CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-817

Trade Name: Reclast injection

Generic Name: zoledronic acid

Sponsor: Novartis Pharmaceuticals Company

Approval Date: April 19, 2007

Indications: For the treatment of Paget's disease of bone.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-817

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	X
Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	X
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative/Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-817

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-817

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms Mellor:

Please refer to your new drug application (NDA) dated and received September 21, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reclast (zoledronic acid) Injection.

We also acknowledge receipt of you submissions dated October 13, 2006, and April 13, 2007. The October 13, 2006 submission constituted a complete response to our February 22, 2006 action letter.

This new drug application provides for the use of Reclast (zoledronic acid) Injection for the treatment of Paget's disease of bone.

We have completed the review of this application, as amended. It is approved effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, patient package insert carton and container labels submitted April 13, 2007).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDA*. For administrative purposes, designate this submission "**FPL for approved NDA 21-817**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitment in your submission dated April 13, 2007. This commitment is listed below.

1. You agreed to perform a registry study to determine the incidence of hypocalcemia post Reclast treatment in patients with Paget's Disease.

Protocol Submission:	by September 30, 2007
Study Start:	by March 31, 2008
Final Report Submission:	by September 30, 2010

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."

We also note in your April 13, 2007 letter that you will submit expedited reports of all hypocalcaemia adverse events for the first 2 year post-launch, and a detailed analysis of hypocalcemia adverse events in the US Periodic Report. Further, you agreed to implement physician and patient education initiatives. In addition, we note that you agreed to submit results from your Reclast safety database of medication errors that occur in the United States for two years following the date of approval on a quarterly basis. This data will be included in the US Periodic Report.

Further, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 796-1224.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Eric Colman
4/16/2007 05:54:53 PM
Eric Colman for Mary Parks

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-817

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-817

Novartis Pharmaceuticals Corporation
Attention: Mathias Hukkelhoven
Global Head, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Hukkelhoven:

Please refer to your new drug application (NDA) dated and received September 21, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Reclast (zoledronic acid) Injection.

We also refer to your submission dated August 23, 2005, received August 25, 2005, which was a complete response to our March 18, 2005 action letter.

Further, we acknowledge receipt of your submissions dated November 15, and 18, and December 23, 2005, and interim efficacy and safety data from the osteoporosis fracture prevention trial CZOL446H2301.

This new drug application provides for the use of Reclast (zoledronic acid) Injection for the treatment of Paget's disease of bone. We have completed the review of this application, as amended, and it is approvable. While you have provided evidence to support the efficacy of a single 5 mg infusion of zoledronic acid, and evidence that [redacted] 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.

Also, revision of the draft labeling will be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 796-1224.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Mary Parks
2/22/2006 04:39:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-817

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Mellor:

Please refer to your new drug application (NDA) dated and received September 21, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aclasta (zoledronic acid) Injection.

We acknowledge receipt of your submissions dated September 21, October 4, November 16, and December 6, 15, and 17, 2004, and January 5, 17, 19, 20, 21(2), and 26, February 9, 14, 25, 21, and 25, March 1, February 25(2), and March 1, 9, and 15(2) 2005.

This new drug application provides for the use of Aclasta (zoledronic acid) Injection for the treatment of Paget's disease of bone. We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

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 [redacted] take 1500 mg a day of supplemental calcium [redacted]

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.

Also, revision of the draft labeling will be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

David Orloff
3/18/05 03:42:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-817

LABELING

NOVARTIS

Reclast®

(zoledronic acid) Injection

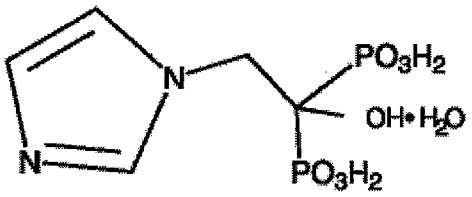
Solution for Intravenous Infusion

Rx only

Prescribing Information

DESCRIPTION

Reclast® contains zoledronic acid which in solution is available as zoledronate at physiological pH. Zoledronate is a bisphosphonate that inhibits osteoclast-mediated bone resorption. The parent compound from which zoledronate is prepared is zoledronic acid monohydrate which is designated chemically as (1-hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zoledronic acid monohydrate is a white crystalline powder with the molecular formula of $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and a molar mass of 290.1g/Mol. Zoledronic acid monohydrate is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.

