.

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/s/

Eric Colman
4/16/2007 12:44:35 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	21-817
Submission Number	000
Submission Code	AZ
Letter Date	10/13/2006
Stamp Date	10/16/2006
PDUFA Goal Date	4/16/2007
Reviewer Name	Theresa Kehoe
Review Completion Date	4/9/2007
Established Name	Zoledronic Acid
(Proposed) Trade Name	Reclast
Therapeutic Class	Bisphosphonate
Applicant	Novartis
Priority Designation	P
Formulation	Intravenous
Dosing Regimen	5 mg
Indication	Treatment of Paget's disease of bone
Intended Population	Patients with Paget's disease

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approve

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

In addition to product labeling, the Sponsor proposes

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address the dual trade name concerns, the Sponsor proposes an educational campaign for physicians outlining that Reclast contains the same active ingredient as Zometa and surveillance of postmarketing events.

1.2.2 Required Phase 4 Commitments

Novartis has committed to conducting a registry study to determine the incidence of hypocalcemia following Reclast treatment in patients with Paget's Disease of bone in order to assess the effectiveness of their educational strategies on calcium and vitamin D supplementation. This study will evaluate serum calcium levels at nadir 10 days after Reclast infusion. The protocol will be submitted by September 30, 2007 and the study started by March 31, 2008. An interim report of the findings will be submitted after the first 50 patients are enrolled and the final study report will be submitted by September 2010.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Sponsor submitted a marketing application for zoledronic acid 5 mg injection for the treatment of Paget's disease of bone in September 24, 2004. Two identical pivotal trials were conducted to support the efficacy and safety: study CZOL446K2304 (2304) and study CZOL446K2305 (2305). Although the submitted trials demonstrated adequate evidence of efficacy, the occurrence of hypocalcemia with zoledronic acid use precluded approval. The Sponsor submitted a response on March 18, 2005. The safety concern was satisfactorily addressed. However, during the review process, the Sponsor notified the Division of findings noted by the Data Safety Monitoring Board (DSMB) regarding an increase in the incidence of

cardiac arrhythmia and cardiac mortality is Study CZOL446H2301 (2301), the pivotal postmenopausal osteoporosis study. The data was undergoing adjudication and the application was found approvable until the adjudicated safety data was available. This submission represents the company's complete response to that approvable letter and contains the requested data from Study 2301.

1.3.2 Efficacy

Studies 2304 and 2305 were identical multinational, randomized, double-blind, active-controlled, 6-month non-inferiority trials. The active comparator was 30 mg oral risedronate daily for 60 days. The study population consisted of men and women with confirmed radiographic evidence of Paget's disease and a serum alkaline phosphatase level at least two times the upper limit of the normal reference range. The primary endpoint was therapeutic response, defined as (1) a reduction of at least 75% from baseline in serum alkaline phosphatase excess (difference between measured level and midpoint of the normal range) or (2) normalization of serum alkaline phosphatase. At Month 6, 96% of zoledronic acid-treated subjects and 74% of risedronate-treated subjects experienced a therapeutic response ($p < 0.001$).

1.3.3 Safety

As previously outlined in Dr. Colman's reviews, hypocalcemia is the predominant safety finding of concern in the Paget's disease population. The Sponsor addressed this concern in the previous resubmission package. Overall, 21% of zoledronic acid-treated subjects, compared to 3% of risedronate-treated subjects developed serum calcium levels below 8.4 mg/dL at Day 10 following treatment. When evaluated based on the amount of calcium and vitamin D supplementation, 50% of zoledronic acid-treated subjects receiving less than 1000 mg a day in calcium supplements developed hypocalcemia at Day 10 and 35% of receiving less than 800 IU a day in vitamin D supplementation developed hypocalcemia at Day 10. One of the strongest predictors for development of hypocalcemia was baseline calcium level. Overall, 28% of subjects with a baseline calcium level less than 9.5 mg/dL developed hypocalcemia at Day 10, and 40% of subjects with a baseline calcium level less than 9.2 mg/dL developed hypocalcemia at Day 10. Baseline 25 hydroxyvitamin D level did not predict a low calcium level at Day 10.

Clinical safety issues raised by the large pivotal trial for the treatment of postmenopausal osteoporosis indication include an increased incidence of cardiovascular mortality, cardiac arrhythmias and ophthalmic adverse events. The safety data provided is mainly from the postmenopausal osteoporosis trials. There are no new trials in Paget's disease in this submission.

Death due to cardiac disease occurred in 1.0% of the zoledronic acid group and 0.8% of the placebo group in study 2301. However, interim data from a second ongoing study in postmenopausal women reveal that death attributed to cardiac disorders occurred in 2.7% of the zoledronic acid group and 3.2% of the placebo group. Deaths due to cerebrovascular accidents occurred in 0.3% of the zoledronic acid group and 0.1% of the placebo group in both studies.

Atrial fibrillation was reported and confirmed as a serious adverse event in 1.2% of subjects in the zoledronic acid group compared to 0.4% of subjects in the placebo group in the pivotal osteoporosis trial. Conversely, in study 2310, 0.3% of subjects in the zoledronic acid group compared to 1.1% of subjects in the placebo group developed atrial fibrillation. All adverse events of atrial fibrillation were reported in 2.4% of zoledronic acid-treated subjects and 1.8% of placebo-treated subjects in study 2301 and in 1.6% of zoledronic acid-treated subjects and 1.9% of placebo-treated subjects in study 2310. No atrial fibrillation signals were noted on AERS database review for any approved intravenous or oral bisphosphonate. Therefore, when all available data is taken together, there are no consistent findings to suggest that treatment with zoledronic acid confers an increased risk of cardiac mortality or atrial fibrillation.

An increased incidence of inflammatory eye disease was noted with zoledronic acid use in study 2301 (six subjects in the zoledronic acid group and no subjects in the placebo group). Currently, all bisphosphonate have language describing the risk of inflammatory eye disease in the Precautions section of the product label. While there is an increased risk of inflammatory eye disease with zoledronic acid use, this risk is a recognized one with bisphosphonate use and can be effectively managed in the outpatient setting.

In summary, a single dose of zoledronic acid 5mg is highly effective in the treatment of Paget's disease of bone. There do not appear to be any significant compelling safety signals to preclude the approval of zoledronic acid for the treatment of Paget's disease of bone.

1.3.4 Dosing Regimen and Administration

The Sponsor proposes a 5mg dose of zoledronic acid for the treatment of Paget's disease of bone. This dose is also under study for treatment of postmenopausal osteoporosis. The 4 mg dose of zoledronic acid is approved for the treatment of hypercalcemia of malignancy, treatment of patients with multiple myeloma or bone metastases from solid tumors. While the 5 mg dose of zoledronic acid is effective in the treatment of Paget's disease of bone, the 4 mg dose was not evaluated and may have been just as effective.

The Sponsor proposes to market the 5 mg dose of zoledronic acid as Reclast. The 4 mg dose of zoledronic acid is marketed as Zometa. The Division of Medication Errors and Technical Support finds the tradename Reclast acceptable from a promotional perspective. However, they do not recommend the use of a second proprietary name for zoledronic acid. If approved as Reclast, labeling recommendations were made to minimize product confusion.

At the time of the initial NDA submission, the Division agreed to allow Novartis to market zoledronic acid as Reclast for the Paget's disease indication. It is unlikely that the treatment populations for the Paget's disease indication and the malignancy indications will significantly overlap.

1.3.5 Drug-Drug Interactions

No new drug interaction studies have been performed in the Paget's disease population. *In-vivo* data do not indicate that zoledronic acid inhibits microsomal CYP450 enzymes.

Caution is warranted when administering zoledronic acid concomitantly with drugs that have the potential to lower serum calcium levels, such as loop diuretics, aminoglycosides, and Dilantin.

1.3.6 Special Populations

Zometa (zoledronic acid injection) treatment in the oncology population requires dose adjustment based on creatinine clearance. Renal function following Reclast (zoledronic acid) treatment in the postmenopausal osteoporosis population was evaluated in a subset of 5000 subjects enrolled in the large fracture study. In the renal substudy, 45% of subjects had a baseline creatinine clearance of less than 60 mL/min. There was no evidence to suggest the need for Reclast dose adjustment in the postmenopausal osteoporosis population, which is very similar to the Paget's disease population.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zoledronic acid, trade named Zometa and proposed trade name Reclast, is a bisphosphonic acid which acts as an inhibitor of osteoclastic bone resorption. The chemical designation of zoledronic acid is (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate. Zoledronic acid (Zometa) 4 mg injection is currently approved for the treatment of hypercalcemia of malignancy and bone metastases. This current application seeks approval for zoledronic acid (proposed trade name Reclast) 5 mg injection for the treatment of Paget's disease of bone.

2.2 Currently Available Treatment for Indications

Drug products currently approved for the treatment of Paget's disease of bone include salmon calcitonin injection (Miacalcin), the injectable bisphosphonate pamidronate disodium (Aredia) and the oral bisphosphonates alendronate sodium (Fosamax), etidronate disodium (Didronel and generic Etidronate), risedronate sodium (Actonel), and tiludronate sodium (Skelid).

2.3 Availability of Proposed Active Ingredient in the United States

Zoledronic acid 4 mg injection is currently approved (4 mg) for the treatment of hypercalcemia of malignancy and for the treatment of patients with multiple myeloma and treatment of patients with documented bone metastases from solid tumors, in conjunction with standard anti-neoplastic therapy. Zoledronic acid 5 mg injection is currently not approved for any indication.

2.4 Important Issues With Pharmacologically Related Products

Zoledronic acid injection (Zometa) has been associated with renal toxicity. In clinical trials, the risk of deterioration in renal function was significantly increased when zoledronic acid was infused over 5 minutes compared with the same dose infused over 15 minutes. In addition, the risk of deteriorating renal function was significantly increased with the 8 mg dose, regardless of the 15 minute infusion time.

Other adverse events occurring with bisphosphonate therapy include osteonecrosis of the jaw, eye inflammation, and musculoskeletal pain. In addition, gastrointestinal adverse events occur with oral bisphosphonate therapy. Safety concerns that appear more prominent with intravenous bisphosphonates include acute phase reactions, hypocalcemia and worsening of renal function. Other concerns that have emerged with postmarketing data include the occurrence of eye inflammation, bone pain and osteonecrosis of the jaw. Class labeling for bisphosphonates regarding the use of these drugs in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug has recently been implemented. Bisphosphonates are used in the prevention and treatment of postmenopausal and corticosteroid-induced osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, and bony metastases.

2.5 Presubmission Regulatory Activity

Appropriate trial designs for the Phase III pivotal trials were discussed at length with the Sponsor. It was agreed that two multinational studies of identical design would be conducted with each study powered to demonstrate that zoledronic acid was non-inferior to the risedronate

sodium regimen approved for the treatment of Paget's disease. It was also agreed that in the event the non-inferiority was demonstrated in the individual studies, data from both studies would be pooled and a test of statistical superiority of zoledronic acid to risedronate would be performed.

2.6 Other Relevant Background Information

The marketing application for zoledronic acid 5mg injection for the treatment of Paget's disease of bone was initially submitted September 24, 2004. Although the submitted trials demonstrated adequate evidence of efficacy, there was insufficient evidence to support the safety of the proposed dosing regimen, particularly with regard to the risk of hypocalcemia and hypophosphatemia. An approvable letter was issued on March 18, 2005. The letter stated:

"In analyses of pooled data from the pivotal studies 2304 and 2305, 21% of the patients who received zoledronic acid, compared with 3% who received risedronate, had serum calcium levels < 2.1 mmol/L at Day 10. Seven patients in the zoledronic acid group and one in the risedronate group had markedly decreased serum calcium levels (i.e., < 1.90 mmol/L) at Day 10. Eighteen percent of the zoledronic acid patients and 1.3% of the risedronate subjects had serum phosphorus levels < 0.71 mmol/L at Day 10.

You have suggested that because no measurements of serum calcium or phosphorus were obtained at Day 29 in the zoledronic acid trials, it is likely that the nadirs for calcium and phosphorus in the risedronate-treated patients were missed, and that there was, therefore, under-reporting of hypocalcemia and hypophosphatemia in these groups. While this may have been the case, data from trial RPD-001694, which served as the basis of approval for the 30 mg regimen of risedronate for Paget's disease, directs an alternative analysis, which we believe is telling.

In the risedronate study RPD-001694, the nadirs for serum calcium and phosphorus occurred between Days 30 to 60. It is therefore reasonable to assume that the nadirs for calcium and phosphorus in risedronate-treated subjects in your pivotal trials could be approximated by measurements at the Day 63 time point. An examination of the Day 63 data from your trials indicates that only 4.8% of the risedronate-treated patients had serum calcium levels < 2.1 mmol/L and none of the patients had serum phosphorus levels < 0.71 mmol/L.

When one then compares the rates of low serum calcium and phosphorus levels at the presumed nadirs for zoledronic acid (Day 10) and risedronate (Day 63), the overall risk of hypocalcemia and hypophosphatemia in Paget's patients is apparently much greater following treatment with zoledronic acid.

You have also pointed out that hypocalcemia was common in the studies used to support regulatory approval of alendronate for the treatment of Paget's disease. You state that 19% of the subjects treated with 40 mg daily alendronate had serum calcium levels < 2.125 mmol/L at one month after initiation of dosing, the presumed nadir for calcium. In addition, you report that one alendronate-treated subject (1.5%) developed a serum calcium value < 2.0 mmol/L.

Although comparisons of data from different studies are by definition unreliable, when one applies to your data the cutoffs used to define hypocalcemia in the alendronate trials as noted in the preceding paragraph, 32% of the zoledronic acid-treated subjects had serum calcium levels < 2.1 mmol/L, and 8% developed values < 2.0 mmol/L at Day 10. These are notably larger percentages than the 19% and 1.5% observed at the presumed nadir following treatment with alendronate.

In sum, we believe that the available data indicate that the risk for hypocalcemia and hypophosphatemia is substantially greater following treatment with a single 5-mg intravenous dose of zoledronic acid than with 30 mg daily risedronate for 2 months.

We do recognize that the vast majority of patients who developed low levels of serum calcium or phosphorus following treatment with zoledronic acid were apparently asymptomatic and experienced spontaneous normalization of these laboratory parameters. Nonetheless, the fact that such a large percentage of the patients who received zoledronic acid developed hypocalcemia and/or hypophosphatemia raises serious concerns regarding the safety of the 5 mg dose of the drug intended for use in a heterogeneous population of patients with Paget's disease, many of whom will have additional risk factors for hypocalcemia including vitamin D deficiency and concomitant use of drugs such as loop diuretics.

In response to our concerns regarding the safety of the 5 mg dose of zoledronic acid, you have proposed, among other things, to include in the product labeling "stronger, more specific recommendations for calcium and vitamin D supplementation." Specifically, you propose to include a recommendation that patients

1500 mg a day of supplemental calcium

We agree, based on the mechanisms responsible for zoledronic acid-induced hypocalcemia and hypophosphatemia, that supplemental calcium and vitamin D would be expected to attenuate the risk for developing low serum calcium and phosphorus levels following administration of zoledronic acid. However, because you do not have information regarding the amounts of supplemental calcium and vitamin D each patient actually took during your pivotal trials, it is not possible to characterize to what extent the rates of hypocalcemia and hypophosphatemia observed were due to noncompliance with the supplements, inadequate doses of the supplements, or to the greater antiresorptive potency of zoledronic acid compared with risedronate. In turn, we believe it is not possible to predict accurately what effect a 1500 mg dose of calcium, consistently taken, would have on mitigating hypocalcemia in high-risk patients.

Thus, while you have demonstrated that zoledronic acid is more effective than risedronate in lowering serum alkaline phosphatase levels in patients with Paget's disease, we do not believe that you have submitted sufficient information to support the safety of zoledronic acid 5 mg when used in the broad population of patients with Paget's disease.

Before the 5 mg dose of zoledronic acid can be approved for the treatment of Paget's disease, you must provide adequate evidence that administration of supplemental calcium

and/or vitamin D to patients treated with zoledronic acid satisfactorily attenuates the risk for hypocalcemia and hypophosphatemia.”

Novartis submitted a complete response to the approvable letter on August 24, 2005. In their response, the Sponsor provided further, detailed information on the amount of supplemental calcium and vitamin D patients took during the two Paget's trials. These data were obtained from questionnaires filled out by investigative-site personnel after the trials were completed. Novartis states that only information from source documents was used to complete the questionnaires. Data on calcium and vitamin D supplementation were obtained from 98% of the patients. Upon review, the data suggested that intake of at least 1000 mg per day of supplemental calcium and/or 800 IU per day of supplemental vitamin D reduces the risk for developing hypocalcemia in Paget's disease patients treated with a 5 mg intravenous zoledronic acid. It was felt that the risk of hypocalcemia and the need for sufficient calcium and vitamin D intake could be addressed with adequate product labeling. However, in a submission dated 24 January 2006, Novartis provided the Division with interim safety data from the nearly-completed 3-year osteoporosis fracture trial 2301 which randomized approximately 8000 postmenopausal women to treatment with once-yearly 5-mg zoledronic acid or placebo. There was a statistically significant increase in the incidence of cardiac arrhythmias in the zoledronic acid group compared with the placebo group (5.7% vs. 4.1%; nominal p=0.0006). The arrhythmias reported included atrial fibrillation, 1st degree AV block, SV extrasystoles, SV tachycardia, tachycardia, and sick sinus syndrome. Serious arrhythmias were reported in 2.2% of zoledronic acid vs. 1.3% of placebo-treated patients (nominal p=0.001). The overall rates of death were 2.8% vs. 2.4% in the active compared with the placebo treatment groups. An increase in serious ophthalmic adverse events was also reported. The data were to be adjudicated by the study's Data Safety Monitoring Board by mid-March 2006.