Reclast® (zoledronic acid) Injection is available as a sterile solution in bottles for intravenous infusion. One bottle with 100 mL solution contains 5.330 mg of zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis. *Inactive Ingredients*: mannitol, USP, as bulking agent, and sodium citrate, USP, as buffering agent, water for injection, USP. Zoledronic acid is marketed for oncology indications under the brand name Zometa® (zoledronic acid) Injection 4 mg concentrate for intravenous infusion.

CLINICAL PHARMACOLOGY

Mechanism of Action/Pharmacodynamics

Reclast (zoledronic acid) Injection belongs to the bisphosphonate class and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Intravenously administered zoledronic acid rapidly partitions to bone and as other bisphosphonates, localizes preferentially at sites of high bone turnover. The main

molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase, but this does not exclude other inhibitory mechanisms. The relatively long duration of action of zoledronic acid is attributable to its strong binding affinity to bone mineral. Histomorphometric data from rat and monkey studies showed a dose-dependent reduction in osteoclastic bone resorption and bone turnover.

Paget's Disease of Bone

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoclastic bone resorption is followed by irregular osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

Pharmacokinetics

Pharmacokinetic data in patients with Paget's disease of bone are not available.

Distribution

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve ($AUC_{0\text{-}24h}$) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean $AUC_{0\text{-}24h}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 22% and was independent of the concentration of zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases on average (± s.d.) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 403 ± 118 ng/mL vs 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations

Pharmacokinetic data in patients with Paget's disease of bone are not available.

Pediatrics: Pharmacokinetic data in pediatric patients are not available.

Geriatrics: The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases whose age ranged from 38 years to 84 years.

Race: The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer and bone metastases.

Hepatic Insufficiency: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid. Zoledronic acid does not inhibit human P450 enzymes in vitro, shows no biotransformation, and in animal studies < 3 % of the administered dose was recovered in the feces. This suggests no relevant role of liver function in the pharmacokinetics of zoledronic acid and no required dosage adjustment.

Renal Insufficiency: The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately-impaired renal function. Compared to patients with normal renal function (creatinine clearance > 80 mL/min, N=37), patients with mild renal impairment (creatinine clearance = 50-80 mL/min, N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (creatinine clearance = 30-50 mL/min, N=11) showed an average increase in plasma AUC of 43%. No dosage adjustment is required in patients with a creatinine clearance of > 30mL/min. Reclast (zoledronic acid) is not recommended for patients with severe renal impairment (creatinine clearance <35 mL/min) due to lack of adequate clinical experience in this population. (See PRECAUTIONS.)

CLINICAL STUDIES

Paget's Disease of the Bone

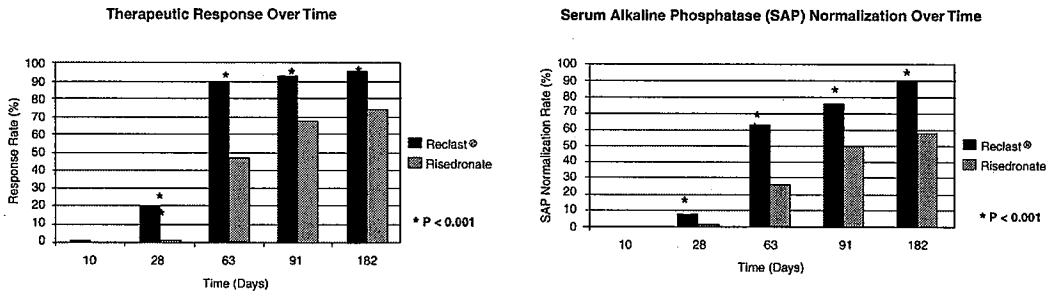
Reclast® (zoledronic acid) Injection was studied in male and female patients with moderate to severe disease (serum alkaline phosphatase level at least twice the upper limit of the age-specific normal reference range at the time of study entry), with confirmed Paget's disease of bone. Diagnosis was confirmed by radiographic evidence.