Therefore, it was felt that the adjudicated safety data should be reviewed and factored into zoledronic acid's risk-benefit profile before a final decision was made regarding approval of zoledronic acid 5mg for the treatment of Paget's disease of bone. An approvable letter was issued on February 22, 2006, which stated:

While you have provided evidence to support the efficacy of a single 5 mg infusion of zoledronic acid, and evidence that 5 mg per day of supplemental calcium and 800 IU per day of supplemental vitamin D attenuate the risk for hypocalcemia, interim data from study CZOL446H2301 raise the possibility that zoledronic acid may increase the risk for cardiovascular mortality, cardiac arrhythmias, and serious ophthalmic disorders.

Before this application may be approved, you must submit adjudicated cardiovascular mortality, cardiac arrhythmia, and ophthalmic data from study CZOL446H2301. All conclusions and recommendations made by the Data Safety Monitoring Board overseeing study CZOL446H2301 in reference to the safety of zoledronic acid should be submitted as well.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

From a CMC perspective, this NDA can be approved with recommended labeling changes. Please see Dr. Lewis's review of the initial NDA submission and Dr. Tran's review of this resubmission.

3.2 Animal Pharmacology/Toxicology

From a Pharmacology/Toxicology perspective, this NDA can be approved with recommended labeling changes. Please refer to Dr. Kuijpers's review of the initial NDA submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

No new clinical studies in the treatment of Paget's disease of bone have been conducted. The new clinical data submitted to support the Paget's indication include studies conducted for the treatment of postmenopausal osteoporosis indication. The pivotal trial supporting the osteoporosis indication is study CZOL446H2301 (2301). Study 2301 is ongoing and data presented is up to 6 Aug 2005, with additional data for ocular events, deaths and cardiovascular events up to 31 March 2006. Partially unblinded data from the ongoing recurrent fracture trial, study CZOL446L2310 (2310) is also included. Other completed supportive studies provided are CZOL446H2313 (2313), CZOL446H2315 (2315), and CZOL446H2407. Studies 2313 and 2315 compared zoledronic acid and weekly alendronate in postmenopausal women with low bone mass. Study 2407 evaluated the use of acetaminophen or ibuprofen to ameliorate the acute phase reaction-like symptoms that can occur with intravenous zoledronic acid use.

4.2 Tables of Clinical Studies

Intravenous Zoledronic Acid Studies used to Support the Paget's Disease Indication						
		N	Age years	Population	Study Duration	Primary Endpoint
Previously Submitted and Reviewed Clinical Studies in Paget's Disease Subjects						
2304 P3, R, DB	Zol iv 5mg , 1 dose Ris po 30 mg/d x 60d	172	42 - 94	men and women with confirmed Paget's disease	6 month	therapeutic response
2305 P3, R, DB	Zol iv 5mg , 1 dose Ris po 30 mg/d x 60d	185	34 - 92	men and women with confirmed Paget's disease	6 month	therapeutic response
PMO Trials Submitted in Support of the Paget's Disease Indication						
2301 P3, R, PC	Zol iv 5mg q12mo placebo iv q 12mo	7765	65 - 89	postmenopausal women with osteoporosis	36 month	fracture rate BMD

Intravenous Zoledronic Acid Studies used to Support the Paget's Disease Indication						
		N	Age years	Population	Study Duration	Primary Endpoint
2310 P3, R, PC	Zol iv 5mg q12mo placebo iv q 12mo	2126	> 50	men and women with hip fracture	60 month	fracture rate BMD
2313 R,AC, DD	Zol iv 5mg Alen 70mg q week	220	> 45	women with low bone mass or OP	12 month	BMD noninferiority
2315 R,AC, DD	Zol iv 5mg Alen 70mg q week	120	> 45	women with low bone mass or OP	24 week	bone turnover markers
2407 R	Zol iv 5mg or placebo iv AND acetaminophen or ibuprofen or placebo	455	45 - 75	postmenopausal women, bisphosphonate naïve, with low bone mass or OP	6 month	temperature safety BMD

4.3 Review Strategy

This review focuses on the safety data from Study 2301 with emphasis on the specific adverse events noted in the Approvable letters.

4.4 Data Quality and Integrity

The Division of Scientific Investigations has previously inspected clinical sites for the Paget's disease trials and no major violations were found. Inspections of clinical sites for the osteoporosis indication have been requested for that pending new drug application.

4.5 Compliance with Good Clinical Practices

All trials discussed appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

4.6 Financial Disclosures

Financial disclosure data for the Paget's disease trials has been reviewed previously by Dr. Colman.

5 CLINICAL PHARMACOLOGY

Please see Dr. Suarez-Sharp's review for complete details.

A key clinical pharmacology issue is the renal toxicity of the drug which appears to be correlated with zoledronic acid AUC. Dr. Suarez-Sharp's conclusions and recommendations were that the

efficacy and safety of the proposed single 5 mg dose of zoledronic acid infused over 15 minutes are not supported by the dose-response studies conducted in patients with Paget's disease of bone (doses tested ranged from 50 to 400 mcg). Therefore, the renal safety of a single dose of 5 mg zoledronic acid should be determined by the medical reviewer based on the safety data reported from the clinical trials. A dose adjustment in patients with moderate renal impairment is suggested for labeling, contrary to the sponsor's recommendation. These conclusions are based on the available data and findings from zoledronic acid use in the oncology population. No new pharmacokinetic data has been submitted for the non-oncology populations.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Treatment of Paget's Disease of Bone

No new efficacy data has been submitted. Data presented here are summarized from Drs. Colman's and Sahlroot's review of the original NDA submission.

Two pivotal trials were conducted to support the efficacy and safety of 5 mg intravenous zoledronic acid in Paget's disease. Studies CZOL446K2304 (2304) and CZOL446K2305 (2305) were identical multinational, randomized, double-blind, active-controlled, 6-month non-inferiority trials. The active comparator was 30 mg oral risedronate daily for 60 days. The study population consisted of men and women with confirmed radiographic evidence of Paget's disease and a serum alkaline phosphatase level at least two times the upper limit of the normal reference range. The primary endpoint was therapeutic response, defined as (1) a reduction of at least 75% from baseline in serum alkaline phosphatase excess (difference between measured level and midpoint of the normal range) or (2) normalization of serum alkaline phosphatase. As outlined in the table below, a significantly greater proportion of Zometa patients experienced therapeutic response than did patients receiving the active control, risedronate ($p < 0.001$).

Table 1. Therapeutic response (6 months)

	Aclastia	Risedronate	Trt difference (95% CI, p-value) ¹
<u>Trial 2304</u> No. (%) patients with therapeutic response	85/88 97%	60/82 73%	24% (12%, 35%) p<.0001
<u>Trial 2305</u> No. (%) patients with therapeutic response	84/88 95%	67/89 75%	20% (9%, 31%) p=.0002
<u>Pooled studies</u> No. (%) patients with therapeutic response	169/176 96%	127/171 74%	22% (14%, 30%) p<.0001

¹ CI based on Fleiss' normal approximation to the binomial. P-value from Fisher's Exact test.

Updated efficacy data for an extended observation period of the two Paget's disease trials K2304 and K2305, to the cut-off date of October 21, 2005 were outlined. Overall, 152 zoledronic acid-

treated subjects and 115 risedronate-treated subjects provide the long-term efficacy data, with a minimum of 2 years exposure. Long term efficacy variables include loss of therapeutic response (the occurrence of a SAP level that no longer meets the criteria of a therapeutic response, defined as less than 75% reduction in SAP excess and/or SAP above the upper limit of the normal range); time to first partial disease relapse (an increase in SAP of at least 50% from the SAP measurement at Month 6 and at least 1.25 times the upper normal limit), time to first disease relapse (the occurrence on an SAP level within 20% of the baseline SAP value).

Overall, 57/115 risedronate-treated subjects and 3/152 zoledronic acid-treated subjects exhibited a loss of therapeutic response, 49 risedronate-treated subjects and three zoledronic acid-treated subjects had a partial disease relapse and nine risedronate-treated subjects and no zoledronic acid-treated subjects had a disease relapse.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

A complete review of the studies 2304 and 2305 can be found in Dr. Colman's initial medical review dated March 18, 2005. A complete review of the Sponsor's complete response to the initial approvable letter can be found in Dr. Colman's medical review dated February 21, 2006. This review focuses on the Sponsor's complete response to the second approvable letter. In addition to the general overview of safety data from Study 2301, the Sponsor has provided in-depth analyses of the cardiovascular adverse events, ocular adverse events, delayed fracture healing and avascular necrosis adverse events, maxillofacial adverse events, hypocalcemia adverse events, and renal effects of zoledronic acid. Data presented for study 2301 is up to 6 Aug 2005. Additional data is provided for ocular, deaths and cardiovascular events up to 31 March 2006.

7.1.1 Deaths

As reported up to the cut-off date of August 6, 2005, a total of 200 (2.6%) subjects (93 (2.4%) in the placebo group and 107 (2.8%) in the zoledronic acid group), died during the conduct of Study 2301. At the March 31, 2006 cut-off date, 238 (3%) subjects, 109 (2.8%) in the placebo group and 129 (3.3%) in the zoledronic acid group, had died. At both cut-off dates, the main system/organ/class (SOC) causes of death were cardiac disorders, neoplasms, and nervous system disorders. Deaths due to cardiac disorders and nervous system disorders are discussed in great depth in following section.

Study 2301: Deaths by System Organ Class				
Study Cut-Off Date	August 6, 2005		March 31, 2006	
	placebo	zoledronate	placebo	zoledronate
N	3852	3862	3852	3862
Body System Organ Class				
All, n (%)	93 (2.4)	107 (2.8)	109 (2.8)	129 (3.3)
Cardiovascular System	27 (0.7)	33 (0.8)	31 (0.8)	39 (1.0)
Myocardial infarction*	7 (0.2)	13 (0.3)	8 (0.2)	15 (0.4)
Gastrointestinal	4 (0.1)	4 (0.1)	4 (0.1)	4 (0.1)

Study 2301: Deaths by System Organ Class				
General Disorders	11 (0.3)	7 (0.2)	11 (0.3)	11 (0.3)
Hepatobiliary	1 (0.0)	0	1 (0.0)	0
Infections	9 (0.2)	12 (0.3)	11 (0.3)	14 (0.4)
Injury, poisoning	3 (0.1)	1 (0.0)	3 (0.1)	1 (0.0)
Metabolic and Nutritional System	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
Musculoskeletal System	0	1 (0.0)	0	1 (0.0)
Neoplasms	17 (0.4)	18 (0.5)	23 (0.6)	23 (0.6)
Nervous System	9 (0.2)	19 (0.5)	12 (0.3)	22 (0.6)
Cerebrovascular accident**	4 (0.1)	14 (0.3)	8 (0.2)	16 (0.4)
Psychiatric disorders	0	1 (0.0)	0	1 (0.0)
Renal and urinary disorders	0	1 (0.0)	0	2 (0.0)
Respiratory System	8 (0.2)	8 (0.2)	9 (0.2)	9 (0.2)
Vascular System	3 (0.1)	1 (0.0)	3 (0.1)	1 (0.0)
*includes myocardial infarction and acute myocardial infarction				
**includes cerebrovascular accident, ischemic stroke, cerebral infarction and hemorrhagic stroke				

7.1.2 Other Serious Adverse Events

As noted in the table below, the incidence of serious adverse events (including death) was similar between the two treatment groups. The SOC categories where there were higher numbers of events in the zoledronic acid group were cardiac disorders (221 (5.7%) subjects in the zoledronic acid group vs. 191 (5.0%) subjects in the placebo group); and infections and infestations (189 (4.9%) subjects in the zoledronic acid group vs. 178 (4.6%) subjects in the placebo group).

Study 2301: Serious Adverse Events by System Organ Class				
Study Cut-Off Date	August 6, 2005		March 31, 2006	
	placebo	zoledronate	placebo	zoledronate
N	3852	3862	3852	3862
Body System Organ Class				
All, n (%)	1020 (26.5)	999 (25.9)	1151 (29.9)	1114 (28.5)
Blood and Lymphatic System	20 (0.5)	31 (0.8)	22 (0.6)	34 (0.9)
Anemia	11 (0.3)	22 (0.6)	12 (0.3)	23 (0.6)
Cardiovascular System	168 (4.4)	195 (5.0)	191 (5.0)	221 (5.7)
Atrial fibrillation	16 (0.4)	44 (1.1)	17 (0.4)	48 (1.2)
Myocardial infarction*	43 (1.1)	42 (1.1)	47 (1.2)	48 (1.2)
Congenital, Familial and Genetic disorders	3 (0.1)	3 (0.1)	4 (0.1)	7 (0.2)
Ear and labyrinth disorders	12 (0.3)	16 (0.4)	17 (0.4)	19 (0.5)
Endocrine System	10 (0.3)	6 (0.2)	10 (0.3)	8 (0.2)
Eye disorders	31 (0.8)	38 (1.0)	42 (1.1)	42 (1.1)
Cataract	14 (0.4)	22 (0.6)	21 (0.6)	24 (0.6)
Gastrointestinal	122 (3.2)	136 (3.5)	150 (3.9)	153 (4.0)
General Disorders	61 (1.6)	59 (1.5)	67 (1.7)	71 (1.8)
Hepatobiliary	38 (1.0)	30 (0.8)	44 (1.1)	33 (0.8)
Immune system disorders	2 (0.1)	5 (0.1)	2 (0.1)	5 (0.1)
Infections	162 (4.2)	163 (4.2)	178 (4.6)	189 (4.9)
Injury, poisoning **	252 (6.5)	161 (4.2)	298 (7.7)	196 (5.1)
Investigations	14 (0.4)	15 (0.4)	14 (0.4)	16 (0.4)

Study 2301: Serious Adverse Events by System Organ Class				
Metabolic and Nutrition disorders	30 (0.8)	37 (1.0)	33 (0.9)	42 (1.1)
Musculoskeletal System	129 (3.4)	122 (3.2)	150 (3.9)	139 (3.6)
Neoplasms	146 (3.8)	148 (3.8)	164 (4.3)	175 (4.5)
Nervous System	140 (3.6)	143 (3.7)	169 (4.4)	162 (4.2)
Cerebrovascular accident***	37 (1.0)	51 (1.3)	44 (1.1)	55 (1.4)
Pregnancy, puerperium, perinatal conditions	0	1 (0.03)	0	1 (0.03)
Psychiatric disorders	21 (0.6)	24 (0.6)	24 (0.6)	25 (0.6)
Renal and urinary disorders	41 (1.1)	36 (0.9)	45 (1.2)	47 (1.2)
Reproductive and breast disorders	18 (0.5)	19 (0.5)	18 (0.5)	22 (0.6)
Respiratory System	80 (2.1)	78 (2.0)	95 (2.5)	94 (2.4)
Skin and subcutaneous disorders	9 (0.2)	7 (0.2)	10 (0.3)	8 (0.2)
Social circumstances	0	1 (0.03)	0	1 (0.03)
Surgical and medical procedures	8 (0.2)	8 (0.2)	7 (0.2)	10 (0.3)
Uncoded	1 (0.03)	0	1 (0.03)	0
Vascular System	59 (1.51)	60 (1.6)	64 (1.7)	68 (1.8)
*includes terms myocardial infraction and acute myocardial infarction				
**includes fractures				
***includes cerebrovascular accident, ischemic stroke, cerebral infarction and hemorrhagic stroke				

Comment: It is highly unusual to see an adverse event listed under SOC “pregnancy, puerperium, perinatal conditions” in a trial where the enrolled population is postmenopausal women. The Sponsor has clarified that there were no pregnancies during this trial and this event of “perineal hematoma” is incorrectly classified.

7.1.3 Dropouts and Other Significant Adverse Events

Up to the cut-off date of August 6, 2005, a total of 54 (1.4%) in the placebo group and 62 (1.6%) in the zoledronic acid group withdrew from study participation due to adverse events. At the 3/31/06 cut-off date, 73 (1.9%) placebo-treated subjects and 78 (2.0%) zoledronic acid-treated subjects withdrew from study participation due to an adverse event.

As reported up to the cut-off date of August 6, 2005, a total of 181 (4.7%) subjects in the placebo group and 195 (5.0%) subjects in the zoledronic acid group discontinued study drug due to an adverse event. At the 3/31/06 cut-off date, 196 (5.1%) placebo-treated subjects and 210 (5.4%) zoledronic acid-treated subjects had discontinued study drug due to an adverse event.