The efficacy of one infusion of 5-mg Reclast vs oral daily doses of 30 mg-risedronate for 2 months was demonstrated in two identically designed 6-month randomized, double blind trials. The mean age of patients in the two trials was 70. Ninety-three percent (93%) of patients were Caucasian. Therapeutic response was defined as either normalization of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of 6 months. SAP excess was defined as the difference between the measured level and midpoint of normal range.

In both trials Reclast demonstrated a superior and more rapid therapeutic response compared with risedronate and returned more patients to normal levels of bone turnover, as evidenced by biochemical markers of formation (SAP, serum N-terminal propeptide of type I collagen [P1NP]) and resorption (serum CTx 1 [cross-linked C-telopeptides of type I collagen] and urine α-CTx).

The 6-month combined data from both trials showed that, 96% (169/176) of Reclast-treated patients achieved a therapeutic response as compared with 74% (127/171) of patients treated with risedronate. Most Reclast patients achieved a therapeutic response by the Day 63 visit. In addition, at 6 months, 89% (156/176) of Reclast-treated patients achieved normalization of SAP levels, compared to 58% (99/171) of patients treated with risedronate ($p<0.0001$) (see Figure 1).

Figure 1. Therapeutic Response/ Serum Alkaline Phosphatase (SAP) Normalization Over Time



The therapeutic response to Reclast was similar across demographic and disease-severity groups defined by gender, age, previous bisphosphonate use, and disease severity (see Table 1). At 6 months, the percentage of Reclast-treated patients who achieved therapeutic response was 97% and 95%, respectively, in each of the baseline disease severity subgroups (baseline SAP < 3xULN, ≥ 3xULN) compared to 75% and 74%, respectively, for the same disease severity subgroups of risedronate-treated patients.

In patients who had previously received treatment with oral bisphosphonates, therapeutic response rates were 96% and 55% for Reclast and risedronate, respectively. The comparatively low risedronate response was due to the low response rate (7/23, 30%) in patients previously treated with risedronate. In patients naïve to previous treatment, a greater therapeutic response was also observed with Reclast (98%) relative to risedronate (86%). In patients with symptomatic pain at screening, therapeutic response rates were 94% and 70% for Reclast and risedronate respectively. For patients without pain at screening, therapeutic response rates were 100% and 82% for Reclast and risedronate respectively.

Bone histology was evaluated in 7 patients with Paget's disease 6 months after being treated with Reclast 5 mg. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodeling and no evidence of mineralization defect.

ANIMAL PHARMACOLOGY

Zoledronic acid is a potent inhibitor of osteoclastic bone resorption. In the ovariectomized rat, single iv doses of zoledronic acid of 4-500 μg/kg (<0.1 to 3.5 times human exposure at the 5 mg intravenous dose, based on mg/m2 comparison) suppressed bone turnover and protected against trabecular bone loss, cortical thinning and the reduction in vertebral and femoral bone strength in a dose-dependent manner. At a dose equivalent to human exposure at the 5 mg intravenous dose, the effect persisted for 8 months, which corresponds to approximately 8 remodeling cycles or 3 years in humans.

In ovariectomized rats and monkeys, weekly treatment with zoledronic acid dose-dependently suppressed bone turnover and prevented the decrease in cancellous and cortical BMD and bone strength, at yearly cumulative doses up to 3.5 times the intravenous human dose of 5 mg, based on mg/m2 comparison. Bone tissue was normal and there was no evidence of a mineralization defect, no accumulation of osteoid, and no woven bone.

INDICATIONS AND USAGE

Paget's Disease

Reclast® (zoledronic acid) Injection is indicated for the treatment of Paget's disease of bone in men and women.

Treatment is indicated in patients with Paget's disease of bone with elevations in serum alkaline phosphatase of two times or higher than the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease, to induce remission (normalization of serum alkaline phosphatase).