7.1.4 Common Adverse Events

As outlined in the table below, there were similar rates of adverse event reports between the two treatment groups. General disorders and administration site conditions was the SOC with a twofold or greater incidence of adverse events for zoledronic acid (41% for the zoledronic acid group and 19% for the placebo group). Symptoms of acute phase reaction were included in this SOC and predominantly account for the imbalance seen. The most common adverse events in the zoledronic acid group occurring at twofold or greater frequency relative to placebo were pyrexia (689 (18%) subjects in the zoledronic acid group vs. 173 (4%) subjects in the placebo group), myalgia (448 (12%) subjects in the zoledronic acid group vs. 141 (4%) subjects in the

placebo group), influenza like illness (3429 (9%) subjects in the zoledronic acid group vs. 103 (3%) subjects in the placebo group), bone pain (216 (6%) subjects in the zoledronic acid group vs. 83 (2%) subjects in the placebo group), and chills (206 (5%) subjects in the zoledronic acid group vs. 38 (1%) subjects in the placebo group),

Study 2301: Adverse Events by Body System Organ Class		
Body System Organ Class	zoledronate	placebo
N	3862	3852
All, n (%)	3686 (95.4)	3611 (93.7)
Blood and Lymphatic System	233 (6.0)	213 (5.5)
Cardiovascular System	536 (13.9)	477 (12.4)
Congenital, Familial and Genetic disorders	30 (0.8)	28 (0.7)
Ear and labyrinth disorders	262 (6.8)	261 (6.8)
Endocrine System	100 (2.6)	137 (3.6)
Eye disorders	521 (13.5)	490 (12.7)
Gastrointestinal	1473 (38.1)	1356 (35.2)
General Disorders	1666 (43.1)	835 (21.7)
Hepatobiliary	111 (2.9)	142 (3.7)
Immune system disorders	80 (2.1)	71 (1.8)
Infections	1952 (50.5)	1917 (49.8)
Injury, poisoning*	1046 (27.1)	1237 (32.1)
Investigations	435 (11.3)	356 (9.2)
Metabolic and Nutrition disorders	575 (14.9)	555 (14.4)
Musculoskeletal System	2485 (64.3)	2291 (59.5)
Neoplasms	287 (7.4)	268 (7.0)
Nervous System	1253 (32.4)	1077 (28.0)
Pregnancy, puerperium, perinatal conditions	1 (0.03)	0
Psychiatric disorders	452 (11.7)	433 (11.2)
Renal and urinary disorders	383 (9.9)	336 (8.7)
Reproductive and breast disorders	153 (4.0)	149 (3.9)
Respiratory System	552 (14.3)	588 (15.3)
Skin and subcutaneous disorders	405 (10.5)	426 (11.1)
Social circumstances	7 (0.2)	2 (0.0)
Surgical and medical procedures	61 (1.6)	53 (1.4)
Uncoded	7 (0.2)	4 (0.1)
Vascular System	755 (19.6)	741 (19.2)
*includes fractures		

7.1.5 Specific Adverse Events Addressed in the Sponsor's Response to the Approvable Letter

In the approvable letter dated February 22, 2006, the Division requested that the Sponsor submit the adjudicated cardiovascular mortality, cardiac arrhythmia, and ophthalmic data from study 2301, as well as all conclusions and recommendations made by the Data Safety Monitoring Board. In addition, the Sponsor provided data from the ongoing trial CZOL446H2310 (2310), a randomized, double-blind, placebo-controlled trial assessing the efficacy of zoledronic acid in preventing subsequent osteoporotic fractures after hip fracture. This trial enrolled 2126 subjects

(1061 in the placebo group and 1065 in the zoledronic acid group). The external expert reviewer remained blinded to study drug designation. The data presented are from an interim data analysis with a cutoff date of July 5, 2006.

7.1.5.1 Cardiovascular mortality

Overall, in Study 2301, 238 (3%) subjects, (109 (2.8%) in the placebo group and 129 (3.3%) in the zoledronic acid group), had died during the study up to the cut-off date of March 31, 2006. Death attributed to cardiac disorders occurred in 31 subjects in the placebo group and 39 subjects in the zoledronic acid group. As outlined in the table below, cardio-respiratory arrest and acute myocardial infarction accounted for the largest disparity between treatment groups. Death attributed to nervous system disorders occurred in 12 subjects in the placebo group and 22 subjects in the zoledronic acid group. The disparity between groups in the number of deaths due to cerebrovascular accident accounted for the difference seen.

In Study 2310, up to the cut-off date of July 5, 2006, a total of 191 (9.0%) subjects had died (105 (9.9%) in the placebo group and 86 (8.1%) in the zoledronic acid group). Death attributed to cardiac disorders occurred in 34 subjects in the placebo group and 29 subjects in the zoledronic acid group. Death attributed to nervous system disorders occurred in six subjects in the placebo group and four subjects in the zoledronic acid group.

No deaths occurred in Studies 2313, 2315, and 2407.

Deaths attributed to Cardiac and Nervous System Disorders, Unadjudicated				
	Study 2301		Study 2310	
	Zoledronate	Placebo	Zoledronate	Placebo
N	3862	3852	1065	1061
All deaths	129 (3.3)	109 (2.8)	86 (8.1)	105 (9.9)
Cardiac disorders, all	39 (1.0)	31 (0.8)	29 (2.7)	34 (3.2)
Cardio-respiratory arrest	8 (0.2)	2 (0.0)	4 (0.4)	5 (0.5)
Acute myocardial infarction	7 (0.2)	1 (0.03)	2 (0.2)	2 (0.2)
Myocardial infarction	7 (0.2)	7 (0.2)	3 (0.3)	4 (0.4)
Cardiac failure	6 (0.2)	7 (0.2)	4 (0.4)	4 (0.4)
Cardiac arrest	4 (0.1)	7 (0.2)	10 (0.9)	10 (0.9)
Myocardial ischemia	3 (0.1)	0	0	0
Cardiac failure congestive	2 (0.0)	0	3 (0.3)	4 (0.4)
Angina unstable	1 (0.03)	0	0	0
Arrhythmia	1 (0.03)	0	0	1 (0.1)
Atrioventricular block complete	0	1 (0.03)	0	0
Cardiac failure chronic	0	1 (0.03)	0	0
Cardiogenic shock	0	1 (0.03)	0	1 (0.1)
Cardiomyopathy	0	1 (0.03)	0	0
Coronary artery disease	0	1 (0.03)	1 (0.1)	0
Palpitations	0	1 (0.03)	0	0
Pericardial hemorrhage	0	1 (0.03)	0	0
Cardiopulmonary failure	0	0	1 (0.1)	1 (0.1)

Deaths attributed to Cardiac and Nervous System Disorders, Unadjudicated				
	Study 2301		Study 2310	
	Zoledronate	Placebo	Zoledronate	Placebo
N	3862	3852	1065	1061
Ventricular fibrillation	0	0	1 (0.1)	0
Cardiac failure, acute	0	0	0	1 (0.1)
Cardiovascular disorder	0	0	0	1 (0.1)
Sudden cardiac death*	0	0	1 (0.1)	0
Cardiac death*	1 (0.0)	1 (0.0)	0	1 (0.1)
Nervous system disorders, all	22 (0.6)	12 (0.3)	4 (0.4)	6 (0.6)
Cerebrovascular accident	13 (0.3)	5 (0.1)	3 (0.3)	1 (0.1)
Hemorrhage intracranial	2 (0.0)	1 (0.0)	0	1 (0.1)
Ischemic stroke	2 (0.0)	1 (0.0)	0	0
Cerebral hemorrhage	1 (0.0)	1 (0.0)	0	1 (0.1)
Cerebral infarction	1 (0.0)	0	0	1 (0.1)
Parkinson's disease	1 (0.0)	1 (0.0)	0	2 (0.2)
Spinal epidural hemorrhage	1 (0.0)	0	0	0
Subarachnoid hemorrhage	1 (0.0)	0	0	0
Cerebrovascular disorder	0	1 (0.0)	0	0
Hemorrhagic stroke	0	2 (0.0)	1 (0.1)	0

*appear under SOC General Disorders

7.1.5.2 Cardiac arrhythmia

The expert panel predefined the criteria for identification of potential cases and the following MedDRA terms met the predefined criteria: Adams-Stokes syndrome, arrhythmia, arrhythmia supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block, atrioventricular block complete, atrioventricular block second degree, bradyarrhythmia, bradycardia, cardiac arrest, cardiac fibrillation, cardiac flutter, circulatory collapse, loss of consciousness, paroxysmal arrhythmia, sick sinus syndrome, sinoatrial block, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, syncope, tachyarrhythmia, tachycardia, tachycardia paroxysmal, ventricular arrhythmia, and ventricular tachycardia.

In study 2301, cardiac arrhythmias were reported as serious adverse events in 109 (2.8%) of subjects in the zoledronic acid group and 77 (2.0%) of subjects in the placebo group. Atrial fibrillation accounted for the imbalance and was reported at a much higher rate in subjects treated with zoledronic acid: 48 (1.2%) of subjects in the zoledronic acid group and 17 (0.4%) of subjects in the placebo group. There was no difference in other arrhythmias between groups. The expert adjudication panel confirmed the atrial fibrillation events for all but one placebo-treated subject: 48 (1.2%) of subjects in the zoledronic acid group and 16 (0.4%) of subjects in the placebo group. Of the subjects with confirmed atrial fibrillation, 35 (73%) of zoledronic acid-treated subjects and 14 (88%) placebo-treated subjects had underlying medical conditions that could contribute the event.

The timing of the events in relation to dose administration was investigated. The majority of the atrial fibrillation SAEs occurred more than 30 days after dosing. This would suggest that the occurrence of atrial fibrillation is not an acute event related to infusion of study drug.

Risk factors associated with the occurrence of atrial fibrillation were evaluated using a logistic regression model. As outlined in the table below, age and active tachyarrhythmia at randomization were the risk factors that characterized patients at greatest risk of an atrial fibrillation event. While treatment did have an odds ratio of 1.3, it was not statistically significant.

Study 2301: Risk factors Associated with Atrial fibrillation			
Factor	Estimate (SE)	Adjusted Odds-ratio	p-value
Treatment	0.2594 (0.1598)	1.296	0.1044
Stratum	-0.1884 (0.1843)	0.828	0.3068
Age	0.0572 (0.0142)	1.059	<0.0001
Active tachyarrhythmia at randomization	1.3214 (0.2060)	3.749	<0.0001
Active cardiomyopathy at randomization	0.7730 (0.3188)	2.166	0.0153

Additional information was evaluated from the ongoing study 2310. Cardiac serious adverse events were reported in 60 (5.6%) of subjects in the zoledronic acid group and 86 (8.1%) of subjects in the placebo group. Atrial fibrillation serious adverse events were reported in three (0.3%) of subjects in the zoledronic acid group and 12 (1.1%) of subjects in the placebo group.

As noted in the table below, in Study 2301 there was a higher incidence of atrial fibrillation adverse events in subjects treated with zoledronic acid compared to those treat with placebo (91 (2.4%) zoledronic acid, 70 (1.8%) placebo). In study 2310, the incidence of atrial fibrillation was slightly higher in the placebo group (17 (1.6%) zoledronic acid, 20 (1.9%) placebo)

Zoledronic Acid PMO studies: Cardiovascular Data, Unadjudicated				
	Study 2301		Study 2310	
	Zoledronate	Placebo	Zoledronate	Placebo
N	3862	3852	1065	1061
Adams-Stokes syndrome	0	1 (0.0)	-----	-----
Arrhythmia	53 (1.4)	37 (1.0)	4 (0.4)	8 (0.8)
Arrhythmia supraventricular	0	1 (0.0)	3 (0.3)	3 (0.3)
Atrial fibrillation	91 (2.4)	70 (1.8)	17 (1.6)	20 (1.9)
Atrial flutter	3 (0.1)	3 (0.1)	1 (0.1)	1 (0.1)
Atrial tachycardia	1 (0.0)	5 (0.1)	-----	-----
Atrioventricular block	4 (0.1)	4 (0.1)	1 (0.1)	1 (0.1)
Atrioventricular block complete	7 (0.2)	5 (0.1)	1 (0.1)	1 (0.1)
Atrioventricular block second degree	1 (0.0)	0	-----	-----
Bradycardia	3 (0.1)	2 (0.0)	-----	-----
Bradyarrhythmia	12 (0.3)	11 (0.3)	3 (0.3)	13 (1.2)
Cardiac arrest	-----	-----	9 (0.8)	12 (1.1)

Zoledronic Acid PMO studies: Cardiovascular Data, Unadjudicated				
	Study 2301		Study 2310	
	Zoledronate	Placebo	Zoledronate	Placebo
N	3862	3852	1065	1061
Cardiac fibrillation	4 (0.1)	0	0	1 (0.1)
Cardiac flutter	2 (0.0)	0	-----	-----
Paroxysmal arrhythmia	1 (0.0)	0	-----	-----
Sick sinus syndrome	11 (0.3)	5 (0.1)	-----	-----
Sinoatrial block	1 (0.0)	0	-----	-----
Sinus bradycardia	5 (0.1)	8 (0.2)	-----	-----
Sinus tachycardia	7 (0.2)	4 (0.1)	2 (0.2)	1 (0.1)
Supraventricular tachycardia	8 (0.2)	3 (0.1)	-----	-----
Tachyarrhythmia	3 (0.1)	3 (0.1)	-----	-----
Tachycardia	28 (0.7)	16 (0.4)	4 (0.4)	3 (0.3)
Tachycardia paroxysmal	4 (0.1)	1 (0.0)	-----	-----
Ventricular arrhythmia	0	2 (0.0)	1 (0.1)	0
Ventricular tachycardia	2 (0.0)	2 (0.1)	2 (0.2)	2 (0.2)

The Sponsor states that based on the data from the ECG substudy data, there appears to be an under-reporting of atrial fibrillation in study 2301. In the ECG substudy the incidence of atrial fibrillation was 6 (2.2%) subjects in the zoledronic acid group and 8 (2.5%) subjects in the placebo group, compared to the AE report rates of 2.5% in the zoledronic acid group and 1.8% in the placebo group. However, when data from study 2310 is included, the reporting rates for atrial fibrillation are consistent in the placebo groups – 1.8% in study 2301 and 1.9% in study 2310. There is a disparity between the two studies in the rate of atrial fibrillation in the zoledronic acid groups: 2.4% in study 2301 and 1.6% in study 2310.

7.1.5.3 Ocular adverse events

An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. Ocular adverse events were noted by the DSMB for Study 2301. In this study, 521 (13.5%) of subjects in the zoledronic acid group and 490 (12.7%) subjects in the placebo group reported an ocular adverse event. For the ongoing study 2310, 55 (5.2%) of subjects in the zoledronic acid group and 45 (4.2%) subjects in the placebo group reported an ocular adverse event. In Studies 2313 and 2315, 7 (3.8%) subjects in the zoledronic acid group and 8 (4.7%) subjects in the alendronate group reported eye adverse events. In Study 2407, none of the 481 subjects enrolled in the study reported an ocular adverse event.

The following MedDRA terms were identified for follow-up and expert review: blepharitis, eye irritation, lacrimation, increased photophobia, conjunctivitis, eye pain, ocular icterus, scleritis, diplopia, iridocyclitis, optic neuritis, uveitis, episcleritis, iritis, orbital edema, and vision blurred. None of the eye disorders reported in studies 2313, 2315, and 2407 matched the predefined search term events.

As outlined in the table below, conjunctivitis and uveitis were reported at a much higher rate in zoledronic acid-treated subjects. Following expert review, conjunctivitis was reported in 52

into one of four treatment arms: zoledronic acid 5 mg plus placebo (zol+plac); zoledronic acid 5 mg plus 1000 mg acetaminophen four hours after infusion (zol+apap), then 1000 mg every 6 hours for 3 days; zoledronic acid 5 mg plus ibuprofen 400 mg four hours after infusion, then 400 mg every 6 hours for 3 days (zol+ibu); or placebo plus placebo (plac+plac). The mean age of the study population was 60 years. A clinically significant increase in temperature (defined as an increase of at least 1 C to a value above 37.5 C in the three day period after study drug administration) was observed in 11% subjects in the plac+plac group 64% of subjects in the zol+plac group, 37% of subjects in the zol+apap group, and 37% of subjects in the zol+ibu group. Rescue medication was used by no subjects in the plac+plac group, 22% of subjects in the zol+plac group, 10% of subjects in the zol+apap group, and 10% of subjects in the zol+ibu group.

7.1.6.2 Musculoskeletal pain

An increased incidence of bony pain has been reported with bisphosphonate use. Overall in Study 2301, musculoskeletal symptoms occurred in 64% of zoledronic acid-treated subjects and 59% of placebo-treated subjects. Specifically, bone pain was reported by 216 (5.6%) of subjects in the zoledronic acid group and 83 (2.2%) subjects in the placebo group.

The Sponsor proposes to include language in the Precautions section of the product label regarding musculoskeletal pain symptoms.

7.1.6.3 Jaw osteonecrosis and maxillofacial adverse events

Zoledronic acid and other intravenous (and rarely, oral) bisphosphonates have been associated with osteonecrosis of the jaw (ONJ). To independently assess maxillofacial adverse events and to identify possible causal relationships, an adverse event review process was established for Study 2301. The review process has been conducted by a committee of dental specialists. The members of the committee remained blinded to study treatment throughout the review process.

The committee has defined osteonecrosis of the jaws as an area of exposed bone for longer than 6 weeks with delayed healing despite adequate medical therapy. The predefined criteria for identification of potential cases included fifty search terms. After review, one subject in the zoledronic acid group met the predefined criteria for ONJ and 2 subjects in the placebo group were classified as possible ONJ.

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The Sponsor proposes to include language in the Precautions section of the product label regarding jaw osteonecrosis.

7.1.7 Laboratory Findings

7.1.7.1 Calcium

Bisphosphonate use, most notably intravenous bisphosphonates, has been associated with hypocalcemia. Dr. Colman has extensively reviewed the hypocalcemia risk in the higher-risk Paget's disease population. Please refer to his reviews for that discussion.

The enrolled population for study 2301 is postmenopausal women with osteoporosis. This is considered a population at lower risk of hypocalcemia because of the lower rates of bone turnover compared to active Paget's disease. In study 2301, subjects with a baseline calcium level < 8.0 mg/dl or > 11.0 mg/dL were excluded from study entry. There were no specific inclusion or exclusion criteria related to vitamin D levels. Study participants were provided 1000 – 1500 mg calcium and 400 – 1200 IU vitamin D daily. The baseline mean serum calcium level was 9.6 mg/dL.

Overall, there were 11 (0.3%) subjects in the zoledronic acid group and 5 (0.1%) subjects in the placebo group who had an adverse event of hypocalcemia (defined as calcium < 7.5 mg/dL). There were no hypocalcemia serious adverse events reported and no subjects discontinued from the study due to a hypocalcemic event.

Calcium levels at the presumed nadir of 9-11 days post injection were evaluated in the renal safety substudy of study 2301. Following the first study drug dose, the incidence of serum calcium levels less than 8.3 mg/dL (lower limit of the reference range) was 49/2015 (2.3%) of subjects in the zoledronic acid group and 1/2491 (<0.1%) of subjects in the placebo group.

In the zoledronic acid group, the mean calcium level was 9.57 mg/dL at baseline; 9.60 mg/dL at Month 12; 9.64 mg/dL at Month 24; and 9.75 mg/dL at Month 36. In the placebo group, the mean calcium level was 9.57 mg/dL at baseline; 9.66 mg/dL at Month 12; 9.68 mg/dL at Month 24; and 9.80 mg/dL at Month 36.

The Sponsor proposes to include language in the Contraindications section of the product label regarding patients with preexisting risk factor for hypocalcemia and in the Precautions section of the product label regarding mineral metabolism.

7.1.7.2 Renal

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; this dose has been discontinued from clinical development. In study 2301, subjects with a baseline calculated creatinine clearance < 30 mL/min, urine dipstick protein \geq 2+, or an increase in serum creatinine > 0.5mg/dL between the two screening visits were excluded from the study.

As outlined in the table below, adverse events associated with renal toxicity were reported in 174 (4.5%) subjects in the zoledronic acid group and 151 (3.9%) subjects in the placebo group. Renal failure (including acute renal failure) was reported in 40 (1.0%) subjects in the zoledronic acid group and 29 (0.8%) subjects in the placebo group. Of the 40 zoledronic-acid subjects experiencing renal failure, there was no temporal relationship to dose infusion. Eighteen of the 40 zoledronic-acid treated subjects had resolution of their renal failure during the study. Renal impairment was reported in 34 (0.9%) subjects in the zoledronic acid group and 32 (0.8%) subjects in the placebo group. Increased blood creatinine was reported in 29 (0.8%) subjects in the zoledronic acid group and 10 (0.3%) subjects in the placebo group.

Study 2301: Renal Adverse Events		
	Zoledronate	Placebo
N	3862	3852
All	174 (4.5)	151 (3.9)
Creatinine renal clearance decreased	64 (1.7)	75 (2.0)
Renal impairment	34 (0.9)	32 (0.8)
Blood creatinine increased	29 (0.8)	10 (0.3)
Renal failure	28 (0.7)	23 (0.6)
Proteinuria	13 (0.3)	8 (0.2)
Renal failure acute	12 (0.3)	6 (0.2)
Azotemia	4 (0.1)	0
Nephritis	2 (0.5)	0
Glomerulonephritis	1 (0.0)	1 (0.0)
Glomerulonephritis acute	1 (0.0)	0
Glomerulonephritis membranoproliferative	1 (0.0)	0
Glomerulonephritis proliferative	1 (0.0)	0
Renal failure chronic	1 (0.0)	4 (0.1)
Scleroderma renal crisis	1 (0.0)	0
Acute prerenal failure	0	2 (0.0)
Nephrotic syndrome	0	1 (0.0)

Study 2301 included a renal substudy which closely evaluated the effects of zoledronic acid infusion on renal function. A total of 4708 subjects were enrolled in this substudy. Creatinine clearance at baseline was below 60 mL/min for 45% of the population. Overall, 31 (1.8%) subjects in the zoledronic acid group and 19 (0.8%) subjects in the placebo group exhibited an increase in serum creatinine > 0.5 mg/dL when measured 9 – 11 days post infusion. When evaluated based on baseline creatinine clearance, the largest imbalance was seen in subjects with a baseline creatinine clearance less than 35 ml/min (5/47 subjects in the zoledronic acid group and 2/65 subjects in the placebo group).

When evaluated for long-term changes in renal function at end of study, 88 (2.4%) subjects in the zoledronic acid group and 94 (2.6%) subjects in the placebo group developed a creatinine clearance change to < 30 ml/min; 25 (0.7%) subjects in the zoledronic acid group and 27 (0.7%) subjects in the placebo group exhibited an increase in serum creatinine > 0.5 mg/dL relative to baseline and 5 (0.1%) subjects in the zoledronic acid group and 11 (0.3%) subjects in the placebo group developed proteinuria (> 2+ protein on dipstick) at some time during the study.

The Sponsor proposes to include language in the Adverse Events section of the product label regarding renal dysfunction. This language should be moved to the Precautions section.

Comment: The clinical pharmacology reviewer recommends dose adjustment of Reclast based on creatinine clearance. This recommendation is based on the findings in the oncology patient population where dosing of zoledronic acid is more frequent and the patient population has multiple factors (concomitant medications, underlying disease process) contributing to the risk of renal toxicity. However, in this reviewer's opinion, the findings from the renal substudy in the postmenopausal patient population do not suggest that there is a need to recommend dose adjustment for the one time use of zoledronic acid in the Paget's disease population.

7.1.17 Postmarketing Experience

Zoledronic acid 5 mg for the treatment of non-oncology indications including Paget's disease of bone, is marketed in 34 countries. Zoledronic acid, marketed as Aclasta, was initially approved in the EU on April 15, 2005. The Sponsor has submitted a Periodic Safety Update Report for the period of April 15, 2005 to October 31, 2005. In the time period reported, estimated exposure with the marketed drug is 507 patient-years. One spontaneous case report was received. A 66 year old woman complained of dizziness, bone pain, joint pain, and muscle pain one day after receiving Aclasta.

In ongoing clinical trials, approximately 2922 patients received treatment with Aclasta. A total of five serious adverse events were reported: A 78-year old developed syncope and bradyarrhythmia requiring pacemaker insertion 9 months after her 3rd yearly injection of study drug. A 69-year old woman developed osteomyelitis of the alveolar socket 613 days after study drug administration. A 7-year old experienced pyrexia 2 days after study drug injection. A 15-year old developed hypocalcemia, severe vomiting and pyrexia 3 days after study drug injection. An 8-year old experience repeat fracture, and fracture malunion 422 days after receiving study drug.

The following information has been added to the European Union Summary of Product Characteristics (EU SmPC):

Special Warnings and Precautions:

- Caution is indicated when Aclasta is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration).

- Patients should be informed about symptoms of hypocalcaemia and receive adequate clinical monitoring during the period of risk.
- Specific recommendation given to Paget's patients to take a dose of calcium of at least 500 mg twice daily as opposed to "Paget's patients should receive adequate recommended daily allowance of calcium and vitamin D".

Undesirable effects:

Undesirable effects such as renal dysfunction, conjunctivitis and osteonecrosis of the jaw (ONJ) have been added to the EU SmPC since these side effects have been observed in patients treated with bisphosphonates, although no cases have been reported in the Paget's trials with Aclasta so far.

The following information has been added to the Canadian PI:

Warnings and Precautions

- It is recommended that patients with Paget's disease of bone have their serum calcium levels assessed before treatment with Aclasta (e.g. as part of their annual examination).
- Both renal dysfunction and ONJ have been reported as class label under "special warnings and precautions for use" and "adverse drug reactions" but have not been observed in the Paget's disease trials with Aclasta so far.

7.2 Adequacy of Patient Exposure and Safety Assessments

No new data regarding the safety of zoledronic acid use for treatment of Paget's disease of bone has been submitted. The primary source of safety information is Study 2301. This study was conducted in postmenopausal women. Overall, 7736 subjects were enrolled into this trial, 3861 received placebo and 3875 received zoledronic acid. The mean age of the population is 73 years and 79% of the population was Caucasian. Subjects received zoledronic acid 5 mg or placebo once yearly by 15 minute intravenous infusion. The secondary source of safety information is interim data from the ongoing study 2310. This study was also conducted in postmenopausal women. Overall, 2126 subjects were enrolled into this trial, 1061 received placebo and 1065 received zoledronic acid. The study remains blinded and demographic data is not available.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There are no new trials in Paget's disease. The data provided is from the postmenopausal osteoporosis trials.

Hypocalcemia was the predominant safety finding of concern in the Paget's disease population. The Sponsor addressed this concern in the previous resubmission package. As outlined by Dr. Colman, 21% of zoledronic acid-treated subjects, compared to 3% of risedronate-treated subjects developed serum calcium levels below 8.4 mg/dL at Day 10 following treatment. When evaluated based on the amount of calcium and vitamin D supplementation received, 50% of

zoledronic acid-treated subjects receiving less than 1000 mg a day in calcium supplements developed hypocalcemia at Day 10 and 35% of receiving less than 800 IU a day in vitamin D supplementation developed hypocalcemia at Day 10. One of the strongest predictors for development of hypocalcemia was baseline calcium level. Overall, 28% of subjects with a baseline calcium level less than 9.5 mg/dL developed hypocalcemia at Day 10, and 40% of subjects with a baseline calcium level less than 9.2 mg/dL developed hypocalcemia at Day 10. Baseline 25 hydroxyvitamin D level did not predict a low calcium level at Day 10.

Clinical safety issues raised by the large pivotal trial for the treatment of postmenopausal osteoporosis indication include an increased incidence of cardiovascular mortality, cardiac arrhythmias and ophthalmic adverse events. Death due to cardiac disease occurred in 1.0% of the zoledronic acid group and 0.8% of the placebo group in study 2301. Cardio-respiratory arrest and acute myocardial infarction accounted for the largest disparity between treatment groups. Death attributed to nervous system disorders occurred in 0.6% of the zoledronic acid group and 0.3% of the placebo group. The main differences occurred in the number of deaths due to cerebrovascular accidents (0.3% of the zoledronic acid group and 0.1% of the placebo group). Importantly, this same pattern is not seen in the interim data of study 2310. In fact, the opposite pattern is observed: death attributed to cardiac disorders occurred in 2.7% of the zoledronic acid group and 3.2% of the placebo group. Death attributed to nervous system disorders occurred in 0.4% of the zoledronic acid group and 0.6% of the placebo group.

In Study 2301 which enrolled 7736 subjects, cardiac arrhythmias were reported as serious adverse events in 2.8% of zoledronic acid-treated subjects 2.0% placebo-treated subjects. This disparity was driven by atrial fibrillation events. Atrial fibrillation was reported and confirmed as a serious adverse event in 1.2% of subjects in the zoledronic acid group compared to 0.4% of subjects in the placebo group. There was no evidence to suggest that the occurrence of atrial fibrillation is an acute event related to infusion of study drug. All adverse events of atrial fibrillation were reported in 2.4% of zoledronic acid-treated subjects and 1.8% of placebo-treated subjects. Age and active tachyarrhythmia at randomization were the risk factors that characterized patients at greatest risk of an atrial fibrillation event.

When one includes the interim data from the second large osteoporosis recurrent fracture trial (study 2310), there is no consistent pattern of atrial fibrillation events. In study 2310, atrial fibrillation serious adverse events were reported in 0.3% of subjects in the zoledronic acid group compared to 1.1% of subjects in the placebo group. All adverse events of atrial fibrillation were reported in 1.6% of subjects in the zoledronic acid group compared to 1.9% of subjects in the placebo group. The large trials of other bisphosphonates were also reviewed. Studies RHN and RHE evaluated the efficacy of oral risedronate in preventing hip fracture. Approximately 9000 postmenopausal women with an average age of 78 years were enrolled. The incidence of atrial fibrillation over this three year study was 1.6% in the placebo group, 1.9% with risedronate 2.5 mg daily, and 1.6% with risedronate 5 mg daily (see table in Appendix 1). Two trials evaluating intravenous ibandronate enrolled postmenopausal women with a mean age of 67 years. In the three-year study MF4380 the atrial fibrillation events occurred in 0.8% of the placebo group, 1.2% of the ibandronate 0.5 mg iv q3months group and 0.7% of the 1.0 mg iv q3 months group. In the one year study BM16550, atrial fibrillation occurred in 0.9% of the 2.0 mg iv q2month

group and 0.4% of the 3.0 mg iv q3 month group. Review of the AERS database revealed no signal for any approved intravenous or oral bisphosphonates and atrial fibrillation.

When all available data is taken together, there are no consistent findings to suggest that treatment with zoledronic acid confers an increased risk of cardiac mortality or atrial fibrillation.

Ocular adverse events were noted by the DSMB for Study 2301. Confirmed cases of uveitis were reported in six subjects in the zoledronic acid group and no subjects in the placebo group. An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. Currently, all bisphosphonate have language describing the risk of inflammatory eye disease in the Precautions section of the product label. While there is an increased risk of inflammatory eye disease with zoledronic acid use, this risk is a recognized one with bisphosphonate use and can be effectively managed in the outpatient setting.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The Sponsor proposes a 5mg dose of zoledronic acid for the treatment of Paget's disease of bone. This dose is also under study for treatment of postmenopausal osteoporosis. The 4 mg dose of zoledronic acid is approved for the treatment of hypercalcemia of malignancy, treatment of patients with multiple myeloma or bone metastases from solid tumors. While the 5 mg dose of zoledronic acid is effective in the treatment of Paget's disease of bone, the 4 mg dose was not evaluated and may have been just as effective.

The Sponsor proposes to market the 5 mg dose of zoledronic acid as Reclast. The 4 mg dose of zoledronic acid is marketed as Zometa. The Division of Medication Errors and Technical Support finds the tradename Reclast acceptable from a promotional perspective, they do not recommend the use of a second proprietary name for zoledronic acid. If approved as Reclast, labeling recommendations were made to minimize product confusion.

At the time of the initial NDA submission, the Division agreed to allow Novartis to market zoledronic acid as Reclast for the Paget's disease indication. It is unlikely that the treatment populations for the Paget's disease indication and the malignancy indications will significantly overlap.

8.4 Pediatrics

A waiver for conducting pediatric studies for this application seeking an indication for Paget's disease of bone was granted in September 2005. This disease is typically manifested by focal increases in the rate of bone turnover in middle-aged or elderly individuals. The Sponsor is currently conducting pediatric studies evaluating the use of zoledronic acid in children with osteogenesis imperfecta.

8.7 Postmarketing Risk Management Plan

The Sponsor has been asked to confirm their risk management plan to address both the hypocalcemia risk and the dual tradename concerns.

9 OVERALL ASSESSMENT

9.1 Conclusions

A single dose of zoledronic acid 5mg is effective in the treatment of Paget's disease of bone. In the 6-month controlled studies, a therapeutic response was achieved by 96% of zoledronic acid-treated subjects and 74% of risedronate-treated subjects. The treatment difference was 22% (95% CIs 14% , 30%, $p < 0.001$).

Hypocalcemia is a significant risk for subjects being treated with zoledronic acid 5 mg. Overall, 50% of zoledronic acid-treated subjects receiving less than 1000 mg a day in calcium supplements and 35% of receiving less than 800 IU a day in vitamin D supplementation developed asymptomatic hypocalcemia at Day 10. In addition, one of the strongest predictors for development of hypocalcemia was baseline calcium level, with 40% of subjects with a baseline calcium level less than 9.2 mg/dL and 28% of subjects with a baseline calcium level less than 9.5 mg/dL developing hypocalcemia at Day 10. Baseline 25 hydroxyvitamin D level did not predict a low calcium level at Day 10. Based on these findings, it appears that calcium and vitamin D supplementation of at least 1000 mg calcium and 800 IU vitamin D daily can mitigate the risk of hypocalcemia with zoledronic acid use. The Sponsor is currently proposing labeling language recommending that all patients with Paget's disease receive 1500 mg calcium daily in divided doses. In this reviewer's opinion, it would also be beneficial to recommend 800 IU vitamin D per day.

Other clinical safety issues raised by the large pivotal trial for the treatment of postmenopausal osteoporosis indication include an increased incidence of cardiovascular mortality, cardiac arrhythmias and ophthalmic adverse events. In that single study, death due to cardiac disease occurred in 1.0% of the zoledronic acid group and 0.8% of the placebo group. However, interim data from a second ongoing study in postmenopausal women reveal that death attributed to cardiac disorders occurred in 2.7% of the zoledronic acid group and 3.2% of the placebo group. Deaths due to cerebrovascular accidents occurred in 0.3% of the zoledronic acid group and 0.1% of the placebo group in both studies.

Atrial fibrillation was reported and confirmed as a serious adverse event in 1.2% of subjects in the zoledronic acid group compared to 0.4% of subjects in the placebo group in the pivotal osteoporosis trial. Conversely, in study 2310, 0.3% of subjects in the zoledronic acid group compared to 1.1% of subjects in the placebo group developed atrial fibrillation. All adverse events of atrial fibrillation were reported in 2.4% of zoledronic acid-treated subjects and 1.8% of placebo-treated subjects in study 2301 and in 1.6% of zoledronic acid-treated subjects and 1.9% of placebo-treated subjects in study 2310. No atrial fibrillation signals were noted in large, long-term trials of elderly subjects taking risedronate or intravenous and oral ibandronate. There is also an absence of a signal in AERS for atrial fibrillation with any of the approved

bisphosphonates. Therefore, when all available data is taken together, there are no consistent findings to suggest that treatment with zoledronic acid confers an increased risk of cardiac mortality or atrial fibrillation.

An increased incidence of inflammatory eye disease was noted with zoledronic acid use in study 2301 (six subjects in the zoledronic acid group and no subjects in the placebo group). Currently, all bisphosphonate have language describing the risk of inflammatory eye disease in the Precautions section of the product label. While there is an increased risk of inflammatory eye disease with zoledronic acid use, this risk is a recognized one with bisphosphonate use and can be effectively managed in the outpatient setting.

In summary, a single dose of zoledronic acid 5mg is highly effective in the treatment of Paget's disease of bone. There do not appear to be any significant compelling safety signals to preclude the approval of zoledronic acid for the treatment of Paget's disease of bone.

9.2 Recommendation on Regulatory Action

Approve, with adequate labeling and a confirmed risk management plan.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

9.3.2 Required Phase 4 Commitments

none

9.3.3 Other Phase 4 Requests

none

9.4 Labeling Review

See separate document

9.5 Comments to Applicant

None

10 APPENDICES

10.1 Comparison of Cardiovascular Arrhythmia Occurrence For Other Bisphosphonate Preparations

	Risedronate po				Ibandronate iv				
	Studies RHN and RHE (3 year)		Study MF 4380 (3 year)		Study BM16550 (1 year)		Study BM16550 (1 year)		
	placebo	ris 2.5 qd	ris 5 qd	placebo	Iban 0.5 q3m	Iban 1.0 q3m	Iban 2.0 q2m	Iban 3.0 q3m	Iban 2.5 po qd
N	3134	3093	3104	949	950	961	448	469	465
Age, mean	78	78	78	67	67	68	67	66	66
Death, all	178 (5.7)	178 (5.8)	167 (5.4)	11 (1.2)	7 (1)	11 (1.2)	1 (0.2)	2 (0.4)	1 (0.2)
SAE, Cardiovascular, all	331 (10.6)	347 (11.2)	351 (11.3)	68 (7)	63 (7)	66 (7)	7 (1.6)	4 (0.9)	3 (0.6)
SAE, A fib	18 (0.6)	21 (0.7)	22 (0.7)	3 (<1)	3 (<1)	3 (<1)	2 (0.4)	0	0
SAE, myocardial infarction	45 (1.4)	48 (1.6)	51 (1.6)	11 (1)	6 (<1)	12 (1)	2 (0.4)	2 (0.4)	0
SAE, cerebrovascular accident	59 (1.9)	48 (1.6)	51 (1.6)	4 (<1)	4 (<1)	6 (<1)	0	0	1 (0.2)
AE, Cardiovascular, all	993 (32)	1037 (34)	1021 (33)	240 (25)	235 (25)	220 (23)	24 (5)	15 (3)	12 (3)
Arrhythmia	60 (1.9)	69 (2.2)	70 (2.3)	13 (1)	11 (1.2)	11 (1.2)	1 (0.2)	3 (0.6)	0
Arrhythmia supraventricular	4 (0.1)	4 (0.1)	10 (0.3)	2 (<1)	2 (<1)	2 (<1)			
Atrial fibrillation	51 (1.6)	58 (1.9)	49 (1.6)	8 (0.8)	11 (1.2)	7 (0.7)	4 (0.9)	2 (0.4)	0
Atrial flutter	3 (0.0)	6 (0.2)	0	2 (<1)	0	0	0	0	1 (0.2)
Atrioventricular block comp	2 (0.0)	3 (0.0)	1 (0.0)	1 (<1)	1 (<1)	0			
Atrioventricular block second	0	2 (0.0)	0	0	0	1 (<1)			
Bradycardia	13 (0.4)	17 (0.5)	13 (0.4)	2 (<1)	1 (<1)	3 (<1)			
Cardiac arrest	14 (0.4)	16 (0.5)	16 (0.5)	2 (<1)	0	0			
Sinus bradycardia	3 (0.0)	5 (0.2)	6 (0.2)	1 (<1)	2 (<1)	1 (<1)			
Tachycardia	22 (0.7)	29 (0.9)	16 (0.5)	3 (<1)	6 (<1)	10 (1)	1 (0.2)	1 (0.2)	0
Ventricular arrhythmia				0	0	1 (<1)	0	1 (0.2)	0
Ventricular tachycardia	0	1 (0.0)	1 (0.0)						
Myocardial infarction	47 (1.5)	51 (1.6)	54 (1.7)	13 (1)	7 (<1)	13 (1)	2 (0.4)	1 (0.2)	0
Cerebrovascular accident	74 (2.4)	65 (2.1)	60 (1.9)	4 (<1)	5 (<1)	7 (<1)	0	0	1 (0.2)

10.2 Line-by-Line Labeling Review

See separate document

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/s/

Theresa Kehoe
4/15/2007 11:33:05 AM
MEDICAL OFFICER

Eric Colman
4/16/2007 07:23:49 AM
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CLINICAL REVIEW

Application Type	21-817
Letter Date	23 August 2005
Stamp Date	24 August 2005
PDUFA Goal Date	23 February 2006
Reviewer Name	Eric Colman
Review Completion Date	21 February 2006
Established Name	Zoledronic Acid
(Proposed) Trade Name	Aclasta
Therapeutic Class	Bisphosphonate
Applicant	Novartis
Priority Designation	P – Class 2 Resubmission
Formulation	Intravenous
Dosing Regimen	5 mg
Indication	Paget's disease of bone
Intended Population	Patients with Paget's disease

Clinical Review
{Insert Reviewer Name}
{Insert Application and Submission Number}
{Insert Product Trade and Generic Name}

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approvable. This application should not be approved until after the cardiovascular and ophthalmic safety data from the ongoing osteoporosis fracture trial 2301 have been adjudicated by the study's Data Safety Monitoring Board and the results reviewed by the Division and determined not to adversely affect the benefit-risk profile of zoledronic acid when used to treat Paget's disease.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

If approved for Paget's disease, the zoledronic acid labeling should recommend that: 1) patients take at least 500 mg bid supplemental calcium and 800 IU supplemental vitamin D per day; 2) serum calcium, magnesium, phosphorus, and 25OH vitamin D be measured prior to dosing; 3) low levels of these parameters be normalized prior to drug administration; and 4) serum calcium, magnesium, and phosphorus levels be measured within seven-to-ten days post-dose. The labeling should also stress that patients with a history of thyroid or parathyroid surgery, resection of the proximal small bowel, or significant malabsorption (e.g., celiac disease) are at increased risk for developing hypocalcemia if treated with zoledronic acid.

1.2.2 Required Phase 4 Commitments

Details on phase 4 commitments will be provided if and when the NDA is approved.

1.2.3 Other Phase 4 Requests

Details on other phase 4 requests will be provided if and when the NDA is approved.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In a medical review dated 18 March 2005, I recommended that this application be issued an approvable letter. Although I considered the efficacy of the 5 mg dose of zoledronic acid to be sufficient for approval, I was concerned about the poorly characterized risks for hypocalcemia, and to a lesser extent hypophosphatemia, associated with zoledronic acid. It was my opinion that the benefits of the 5 mg intravenous dose of zoledronic acid did not outweigh the risks for hypocalcemia, and perhaps hypophosphatemia, when compared with the 30 mg oral risedronate regimen in patients with Paget's disease of bone.

In their response to the Division's 18 March 2005 approvable letter, Novartis submitted data which they believe supports the safety, vis-à-vis serum calcium and phosphorus levels, of the single 5 mg infusion of zoledronic acid.

Clinical Review

{Insert Reviewer Name}

{Insert Application and Submission Number}

{Insert Product Trade and Generic Name}

1.3.2 Efficacy

Data from two identical randomized, double-blind, active-controlled, non-inferiority (vs. risedronate) trials provide sufficient evidence to support the efficacy of a single 5 mg intravenous infusion of zoledronic acid in the treatment of Paget's disease of bone. The primary efficacy endpoint in these trials was a comparison of the proportion of patients in each treatment group who either had normalization or a reduction of at least 75% from baseline of their serum bone-specific alkaline phosphatase at the end of 6 months. At Month 6, 96% of the subjects treated with zoledronic acid and 74% of the subjects treated with risedronate achieved a therapeutic response (95% CI for difference 14%, 30%).

1.3.3 Safety

The principal safety concerns that emerged from the pivotal Paget's trials were hypocalcemia, and to a lesser extent, hypophosphatemia. Asymptomatic reductions in serum levels of calcium and phosphorus have been observed in pagetic patients treated with oral alendronate and risedronate, but by comparison, the risk appeared to be greater and occur more rapidly following treatment with 5 mg intravenous zoledronic acid.

At Day 10 of the trials, 32 of the 151 (21%) patients who received zoledronic acid vs. 5 of the 156 (3.0%) who received risedronate, had serum calcium levels below 2.1 mmol/L. Twenty-eight of the 157 (18%) subjects who received zoledronic acid compared with 2 of the 159 (1.3%) treated with risedronate developed serum phosphorus levels below 0.71 mmol/L (2.1 mg/dl) at Day 10. Four of the zoledronic acid subjects and none of the risedronate subjects developed markedly low serum calcium levels (< 1.87 mmol/L) at Day 10.

Although all patients in the two pivotal trials were instructed to take 500 mg bid of daily supplemental calcium and 400 to 1000 IU of daily supplemental vitamin D, the sponsor did not have data to verify if, when, or how much of the supplements were actually taken. Absent this information, it was not possible to judge how effective supplemental calcium and/or vitamin D are in reducing the risk for hypocalcemia and hypophosphatemia, and left unanswered the question of the safety of the proposed dosing regimen.

In their response to the March 2005 approvable letter, Novartis provided information on the amount of supplemental calcium and vitamin D patients took during the two Paget's trials. These data were obtained from questionnaires filled out by investigative-site personnel after the trials were completed. Novartis states that only information from source documents was used to complete the questionnaires. Data on calcium and vitamin D supplementation were obtained from 98% of the patients.

Twenty-four subjects reportedly took < 1000 mg/day of supplemental calcium, 100 took 1000 mg/day, and 27 took > 1000 mg/day of supplemental calcium. The mean percent changes in serum calcium from baseline to Day 10 were -12.0%, -7.0%, and -9.0% in the three groups, respectively.

Of the group that took less than 1000 mg per day, 50% had Day 10 serum calcium levels < 2.1 mmol/L. Seventeen percent of the patients who received 000 mg or more per day of calcium had serum calcium levels < 2.1 mmol/L at Day 10. Of the 63 zoledronic acid subjects who reportedly took less than 800 IU of daily vitamin D, 22 (35%) had a Day 10 serum calcium < 2.1 mmol/L. Of the 82 patients who purportedly took \geq 800 IU of daily vitamin D, 10 (12%) had low serum calcium levels at Day 10.

These data suggest that intake of at least 1000 mg per day of supplemental calcium and/or 800 IU per day of supplemental vitamin D reduces the risk for developing hypocalcemia in pagetic patients treated with a 5 mg intravenous zoledronic acid.

In an analysis of covariance statistical model, treatment with zoledronic acid (vs. risedronate) and low-normal baseline serum calcium level were the two strongest predictors of a Day 10 calcium level < 2.1 mmol/L. Other correlates of lower serum calcium at Day 10 were geographic region (Australia and New Zealand vs. rest of the world), dose of supplemental calcium and vitamin D, low baseline levels of 25OH vitamin D, and high levels of serum alkaline phosphatase and serum phosphate.

Efforts aimed at maintaining normal serum calcium levels following treatment with zoledronic acid, such as ensuring adequate supplemental calcium and vitamin D intake, will minimize increases in PTH and thereby reduce the risk for developing hypophosphatemia, since PTH increases urinary excretion of phosphorus.

In a submission dated 24 January 2006, Novartis provided the Division with interim safety data from the nearly-completed 3-year osteoporosis fracture trial 2301. This study randomized approximately 8000 postmenopausal women to treatment with once-yearly 5-mg zoledronic acid or placebo. There was a statistically significant increase in the incidence of cardiac arrhythmias in the zoledronic acid group compared with the placebo group (5.7% vs. 4.1%; nominal $p=0.0006$). The arrhythmias reported included atrial fibrillation, 1st degree AV block, SV extrasystoles, SV tachycardia, tachycardia, and sick sinus syndrome. Serious arrhythmias were reported in 2.2% of zoledronic acid vs. 1.3% of placebo-treated patients (nominal $p=0.001$). The overall rates of death were 2.8% vs. 2.4% in the active compared with the placebo treatment groups. An increase in serious ophthalmic adverse events was also reported.

These data will be adjudicated by the study's Data Safety Monitoring Board by mid-March 2006. The adjudicated safety data should be reviewed by the Division and factored into zoledronic acid's risk-benefit profile before a final decision is made regarding approval of this NDA.

1.3.4 Dosing Regimen and Administration

Novartis has submitted sufficient evidence that a single infusion of 5 mg zoledronic acid is effective in the treatment of Paget's disease. Information provided in the applicant's complete response to the approvable letter indicates that daily intake of at least ~~2~~ mg bid supplemental calcium and 800 IU supplemental vitamin D attenuates the risk for developing hypocalcemia following treatment with zoledronic acid.

1.3.5 Drug-Drug Interactions

Caution is warranted when administering zoledronic acid concomitantly with drugs that have the potential to lower serum calcium levels, such as loop diuretics, aminoglycosides, and Dilantin. *In-vivo* data do not indicate that zoledronic acid inhibits microsomal CYP450 enzymes.

Special Populations

The dose of zoledronic acid should be reduced in patients with renal insufficiency.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zoledronic acid 4 mg injection is currently approved for the treatment of hypercalcemia of malignancy and the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

Two pivotal trials were conducted to support the efficacy and safety of 5 mg intravenous zoledronic acid in Paget's disease. Trials 2304 and 2305 were identical multinational, randomized, double-blind, active-controlled, 6-month non-inferiority trials in which 30 mg oral risedronate daily x 60 days was the comparator.

2.6 Other Relevant Background Information

2.6.1 Basis for Approvable Regulatory Action

Novartis was sent an approvable letter on March 18, 2005, for the original submission of this NDA because of concern regarding the incidence of hypocalcemia and hypophosphatemia in Paget's patients treated with a single 5 mg intravenous dose of zoledronic acid.

In analyses of pooled data from studies 2304 and 2305, 21% of the patients who received zoledronic acid, compared with 3% who received risedronate, had serum calcium levels < 2.1 mmol/L at Day 10. Seven patients in the zoledronic acid group and one in the risedronate group had markedly decreased serum calcium levels (i.e., < 1.90 mmol/L) at Day 10. Eighteen percent of the zoledronic acid patients and 1.3% of the risedronate subjects had serum phosphorus levels < 0.71 mmol/L at Day 10.

The Approvable Letter stated in part that, "Before the 5 mg dose of zoledronic acid can be approved for the treatment of Paget's disease, you must provide adequate evidence that administration of supplemental calcium and/or vitamin D to patients treated with zoledronic acid satisfactorily attenuates the risk for hypocalcemia and hypophosphatemia."

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Synopsis of Sponsor's Response to the Approvable Letter

This section provides Novartis's verbatim response to the Division's approvable letter. I provide commentary in boxed, bolded font.

Paget's disease of bone is characterized by high bone turnover, and zoledronic acid by virtue of its anti-resorptive mechanism of action, may result in a clinically significant demand for calcium in this population. This demand can be met by:

- Increasing calcium intake, along with adequate vitamin D supplementation to maximize absorption; and
- A normal parathyroid response which helps to maintain normocalcemia by acutely increasing calcium mobilization from the skeleton and reducing urinary calcium excretion.

It is acknowledged that zoledronic acid 5 mg has a greater effect on serum calcium and phosphate than risedronate 30 mg daily for 2 months. In this response, information is presented that provides elucidation of factors that may impact changes in serum calcium following bisphosphonate administration or that may affect whether a patient's serum calcium falls below the lower limit of the normal reference range following infusion of zoledronic acid 5 mg in Paget's disease. After a brief discussion on the analytical methodology employed, data are presented in relation to whether or not a patient experienced a decline in serum calcium such that their Day 10 level was below the LLN (2.10 mmol/L or 8.4 mg/dL).

Data are presented in relation to their impact on the change in corrected serum calcium. The key variables that are discussed include;

- Baseline serum calcium
- Baseline SAP
- Baseline serum vitamin D
- Baseline serum phosphate
- Dose of calcium supplementation
- Dose of vitamin D supplementation
- Regional effects

Information on the dosage of vitamin D and calcium supplementation prescribed to patients was obtained from source data collected from study sites by a standard questionnaire and from adverse events reported by the investigator during the trial. The questionnaire was sent to all study centers and the data on approximately 98% of the patients was collected. All calcium and vitamin D supplementation data utilized in the analyses was obtained from data that existed in the source documentation prior to database lock even though the questionnaire was not sent to all study centers until after clinical database lock.

Telephone interviews were conducted with the principal investigators and study coordinators to better understand the cases of hypocalcemia, with a focus on co-morbidities that could influence

the risk of developing hypocalcemia. This information was not utilized in any of the inferential analyses.

In order to understand factors predictive of “hypocalcemia” (corrected serum calcium < LLN on Day 10) the data were examined in two general ways. In the first approach, descriptive statistics and logistic regression models were used to identify factors predictive of a patient going below the LLN. In the second approach, descriptive statistics and analysis of variance/covariance models were used to identify factors predictive of decreases in corrected serum calcium.

Models were constructed using the laboratory parameters and calcium/vitamin D dosing variables as continuous variables wherever possible. Dichotomization was performed related to calcium and vitamin D supplementation in the logistic regression due to the relative low frequency of events of hypocalcemia.

There is an inherent limitation in the analysis of factors predicting the “event” of hypocalcemia in that some patients presented at baseline near the threshold LLN for serum calcium, where even small changes result in an event. The modeling of changes in corrected serum calcium is the preferred method to explain the biochemical changes that have occurred due to the greater level of sensitivity to associate risk factors with the outcome variable of interest.

In addition to treatment (zoledronic acid, risedronate), the following variables were used in model development and understanding of the factors that contribute to changes in corrected serum calcium:

- Region (Australia/New Zealand, USA/Rest of World)
- Study (CZOL446H2304, CZOL446H2305)
- Dose of calcium supplementation (continuous divided by 100; < 1000 mg/day, ≥ 1000 mg/day)
- Dose of vitamin D supplementation (continuous divided by 100; < median (800 IU), ≥ median (800 IU))
- Baseline SAP (continuous with log-transformation; < 400 U/L, ≥ 400 U/L)
- Baseline vitamin D level (continuous with log-transformation; < median (60 pmol/mL), ≥ median (60 pmol/mL))
- Baseline corrected serum calcium level (continuous; < median (2.37 mmol/L), ≥ median (2.37 mmol/L))
- Baseline phosphate level (continuous; < median (1.135 mmol/L), ≥ median (1.135 mmol/L))

In performing the retrospective analyses, similar procedures to what would have been utilized if the analyses were prospectively defined were used. Thus, if factors are to be dichotomized, the values used to create subgroups should either have some historical basis or be driven by their ability to help explain any two-factor interactions that may exist within the data. This is the reason why observed medians or protocol-specified values were used as the cutpoints to categorize the biochemical and calcium/vitamin D dosing variables used in the statistical models.

A systematic evaluation of factors predictive of patients falling below the LLN was performed.

The number of patients falling below the lower limit of normal (LLN) is 21.2% and 21.8% for zoledronic acid patients with respect to uncorrected and corrected serum calcium compared to 2.6% and 7.1% respectively for risedronate. Because of this larger treatment effect of zoledronic acid, the focus of subgroup differences will be within the zoledronic acid only.

The relationship between levels of the subgroup variables and the incidence of patients falling below the LLN is presented in following Table.

INCIDENCE OF ZOLEDRONIC ACID-TREATED PATIENTS < LLN NORMAL FOR CORRECTED SERUM CALCIUM AT DAY 10 BY SUBGROUPS				
Variable	Subgroup	Zoledronic Acid		P-value (1)
		n/N	(%)	
Baseline SAP (U/L)	< 400	13/96	(13.5)	0.0019
	≥400	19/51	(37.3)	
Dose of calcium supplementation (mg/day)	< 1000	11/22	(50.0)	0.0016
	≥1000	21/123	(17.1)	
Dose of Vitamin D supplementation (IU/day)	< 800	22/63	(34.9)	0.0021
	≥800	10/82	(12.2)	
Region	Australia/New Zealand	21/43	(48.8)	<0.0001
	USA/Rest of World	11/104	(10.6)	
Baseline Phosphate	< Median (1.135)	10/78	(12.8)	0.0095
	> Median (1.135)	22/69	(31.9)	
Baseline Corrected Serum Calcium Category (mmol/L)	< Median (2.37)	21/76	(27.6)	0.1136
Baseline Vitamin D (pmol/mL)	> Median (2.37)	11/71	(15.5)	0.1202
	< Median (60)	10/66	(15.2)	
	> Median (60)	22/81	(27.2)	

(1) P-value is calculated based on a Chi-square test with continuity correction to evaluate the within-treatment difference for the two subgroups within the zoledronic acid treatment group.

There is an approximate twofold or higher incidence of patients falling below the LLN within the zoledronic acid group for individuals who:

- Had a baseline SAP of ≥ 400 U/L
- Received a dose of calcium supplementation < 1000 mg/day
- Received a dose of Vitamin D < 800 IU/day
- Were from Australia/New Zealand
- Had a baseline serum phosphate level ≥ to the median level of 1.135 mmol/L
- Had a baseline corrected serum calcium < the median level of 2.37 mmol/L

Alkaline Phosphatase

For patients who had a baseline SAP ≥ 400 U/L, the risk of falling below the LLN was nearly threefold (37.3%) greater compared to patients who were < 400 U/L at Day 10 (13.5%). This difference may be attributed to the greater change in bone resorption for patients with higher baseline SAP following bisphosphonate therapy.

Supplemental Calcium

The study protocols recommended that 1,000 mg of supplemental calcium be taken daily, but variability in the prescribed dose across study sites was evident. The incidence of corrected serum calcium below the LLN is almost three-fold greater in the zoledronic acid treated group receiving less than the protocol recommended 1,000 mg daily. The incidence $< LLN$ for uncorrected serum calcium corroborate these results where 45.5% of subjects who received less than 1000 mg/day are $< LLN$ compared to 17.3% for subjects who received ≥ 1000 mg/day ($p = 0.0072$). Therefore, a daily calcium intake of $\geq 1,000$ mg results in a substantial reduction in the incidence of low serum calcium. This result is supported by the more than twofold greater incidence rate of corrected serum calcium below the LLN for risedronate-treated patients who received $<$ than 1000 mg daily of calcium supplementation.

Supplemental Vitamin D

The study protocols recommended that patients receive at least 400 IU/day of vitamin D. The median dose of vitamin D received was 800 IU/day. When receiving less than 800 IU/day, the incidence of corrected serum calcium below the LLN is almost three-fold greater (34.9%) relative to those subjects who received at least 800 IU/day (12.2%). This difference is more than four-fold greater with respect to uncorrected serum calcium, 38.1% when receiving < 800 IU/day versus 9.3% when receiving ≥ 800 IU/day.

These differences suggest that adequate doses of vitamin D supplementation also reduce the risk of experiencing corrected serum calcium below the LLN. However, since calcium and vitamin D are commonly provided in fixed combinations, it is difficult to determine if this represents an independent effect of supplemental vitamin D.

Geographical Region

There was a pronounced regional effect whereby 21/32 (65.6%) of the zoledronic acid-treated patients with Day 10 corrected serum calcium $< LLN$ were from New Zealand and Australia, yet only 43/147 (29.3%) of the zoledronic acid-treated patients in the study with corrected serum calcium at baseline and Day 10 were from this region.

- In the Australia/New Zealand region, 21/43 patients (48.8%) in the zoledronic acid group were $< LLN$ on Day 10, versus 11/104 patients (10.6%) in USA/Rest of World
 - In the risedronate treatment group, 7/42 patients (16.7%) from New Zealand/Australia were $< LLN$ at Day 10 compared to 4/112 (3.6%) in the USA/Rest of World
 - ~~performed calcium measurements in regional laboratories.~~
- All patient samples from the New Zealand/Australia region were analyzed in Australia.

- Mean baseline values for corrected serum calcium were approximately 0.09 mmol/L lower in New Zealand/Australia compared to the rest of the world, consistent with the lower normal range identified by _____ for this region of the world.

These findings suggest an inherent difference in baseline values and possibly the response of patients in the Australia/New Zealand region compared to the ROW. Differences might be related to a lower amount of calcium in the diet. There may be less emphasis on the importance of daily vitamin D and calcium supplementation in this region, which is reflected by 18 of 24 zoledronic acid patients from the primary analysis population who received less than the recommended 1000 mg of daily supplemental calcium originating from either Australia or New Zealand.

There were 11 (10.6%) zoledronic acid patients with corrected serum calcium < LLN at Day 10 from USA/ROW. The experience in New Zealand and Australia is not representative of the experience in the USA/ROW. In the USA/ROW, the majority of patients with corrected serum calcium < LLN were just below 2.1 mmol/L which has minimal clinical significance and does not reflect an increased risk of developing serious adverse events. Larger declines in serum calcium can occur from insufficient oral calcium intake, conditions where intestinal absorption of nutrients are impaired, or parathyroid disease secondary to surgical resection. Therefore, mitigation of the risk of hypocalcemia will depend on identification of patients with predisposing disorders of calcium homeostasis, and, most importantly, ensuring administration of appropriate oral calcium and vitamin D intake.

Baseline Serum Phosphorus

The incidence of corrected serum calcium < LLN at Day 10 is approximately 2.5 times more likely when the baseline phosphate level is \geq the median level of 1.135 mmol/L (31.9%) versus those < the median level of 1.135 mmol/L (12.8%) at baseline.

Baseline Serum Calcium

The risk of being < LLN with respect to baseline corrected serum calcium is approximately 1.8 times greater when the baseline level is < the median baseline level (2.37 mmol/L). This risk increases greatly in the lower quartile (\leq 2.30 mmol/L) where the incidence rate was 40.5% (17/42). This subgroup includes many of the patients from Australia/New Zealand who were lower than the remainder of the population with respect to their baseline corrected serum calcium.

In comparing to the uncorrected baseline serum calcium (median baseline level 2.39 mmol/L) results, the incidence of uncorrected serum calcium < LLN at Day 10 is approximately 2.5 times more likely to fall below the LLN (29.9%) when a patient has an uncorrected serum calcium level below the median at baseline than if a patient is \geq median level (12.2%). It should be also noted that the four cases observed below the LLN for risedronate-treated patients all occurred in patients below the median level at baseline.

Baseline Serum Vitamin D

There is no significant association with baseline 25-hydroxy Vitamin D levels on the incidence of corrected serum calcium < LLN. There are 12% fewer patients with corrected serum calcium < LLN who are below the median level of 60 pmol/mL relative to patients \geq median level (27.2%). Further difficulties in interpreting this relationship exist when examining the incidence of falling below the LLN with respect to baseline quartiles of 25-hydroxy Vitamin D levels where the lowest incidence rate occurs in the 2nd quartile (2/33, 6.1%) and the highest incidence occurs within the 3rd quartile (13/43, 30.2%). The lack of an association between baseline 25-hydroxy Vitamin D levels may be related to other factors, such as baseline serum calcium and the dose of supplemental calcium which may exert a greater effect on whether the calcium level falls below the LLN than the baseline serum 25-hydroxy vitamin D level.

REVIEWER COMMENT: Despite the reported findings that baseline level of 25OH vitamin D did not predict a low serum calcium level at Day 10, vitamin D is critical to calcium homeostasis and all patients treated with zoledronic acid should be vitamin D sufficient to maximize calcium balance.

Logistic Regression Models to Identify Risk Factors for Day 10 Corrected Serum Calcium Below the LLN

The simple, dichotomized presentation of the effect of baseline corrected serum calcium presented above does not fully utilize the range of serum calcium values. A more robust approach to understanding risk factors utilizing baseline corrected serum calcium and the other biochemical parameters as continuous variables is presented in this section.

In order to develop an improved understanding of the data, a series of logistic regression models were fitted based on whether or not a patient was below the LLN for corrected serum calcium at Day 10 following treatment with zoledronic acid or risedronate. In the first model that was fitted, treatment, baseline vitamin D level (continuous), and baseline uncorrected serum calcium levels (continuous) were utilized as explanatory variables. This model demonstrated that treatment and low baseline uncorrected serum calcium were strong risk factors for increasing the likelihood of a patients falling below the LLN at Day 10 (both $p < 0.0001$). There was no relationship between baseline vitamin D level and a patient falling below the LLN at Day 10.

With the risk of a hypocalcemia event known to be higher in the zoledronic acid treatment group, an additional logistic regression model was fitted for zoledronic acid patients only looking at the effect of baseline uncorrected serum calcium (continuous) and baseline SAP (continuous). This model demonstrated that low baseline uncorrected serum calcium and high baseline SAP were both significant risk factors (all $p < 0.025$) for increasing the chance of a zoledronic acid-treated patient falling below the LLN at Day 10.

Novartis was encouraged by the Division to investigate the effects of additional risk factors on changes in serum calcium/serum calcium < LLN through statistical modeling. To more thoroughly investigate risk factors associated with patients falling below the LLN at Day 10, an

additional logistic regression model was constructed that included study, treatment, calcium dose (< 1000 mg/day, ≥ 1000 mg/day), vitamin D dose (< 800 IU/day, ≥ 800 mg/day), baseline vitamin D level (continuous, log-transformed), region (Australia/New Zealand, USA/Rest of World), baseline corrected serum calcium (continuous), baseline SAP (continuous, log-transformed), and baseline phosphate (continuous). The estimates of the different risk factors in this logistic regression model have been adjusted for the effects of the other variables presented in the model.

A summary of the model results is provided in the following Table.

**RISK FACTORS FOR THE OCCURRENCE OF LOW SERUM
CALCIUM (<2.1 MMOL/L) AT DAY 10**

Factor	Odds ratio (1)	95% CI for odds ratio	P-value
Study	0.825	(0.367, 1.852)	0.6408
Treatment	4.267	(1.879, 9.690)	0.0005
Calcium Dose	0.528	(0.216, 1.292)	0.1621
Vitamin D Dose	0.466	(0.192, 1.134)	0.0924
Baseline vitamin D level (2)	0.517	(0.136, 1.968)	0.3335
Region	2.711	(1.116, 6.589)	0.0277
Baseline corrected serum calcium	0.002	(<0.001, 0.171)	0.0061
Baseline SAP (2)	1.983	(0.924, 4.255)	0.0787
Baseline Phosphate	11.223	(0.874, 144.103)	0.0634

Source: (1) An odds ratio > 1 for biochemical parameters and dosing variables implies that increasing values for an individual patient are more likely to lead to low serum calcium at Day 10 and an odds ratio < 1 for biochemical parameters and dosing variables implies that decreasing values for a risk factor for an individual patient is more likely to experience a low calcium at Day 10. (2) Variable is log-transformed in the model

In summary, both the descriptive statistics and the results of the logistic regression model are consistent in demonstrating that region, baseline corrected serum calcium, baseline SAP, and baseline phosphate are the most predictive factors in increasing the odds of having a corrected serum calcium < LLN at Day 10.

Patients with > 0.4 mmol/L Decrease in Serum Calcium on Day 10

The mean decrease in corrected serum calcium in the 32 patients with uncorrected serum calcium below the LLN at Day was 0.33 mmol/L, compared with a 0.15 mmol/L mean decrease in the patients above the LLN on Day 10. There were five patients in whom the decrease exceeded 0.4 mmol/L, and two of these patients were symptomatic.

Among these five patients, four did not take their calcium supplements as prescribed and two had an underlying disease that negatively affected calcium absorption or calcium homeostasis. Other details about these subjects are provided below.

Patient 0504 00002

The patient with the greatest drop in corrected serum calcium from the USA, who also had the lowest serum calcium at Day 10, is an extreme example of failure of the physiological mechanisms responsible for maintaining serum calcium following bisphosphonate administration. This individual had significant hypoparathyroidism as a consequence of previous thyroid surgery and was unable to mount an appropriate PTH response to counteract the decline in serum calcium. In addition, this subject did not take any calcium supplementation.

Patient 0401 00233

Patient was from New Zealand, did not take calcium supplements.

Patient 0601 00083

Patient was from the United Kingdom, did not take calcium supplements.

Patient 0102 00114

Subject was from Australia, discontinued calcium supplementation, but the precise timing is unknown. This patient also discontinued from the study and therefore a study close out visit was performed at the day 10 visit.

Patient 0501 00145

Patient was from the USA, was deemed to have malabsorption of oral calcium and other nutrients secondary to extensive small bowel resection.

Analysis of Covariance Model to Identify Risk Factors for the Change in Corrected Serum Calcium at Day 10

An analysis of covariance model (linear model) was fitted to investigate the relationship between different risk factors on the change in corrected serum calcium at Day 10 relative to baseline. All factors that may explain the patient-patient variability in the changes in corrected serum calcium regardless of level of statistical significance were included. To maximize the sensitivity to detect changes, all biochemical parameters, and dosing variables were used as continuous variables in the model along with treatment, region, and study. The exact form of each of the risk factors that were included in the analysis of covariance model were as follows:

- Treatment (Zoledronic acid, risedronate)
- Study (Study 2304, Study 2305)
- Calcium dose (continuous, divided by 100)
- Vitamin D dose (continuous, divided by 100)
- Baseline SAP (continuous, log-transformed)
- Baseline corrected serum calcium (continuous)
- Baseline Vitamin D level (continuous, log-transformed)
- Baseline phosphate level (continuous)
- Region (Australia/New Zealand, USA/Rest of World)

The two dosing variables (Calcium and Vitamin D dose) were divided by 100 so that the parameter estimates would reflect changes that are more likely to occur in a clinical practice based on the formulations of calcium and vitamin D available which are often available in multiples of 100. Baseline SAP and baseline vitamin D levels were log-transformed to lessen the influence of some of outlying baseline values which when transformed are approximately normally distributed.

CHANGE IN CORRECTED SERUM CALCIUM AT DAY 10 MODEL SUMMARY

Explanatory Variable	Estimate	Standard Error	P-value
Study	0.024	0.0131	0.0710
Treatment	-0.105	0.0125	<0.0001
Calcium dose (1)	0.013	0.0031	<0.0001
Vitamin D dose (1)	0.013	0.0031	<0.0001
Baseline vitamin D level (2)	0.053	0.0182	0.0040
Region	-0.031	0.0159	0.0509
Baseline corrected serum calcium	-0.387	0.0710	<0.0001
Baseline SAP (2)	-0.044	0.0139	0.0016
Baseline phosphate	-0.085	0.0414	0.0411

Note: All p-values are from F-test statistics constructed from Type III Sums of Squares.

(1) Values for this variable are divided by 100 for use in the model.

(2) Values for this variable are log-transformed for use in the model.

Key findings include:

- Every 100 mg increase in the dose of supplemental calcium decreases the magnitude of change of corrected serum calcium at Day 10 by 0.013 mmol/L.
- The difference between an individual receiving no calcium supplementation and receiving the recommended daily dose of ≥ 1000 mg/day calcium is a 0.13 mmol/L difference in corrected serum calcium at Day 10 which is similar to the effect of zoledronic acid on the change in corrected serum calcium during this time period.
- Every 100 IU increase in the dose of Vitamin D decreases the magnitude of change of corrected serum calcium at Day 10 by 0.013 mmol/L.
- Every 0.1 mmol/L increase in the corrected serum calcium at baseline resulted in a 0.039 mmol/L greater decrease in corrected serum calcium at Day 10.
- Every one unit increase on the log scale in baseline SAP (2.718 fold increase on the original scale) results in a 0.044 mmol/L greater decrease in corrected serum calcium at Day 10. In other words, an increase in baseline SAP from 200 to 544 U/L resulted in a 0.044 mmol/L greater decrease in corrected serum calcium at Day 10.
- Every one unit increase on the log scale in baseline 25-hydroxy vitamin D level (2.718 fold increase on the original scale) results in a 0.053 mmol/L lesser decrease in corrected serum calcium at Day 10. For example, if baseline 25-hydroxy vitamin D level increases from 60

pmol/mL to 163 pmol/mL, this would result in a 0.053 mmol/L lesser decrease in corrected serum calcium at Day 10. In fitting models separately to patients who received less than 1000 mg/day and patients who received ≥ 1000 mg/day it can be shown that baseline 25-hydroxy vitamin D levels only influence changes in corrected serum calcium in patients who received ≥ 1000 mg/day of calcium, consistent with physiological principles. In the group of patients who received less than 1000 mg/day, for which the changes in corrected serum calcium are the greatest, the clinical benefit of adequate calcium supplementation overshadows the modest influence of vitamin D status.

- Subjects from Australia/New Zealand had a 0.031 mmol/L greater decrease in corrected serum calcium at Day 10 when adjusting for all other factors.

Effect of anticonvulsant therapies on change in serum calcium

It was requested in email correspondence with the FDA on June 8, 2005 to provide information on changes in serum calcium in patients who were receiving concomitant anticonvulsant therapy. A search of the data provided as part of NDA #21-817 revealed five zoledronic acid treated patients from the two Phase III Paget's disease studies who received these medications during the course of their clinical studies. The mean reduction in serum calcium and corrected serum calcium at Day 10 was 0.25 and 0.22 mmol/L respectively for this group compared to 0.21 and 0.18 mmol/L respectively for patients who did not receive anticonvulsant therapy.

REVIEWER COMMENT: Although only 5 patients who received zoledronic acid were taking concomitant anticonvulsant therapy, there was a trend towards a greater mean reduction from baseline to Day 10 in these patients compared with those not taking an anticonvulsant.

Effect of previous thyroid surgery, hypoparathyroidism, or intestinal malabsorption of calcium on changes in serum calcium

Extensive thyroid surgery often results in removal or damage to the parathyroid glands that may predispose patients to large changes in serum calcium following zoledronic acid administration. For patients with partial hypoparathyroidism, the residual parathyroid tissue may be sufficient to maintain serum calcium levels in the normal range in the absence of any significant demands for calcium. Following bisphosphonate treatment, these individuals may not be able to increase their serum PTH levels appropriately and are thus prone to greater decreases in serum calcium. These subjects are primarily dependent on calcium intake through the GI tract, and do correct their serum calcium levels following intake of relatively larger total amounts of calcium.

Given these conditions, a request was made by the FDA on June 8, 2005 to provide information on changes in serum calcium for patients who had previous thyroid surgery, hypoparathyroidism, or intestinal malabsorption. A search of the past medical history data provided as part of NDA #21-817 revealed 5 zoledronic acid treated patients who met the specified criteria. There was one additional subject who had a thyroidectomy documented in the narratives, but not in the medical history. This subject experienced a significant decrease in corrected serum calcium of 0.91

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mmol/L. The summary statistics provided for this small group can be misleading due to the large heterogeneity in the population.

There were two subjects who had prior intestinal surgery. The subject with Crohn's disease did not have clinically active disease and most likely the surgery was in the ileum. The subject with obesity and removal of the principle areas of calcium resorption had a much larger decline in serum calcium. Although the number of subjects is extremely small, it is likely, that changes in serum calcium will be related to the areas of surgical removal, specifically the duodenum where significant calcium absorption occurs. Likewise, sequelae from surgery to the thyroid are expected to relate to the amount of functioning parathyroid tissue post-operatively.

Based on the above data, it is clear that not all patients with a partial thyroidectomy or previous surgery of the small intestine will experience changes in serum calcium that are different from individuals who have not had these types of surgical procedures. Subjects with removal of the proximal small intestine and those with a history of previous thyroid /parathyroid surgery should be carefully evaluated and counseled prior to bisphosphonate therapy for Paget's disease.

REVIEWER COMMENT: I agree with the company that subjects who have had removal of the proximal small bowel and those with a history of thyroid or parathyroid surgery should be more closely monitored prior to and immediately following dosing with zoledronic acid. This information should be included in the labeling.

Recommendations for clinical management

Clinicians should be aware of predisposing conditions that can be diagnosed by history and physical exam (e.g. previous thyroid / parathyroid surgery) or by biochemical assessment (serum alkaline phosphatase), so that appropriate management including communication with the patient is performed. In order to establish reliable clinical practice guidelines for minimizing the risk of hypocalcemia following zoledronic acid administration, it is important to have consistency of results between the various analysis methods for identifying strong risk factors, and it is important to integrate this data with current principles of calcium regulation. Due to multiplicity from the comparisons made, it is clearly possible that the effects of some of the risk factors examined may achieve a significance level <0.05 by chance alone. For this reason our recommendations are based on risk factors that have demonstrated consistent effects.

Recommendations for the clinical management to minimize the risk of hypocalcemia are listed in order of importance.

Underlying medical conditions

It is clear from the review of the patients' narratives with the greatest decreases in serum calcium that the existence of certain conditions needs to be evaluated prior to the administration of zoledronic acid. These conditions include: parathyroidectomy, hypoparathyroidism, surgery to removal the proximal small intestine, gastric bypass surgery, and celiac disease.

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REVIEWER COMMENT: Concomitant use of loop diuretics and some anticonvulsants (e.g., Dilantin) should also be included in the list of conditions that may predispose a patient to develop hypocalcemia following administration of zoledronic acid.

Calcium and vitamin D supplementation

Adequate calcium and vitamin D supplementation consistently demonstrates a beneficial effect on serum calcium levels. Therefore, unless there are specific contraindications in an individual patient, routine supplementation with at least 1000 mg/day of elemental calcium and 800 IU/day of vitamin D is warranted.

REVIEWER COMMENT: Given that the nadir for hypocalcemia and hypophosphatemia appears to be 7-14 days post-zoledronic acid infusion, compliance with supplemental calcium and vitamin D is of particular importance during the first 2 weeks following drug delivery.

Baseline serum calcium

It is consistently demonstrated that the magnitude of decrease in corrected serum calcium increases as the baseline serum calcium increases. However, this magnitude of change does not necessarily equate to the development of hypocalcemia. The risk of developing hypocalcemia is greater if the patient has baseline serum calcium < 2.37 mmol/L. Adequate calcium and vitamin D supplementation will mitigate this risk.

Baseline SAP

It is consistently shown that higher baseline SAP increases the magnitude of the reduction in serum calcium and increases the risk of hypocalcemia. Therefore, careful consideration should be given in patients with higher bone turnover indicated by a baseline SAP of at least 400 U/L prior to administering zoledronic acid.

Regional Effect

The regional differences for developing hypocalcemia and for the magnitude of change in corrected serum calcium are greater in Australia and New Zealand than in the USA/Rest of World. While some of the regional differences are explained by the lower baseline levels in that region, and reduced calcium and vitamin D supplementation in New Zealand, there is a residual effect that remains. Although the source of the residual effect is not completely understood, a potential source of this effect could be the lesser calcium and vitamin D dietary intake, consistent with the lower normative ranges for serum calcium documented for this region.

Baseline vitamin D

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Although log-transformed baseline vitamin D is a significant risk factor for the change in corrected serum calcium, it is not demonstrated that the magnitude of change in corrected serum calcium or the incidence of hypocalcemia increases as the baseline vitamin D level decreases. The statistical significance is driven by the reduced changes in corrected serum calcium with increasing baseline vitamin D levels in subjects who received >1000 mg of supplemental calcium daily. While the effect of baseline Vitamin D on changes in serum calcium is not robust, it is recommended to ensure adequate calcium and Vitamin D supplementation.

Baseline phosphate

The baseline phosphate has an effect that is quantitatively less than that for an equivalent change in serum calcium. Based on the current data, there are no therapeutic interventions that should be recommended based on serum phosphate levels.

Hypophosphatemia

Pathophysiology and Clinical Consequence

The development of hypophosphatemia is linked to a reduction in bone resorption and a physiologically appropriate parathyroid response following zoledronic acid infusion. Actions of PTH on the kidney include the renal conservation of calcium and inhibition of phosphate reabsorption. This is a transient physiological response that resolves as the secondary hypoparathyroidism is corrected with appropriate calcium supplementation.

Regional Differences

Investigation into the subjects with serum phosphate levels <0.71 mmol/L (LLN defined by), reveals two groups. Twelve of 28 subjects (43%) also had concomitant serum calcium levels <2.1 mmol/L while 16 of 28 (57%) had isolated hypophosphatemia. The geographic distribution of these hypophosphatemia cases differs from the hypocalcemia cases. Of these cases, 15/16 (94%) occurred outside of Australia and New Zealand. The one case in Australia occurred in a patient whose baseline phosphate level was 0.96 mmol/L (approximately 0.20 mmol/L below the mean) declining to 0.68 mmol/L at Day 10. Since most subjects would be expected to have an increase in serum PTH following zoledronic acid administration, in those patients with hypophosphatemia without hypocalcemia, the difference likely resides in the greater oral intake of calcium in those with isolated declines in serum phosphate to below 0.71 mmol/L. The magnitude of the transient reduction in serum phosphate was modest, and without clinical consequences.

REVIEWER COMMENT: Mild-to-moderate hypophosphatemia (i.e., serum levels between 0.49 and 0.71 mmol/L) is generally asymptomatic and without clinical consequence. When serum phosphorus levels drop below 0.49 mmol/L patients may develop muscle weakness and in rare cases rhabdomyolysis and hemolysis. The lowest Day 10 serum phosphorus level in the zoledronic acid group was 0.48 mmol/L. This patient's baseline phosphorus was 0.84 mmol/L. I agree with the company that the magnitude of the

reduction in serum phosphorus following treatment with zoledronic acid appears to be modest and without clinical consequence. The risk for developing clinically significant hypophosphatemia would be reduced by ensuring that pre-dose levels of serum phosphorus are normal, that patients take adequate amounts of supplemental calcium and vitamin D following treatment with zoledronic acid, particularly during the first two to three weeks post-dose, and by checking serum phosphorus levels within seven-to-ten days following drug administration.

7.1.18 Safety Update

A safety update consisting of serious adverse event data from the ongoing extension phases of the two pivotal Paget's trials and blinded narratives for all patients experiencing death, serious adverse events, and renal events from the two osteoporosis trials 2301 and 2310 were provided in the 23 August 2005 submission. The cut-off date for most of this information was 1 March 2005.

The data from the extension phases of the pivotal Paget's trials do not raise concern regarding the overall safety of zoledronic acid. The blinded narratives from the osteoporosis trials provide little useful information regarding the safety of zoledronic acid in the treatment of Paget's disease.

Partially blinded (i.e., Treatment groups A and B) interim data on hypocalcemia from the ongoing osteoporosis treatment trial was also provided in the 23 August 2005 submission.

Forty-nine of 2019 (2.4%) of patients in treatment group A vs. 1 of 2040 (<0.1%) of patients in treatment group B developed a serum calcium level < 2.1 mmol/L within 2 weeks of receiving their first dose of study drug or placebo. Two of 1577 (0.1%) and 1 of 1644 (<0.1%) of patients in treatment groups A and B, respectively, developed low serum calcium levels following the second dose of study drug or placebo. A similar percentage of patients developed hypocalcemia in each group following the third dose.

Twelve of 2019 (0.6%) treatment group A subjects developed serum calcium levels < 2.0 mmol/L following the initial dose of study drug compared with 0/2040 treatment group B subjects.

All 12 of the patients who developed serum calcium levels < 2.0 mmol/L were reportedly asymptomatic. Of the 12 patients, 3 had values below 1.8 mmol/L. Two of the three patients had had previous thyroid surgery and exhibited a drop in their serum calcium without a significant drop in serum phosphate as would have been expected with an intact parathyroid function. The third patient had hypothyroidism and a low baseline serum calcium. A review of underlying medical conditions that could potentially predispose to hypocalcemia among the 12 patients is as follows. A total of 7 of the 12 patients had a previous history of thyroid disease, 4 of them treated by subtotal thyroidectomy.

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Other identified contributing causes for reductions in serum calcium included resection of the majority of the small intestine including the proximal portion where the majority of calcium absorption occurs, and gastric resection, with consequent impairment in calcium absorption due to lack of gastric acid secretion. Some subjects had low albumin levels as a result of chronic or acute illness. Corrected serum calcium values for these subjects were frequently within the normal range. There were 2 subjects with values just below 2.0 mmol/L for whom no explanatory conditions were apparent other than receiving infusion of study drug. All 12 subjects reportedly normalized their calcium levels with ongoing oral calcium and vitamin D intake.

REVIEWER COMMENT: Although the relative risk for developing hypocalcemia is much higher in women with postmenopausal osteoporosis who receive zoledronic acid compared with placebo, the absolute risk of hypocalcemia is much lower in osteoporotic vs. Pagetic patients.

Interim Safety Data from the Zoledronic Acid Pivotal Osteoporosis Fracture Trial

In a submission dated 24 January 2006, Novartis provided the Division with interim efficacy and safety data from the nearly-completed 3-year osteoporosis fracture trial 2301. This study randomized approximately 8000 postmenopausal women to treatment with once-yearly 5-mg zoledronic acid or placebo. Of note, there was a statistically significant increase in the incidence of cardiac arrhythmias in the zoledronic acid group compared with the placebo group (5.7% vs. 4.1%; nominal $p=0.0006$). The arrhythmias reported included atrial fibrillation, 1st degree AV block, SV extrasystoles, SV tachycardia, tachycardia, and sick sinus syndrome. Serious arrhythmias were reported in 2.2% of zoledronic acid vs. 1.3% of placebo-treated patients (nominal $p=0.001$). The overall rates of death were 2.8% vs. 2.4% in the active compared with the placebo treatment groups ($p=NS$).

The Data Safety Monitoring Board overseeing conduct of study 2301 made the following recommendations based on the interim efficacy and safety data:

- The anti-fracture efficacy has been established
- There are some safety issues that are not yet resolved, concerning:
 - cardiovascular mortality
 - cardiac arrhythmias
 - ophthalmic disorders
- Resolution of these concerns will require review of adjudicated data on adverse events, serious adverse events and deaths by the DSMB

During a 2 February 2006 teleconference with Novartis, in which the above data were discussed, the company stated that the adjudication of the cardiac and ophthalmic safety data should be completed by mid-March 2006.

REVIEWER COMMENT: Since the population of postmenopausal women from whom the cardiovascular safety data have emerged is similar in age to the Paget's population and the

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dosing regimens for the two indications are similar as well, it would be prudent to delay approval of this supplement until the cardiovascular and ophthalmic safety data from the osteoporosis fracture trial have been adjudicated by the DSMB and the results reviewed and found acceptable by the Division.

8.7 Postmarketing Risk Management Plan

The major features of Novartis's proposed risk management plan for hypocalcemia are provided below.

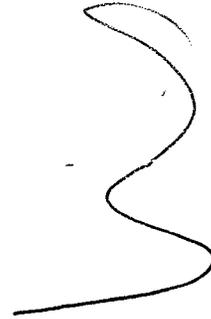
Based on the information presented in this Briefing Book, a minimum of 1000 mg daily of supplemental calcium (elemental) reduces the risk of hypocalcemia in patients with Paget's disease. However, consistent with the recommended daily allowance of calcium for individuals age 65 and over, we recommend all patients with Paget's disease receive a minimum of 1500 mg supplemental calcium daily in divided doses, which will further reduce this risk. This is one component designed to strengthen the language in the Prescribing Information (PRECAUTIONS, Information for Patients, Laboratory Findings sections) and the Patient Product Information. In addition to the labeling, our proposed plan includes enhanced pharmacovigilance activities for hypocalcemia and other risk minimization activities, as follows:

- Expedited reporting of all hypocalcemia adverse events for the first 2 years post-launch and a detailed analysis of hypocalcemia adverse events in the US Periodic Safety Report.

- Patient education materials to reinforce the importance of calcium and vitamin D supplementation via: Patient Prescribing Information (PPI), Patient Brochure, and a consumer web site.

The company is also proposing

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REVIEWER COMMENT: Before this NDA is approved, the Office of Drug Safety will be asked to comment on the likelihood that Novartis's proposed post-approval study would provide meaningful data on the effectiveness of Novartis's risk management plan to minimize hypocalcemia.

9 OVERALL ASSESSMENT

9.1 Conclusions

Novartis has provided sufficient evidence to support the safety of a single infusion of 5 mg zoledronic acid in the treatment of Paget's disease. Patient's taking at least 500 mg bid of supplemental calcium and 800 IU of supplemental vitamin D per day have a notably lower risk of developing hypocalcemia compared with those taking less than these amounts. The risks for hypocalcemia (and hypophosphatemia) would be further reduced if healthcare providers ensure that pre-treatment levels of serum calcium, magnesium (hypomagnesemia can cause hypocalcemia), phosphorus, and 25OH vitamin D are normal. Repeat measurement of serum calcium, magnesium, and phosphorus within seven-to-ten days following drug treatment would also enhance patient safety.

9.2 Recommendation on Regulatory Action

Pending review of adjudicated cardiovascular and ophthalmic safety data from the ongoing osteoporosis trial 2301, this application should be considered approvable.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

If approved for Paget's disease, the zoledronic acid labeling should recommend that: 1) patients take at least 500 mg bid supplemental calcium and 800 IU vitamin D per day; 2) serum calcium, phosphorus, magnesium, and 25OH vitamin D be measured prior to dosing; 3) low levels of these parameters be normalized prior to drug administration; and 4) serum calcium, magnesium, and phosphorus levels be measured within seven-to-ten days post-dose. The labeling should also point out that patients with a history of thyroid or parathyroid surgery, resection of the proximal

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small bowel, or significant malabsorption (e.g., celiac disease) are at increased risk for developing hypocalcemia following treatment with zoledronic acid.

9.3.2 Required Phase 4 Commitments

Details of required phase 4 commitments will be provided at the time of this application's approval.

9.3.3 Other Phase 4 Requests

Details of other required phase 4 requests will be provided at the time of this application's approval.

10 APPENDICES

10.2 Line-by-Line Labeling Review

A detailed labeling review will be conducted prior to an approval action.

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Mary Parks
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concur with Dr. Colman

CLINICAL REVIEW

Application Type 21-817

Letter Date 21 September 2004
Stamp Date 24 September 2004
PDUFA Goal Date 21 March 2005

Reviewer Name Eric Colman
Review Completion Date 18 March 2005

Established Name Zoledronic Acid
(Proposed) Trade Name Aclasta
Therapeutic Class Bisphosphonate
Applicant Novartis

Priority Designation P

Formulation Intravenous
Dosing Regimen 5 mg
Indication Paget's disease of bone
Intended Population Patients with Paget's disease

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Clinical Review
{E. Colman, MD}
{NDA 21-817}
{Zoledronic Acid for Paget's disease}

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This Reviewer recommends that this application be deemed Approvable.

Through conduct of two identical randomized, double-blind, active-controlled, non-inferiority trials, Novartis has provided sufficient evidence to support the efficacy of a single 5 mg intravenous infusion of zoledronic acid in the treatment of Paget's disease of bone. The applicant has not, however, provided adequate evidence to support the safety of the proposed dosing regimen in this population of patients. Approximately 20% of all of the subjects treated with zoledronic acid developed hypocalcemia or hypophosphatemia within 7 to 14 days post-dosing; whereas, very few subjects treated with risedronate did so during this time frame, or at later time points in the trial when, based on previous studies of risedronate in Paget's patients, one would anticipate nadirs for calcium and phosphorus following daily risedronate dosing.

Because the company does not have data regarding the amounts of supplemental calcium and vitamin D the subjects were provided during the early portions of the studies, nor do they have any data on compliance with the recommended supplementation regimen, it is not possible to assess the effect of calcium and vitamin D intake on the risk for developing low levels of serum calcium and phosphorus.

It is this Reviewer's opinion that the submitted data do not support a favorable balance of benefits to risks for zoledronic acid in the treatment of Paget's disease of bone. If the sponsor is able to demonstrate that a regimen of calcium and vitamin D supplementation prior to and/or during the first 2 to 3 weeks following dosing substantially reduces the risk for hypocalcemia and hypophosphatemia, I believe the benefit-risk profile of zoledronic acid would then be favorable and supportive of regulatory approval.

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Zoledronic acid, trade name, Zometa, is an intravenously administered bisphosphonate currently approved (4 mg) for the treatment of hypercalcemia of malignancy and bone metastases in patients with certain types of cancer. The current application seeks approval of a single 5 mg dose of zoledronic acid for the treatment of Paget's disease of bone.

The sponsor conducted two identical multinational, randomized, double-blind, active-controlled 6-month non-inferiority studies to examine the efficacy and safety of zoledronic acid to risedronate in the treatment of Paget's disease. Approximately 360 male and female, 42 to 94-year old, primarily Caucasian patients with Paget's disease of bone, confirmed by serum bone-specific alkaline phosphatase levels at least 2 times the upper limit of normal, were randomized 1:1 to treatment with a single 15-minute infusion of 5 mg of zoledronic acid or to 30 mg daily oral risedronate x 2 months. Although all patients were instructed to take 500 mg of supplemental calcium twice a day and 400 to 1000 IU of daily vitamin D, it is unknown how many actually complied with these directives.

About 50% of the patients in the studies had not received drug therapy prior to enrollment. Approximately 45% of the patients had received at least one course of therapy with an oral or intravenous bisphosphonate before taking part in the zoledronic acid trials. Approximately 93% of the subjects in both treatment groups completed the core 6 months of the trials.

1.3.2 Efficacy

The primary efficacy endpoint was a comparison of the proportion of patients in each treatment group who either had normalization or a reduction of at least 75% from baseline of their serum bone-specific alkaline phosphatase at the end of 6 months. Alkaline phosphatase, a marker of bone formation, is the standard parameter used to evaluate the efficacy of drugs used to treat Paget's disease. While this biochemical marker correlates with the severity of the underlying disease, to this Reviewer's knowledge, there is no evidence that normalization of alkaline phosphatase levels with drug therapy prevents serious morbidity such as fractures associated with long-standing Paget's disease. Nonetheless, reduction in alkaline phosphatase following drug treatment often correlates with a reduction in bone pain – a common presenting symptom of the disease – and this biochemical parameter is a reasonable endpoint upon which to base regulatory approval.

Risedronate 30 mg daily for 2 months is currently approved for Paget's disease and this regimen served as the active control in the two zoledronic acid pivotal studies. The non-inferiority

criterion of -0.16 for the difference between treatment groups in the proportion of therapeutic responders was based on the efficacy results from the pivotal studies conducted to support FDA approval of risedronate for the treatment of Paget's disease. The non-inferiority margin of -0.16 allows 75% of the treatment effect demonstrated by risedronate relative to etidronate to be preserved. In other words, -0.16 is approximately 25% of the observed difference between etidronate and risedronate which was minus 0.65.

At Month 6, 96% of the subjects treated with zoledronic acid and 74% of the subjects treated with risedronate achieved a therapeutic response. The point estimate for the difference between groups in response rates was 22% with a 95% confidence interval of 14% to 30%. From a statistical standpoint, these results demonstrate that zoledronic acid was not only non-inferior to risedronate (i.e., lower bound of the 95% confidence interval for the difference between groups was > -16%), but superior as well.

The response rates to treatment with zoledronic acid and risedronate were similar for subjects < 65 years, 65-75 years, or those ≥ 75 years; for male and female patients; and for subjects with baseline serum alkaline phosphatase levels ≤ or > 3 times the upper limit of normal.

The following table provides the primary efficacy outcome by number of pharmacological treatments received prior to enrollment in the zoledronic acid studies. It is clear that patients who received prior drug treatment for their Paget's disease responded more favorably to zoledronic acid than to risedronate. The lowest response rates in the risedronate-treated subjects were seen in those who had previously received treatment with risedronate.

Proportion of Therapeutic Responders by Number of Previous Drug Treatment Cycles					
Subgroup	Zoledronic acid n/N (Proportion)	Risedronate n/N (Proportion)	Difference ¹ (95% CI)	p-value ² for treatment difference	p-value ³ for subgroup interaction
Previous treatment cycles					
None	80/82 (0.98)	65/76 (0.86)	0.12 (0.02, 0.22)	0.0075	0.3553
1	41/45 (0.91)	32/46 (0.70)	0.22 (0.03, 0.40)	0.0098	
2-3	24/24 (1.00)	16/27 (0.59)	0.41 (0.18, 0.64)	0.0005	
>3	24/25 (0.96)	14/22 (0.64)	0.32 (0.06, 0.59)	0.0020	

¹ Difference is zoledronic acid minus risedronate; 95% CI for the difference is based on the normal approximation to the binomial.
² p-value is based on a Mantel-Haenszel test controlling for study for each category.
³ p-value is based on a Breslow-Day test with the subgroup as a controlling factor.

Regarding secondary efficacy endpoints, the relative reductions in serum CTx at Day 10, urine α-CTx at Day 10, and serum alkaline phosphatase at Day 28 were all statistically significantly larger in the zoledronic acid vs. the risedronate groups. Although pain scores decreased from baseline to the end of the studies in both treatment groups, the differences between the zoledronic acid and risedronate-treated patients were not statistically significant.

1.3.3 Safety

The principal safety concerns that emerged from the pivotal Paget's trials were hypocalcemia and hypophosphatemia. Asymptomatic reductions in serum levels of calcium and phosphorus have been observed in Paget's patients treated with oral alendronate and risedronate, but by comparison, the risk appeared to be greater and occur more rapidly following treatment with 5 mg of intravenous zoledronic acid.

At Day 10 of the trials, 32 of the 151 (21%) patients who received zoledronic acid vs. 5 of the 156 (3.0%) who received risedronate, had serum calcium levels below 2.1 mmol/L. Twenty-eight of the 157 (18%) subjects who received zoledronic acid compared with 2 of the 159 (1.3%) treated with risedronate developed serum phosphorus levels below 0.71 mmol/L (2.1 mg/dl) at Day 10. Four of the zoledronic acid subjects and none of the risedronate subjects developed markedly low serum calcium levels (< 1.87 mmol/L) at Day 10.

At Day 63, a time point where one would more likely see low levels of serum calcium and phosphorus in patients treated with daily risedronate, 2.4% of the zoledronic acid subjects and 4.8% of the risedronate subjects had low serum calcium levels; 0.6% of the zoledronic acid subjects and none of the risedronate subjects had low serum phosphorus levels at Day 63.

Although all patients in the two pivotal trials were instructed to take 500 mg of supplemental calcium twice daily and 400 to 1000 IU of daily vitamin D, the sponsor does not have data to verify if, when, or how much of the supplements were actually taken. Absent this information, it is not possible to judge how effective supplemental calcium and/or vitamin D are in reducing the risk for hypocalcemia and hypophosphatemia, and leaves open to debate the question of the safety of the proposed dosing regimen.

Renal injury, defined as an increase in serum creatinine > 0.5 mg/dl, has been observed in patients, primarily those with cancer, treated with one or more doses of intravenous zoledronic acid. There was no compelling evidence from the Paget's trials that a single 5 mg infusion of zoledronic acid administered over 15 minutes adversely affected renal function when compared with patients treated with 30 mg daily risedronate for 2 months.

Although not a serious safety issue, more zoledronic acid than risedronate-treated subjects reported symptoms consistent with an acute-phase like reaction. These symptoms included influenza-like illness, pyrexia, rigors, and myalgia. By and large, these symptoms occurred soon after administration of zoledronic acid and resolved spontaneously within 72 hours.

1.3.4 Dosing Regimen and Administration

Novartis has provided ample evidence that a single infusion of 5 mg zoledronic acid is effective (i.e., lowers serum alkaline phosphatase levels) in the treatment of Paget's disease. However, the large percentage of patients who developed hypocalcemia and hypophosphatemia within 10 days following dosing raises concern about the safety of this regimen in this population of patients. While it is reasonable to assume that appropriate use of supplemental calcium and vitamin D

prior to and following administration of zoledronic acid will ameliorate or at least attenuate the development of low serum calcium and phosphorus levels, the sponsor does not have empiric evidence to support this claim.

1.3.5 Drug-Drug Interactions

Caution is warranted when administering zoledronic acid concomitantly with drugs that have the potential to lower serum calcium levels, such as loop diuretics or aminoglycosides. *In-vivo* data do not indicate that zoledronic acid inhibits microsomal CYP450 enzymes.

1.3.6 Special Populations

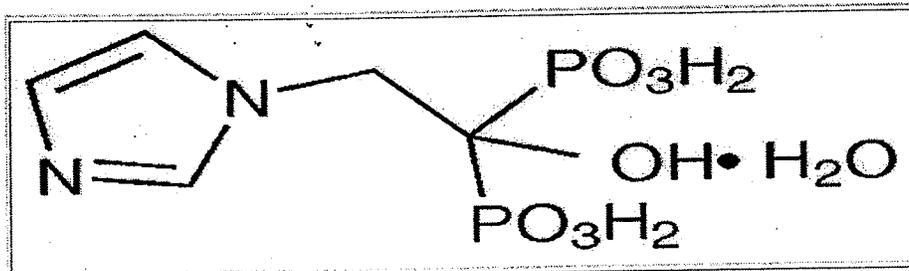
The dose of zoledronic acid should be reduced in patients with renal insufficiency.

Appears This Way
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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zoledronic acid, trade named Zometa, is a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zometa, 4 mg intravenous injection, is approved for the treatment of hypercalcemia of malignancy and for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

2.2 Currently Available Treatment for Indications

The following drugs are approved for the treatment of Paget's disease of the bone:

Actonel Tablets (Procter and Gamble)

Risedronate Sodium

Aredia for Injection (Novartis)

Pamidronate Disodium

Didronel Tablets (Procter & Gamble Pharmaceuticals)

Etidronate Disodium

Fosamax Oral Solution (Merck)

Alendronate Sodium

Fosamax Tablets (Merck)

Alendronate Sodium

Miacalcin Injection (Novartis)

Calcitonin-Salmon

All of the above drugs, with the exception of Miacalcin are bisphosphonates; Miacalcin is a salmon calcitonin product that, like the bisphosphonates, slows bone resorption through inhibition of osteoclast function.

2.3 Availability of Proposed Active Ingredient in the United States

Zoledronic acid, 4 mg intravenous injection, is approved for the treatment of hypercalcemia of malignancy and for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

2.4 Important Issues With Pharmacologically Related Products

The principal safety concern with the intravenous bisphosphonates is renal toxicity. The approval of 4 mg intravenous Zoledronic acid for the treatment of hypercalcemia malignancy was delayed due to concerns about renal injury, i.e., increases in serum creatinine. The dosing regimen was changed to prolong the infusion of drug to 15 minutes.

The following language appears in the Warnings section of the approved labeling for Zometa:

DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOMETA SHOULD NOT EXCEED 4 MG AND THE DURATION OF INFUSION SHOULD BE NO LESS THAN 15 MINUTES.

BECAUSE SAFETY AND PHARMACOKINETIC DATA ARE LIMITED IN PATIENTS WITH SEVERE RENAL IMPAIRMENT:

- **ZOMETA TREATMENT IS NOT RECOMMENDED IN PATIENTS WITH BONE METASTASES WITH SEVERE RENAL IMPAIRMENT.** In the clinical studies, patients with serum creatinine >3.0 mg/dL were excluded.
- **ZOMETA TREATMENT IN PATIENTS WITH HYPERCALCEMIA OF MALIGNANCY SHOULD BE CONSIDERED ONLY AFTER EVALUATING THE RISKS AND BENEFITS OF TREATMENT.** In the clinical studies, patients with serum creatinine >400 mmol/L or >4.5 mg/dL were excluded.

Bisphosphonates, including Zometa[®] (zoledronic acid) Injection, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. In clinical trials, the risk for renal function deterioration (defined as an increase in serum creatinine) was significantly increased in patients who received Zometa over 5 minutes compared to patients who received the same dose over 15 minutes. In addition, the risk for renal function deterioration and renal failure was significantly increased in patients who received Zometa 8 mg, even when given over 15 minutes. While this risk is reduced with the Zometa 4-mg dose administered over 15 minutes, deterioration in renal function can still occur. Risk factors for this deterioration include elevated baseline creatinine and multiple cycles of treatment with the bisphosphonate.

Patients who receive Zometa should have serum creatinine assessed prior to each treatment. Patients treated with Zometa for bone metastases should have the dose withheld if renal function has deteriorated. Patients with hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk.