CONTRAINDICATIONS

- Hypocalcemia
- Hypersensitivity to the active substance or to any of the excipients
- Pregnancy and lactation

WARNINGS

A single dose of Reclast® (zoledronic acid) Injection should not exceed 5 mg and the duration of infusion should be no less than 15 minutes.

Hypocalcemia may occur with Reclast therapy. To reduce the risk of hypocalcemia, all patients should receive 1500 mg elemental calcium daily in divided doses (750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D daily, particularly in the 2 weeks following Reclast administration (see PRECAUTIONS).

Reclast may cause fetal harm when administered to a pregnant woman. Reclast should not be used during pregnancy. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.. (See PRECAUTIONS, Pregnancy Category D.)

PRECAUTIONS

General

Reclast® (zoledronic acid) Injection contains the same active ingredient found in Zometa, used for oncology indications, and a patient already being treated with Zometa should not be treated with Reclast.

Mineral Metabolism

Reclast may cause hypocalcemia. Pre-existing hypocalcemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Reclast. (See CONTRAINDICATIONS.) Disturbances of calcium and mineral metabolism (e.g., hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine) must be effectively treated and clinical monitoring of calcium and mineral levels is highly recommended for these patients.

To reduce the risk of hypocalcemia, all patients should receive 1500 mg elemental calcium daily in divided doses (750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D daily, particularly in the 2 weeks following Reclast administration. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of hypocalcemia. (See WARNINGS , ADVERSE REACTIONS, Laboratory Findings and Information For Patients.)

Renal Insufficiency

Reclast is not recommended for use in patients with severe renal impairment (creatinine clearance <35mL/min) due to lack of adequate clinical experience in this population. (See DOSAGE AND ADMINISTRATION.)

To prevent renal dysfunction, patients, especially those receiving diuretic therapy, should be appropriately hydrated prior to administration of Reclast. (See DOSAGE AND ADMINISTRATION.)

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates including zoledronic acid. Dental surgery may exacerbate the condition. Most cases have been in cancer patients undergoing dental procedures such as tooth extraction. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. The clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates, including Reclast.

Information for Patients

Physicians should instruct their patients to read the Patient Information before starting therapy with Reclast, solution for intravenous infusion. Patients should be made aware that Reclast contains the same active ingredient (zoledronic acid) found in Zometa®, and that patients already being treated with Zometa should not be treated with Reclast.

Before being given Reclast patients should tell their doctor if they have kidney problems and what medications they are taking.

Reclast should not be given if the patient is pregnant or plans to become pregnant, or if they are breast-feeding. (See CONTRAINDICATIONS and WARNINGS.)

If the patient had surgery to remove some or all of the parathyroid glands in their neck, or had sections of their intestine removed, or are unable to take calcium supplements they should tell their doctor.

In Paget's disease, bone breaks down too much and the new bone made is not normal. Because most people do not get enough calcium and vitamin D in their diet, it is important that patients take calcium and vitamin D supplementation (for example, tablets) as directed by their doctor. After getting Reclast it is strongly recommended patients with Paget's disease take calcium in divided doses (for example, 2 to 4 times a day) for a total of 1500 mg calcium a day to keep blood calcium at a healthy level. This is especially important for the two weeks after getting Reclast.

Reclast is given as a single infusion into a vein by a nurse or a doctor, and the infusion time must not be less than 15 minutes. On the day of treatment patients should eat and drink normally, which includes drinking at least 2 glasses of fluid such as water within a few hours prior to the Reclast infusion, as directed by their doctor. (See PRECAUTIONS.)

Patients should also be aware of the most common side effects of therapy. Patients may experience one or more side effects that could include: fever and chills; muscle, bone or joint pain; nausea; fatigue; and headache. Most of these side effects are mild to moderate and occur within 3 days after taking Reclast. They usually go away within 4 days after they start. Patients should consult their physician if they have questions. Some patients may experience low blood calcium after getting Reclast. Symptoms from low blood calcium are uncommon but may include numbness or tingling sensations (especially in the area around the mouth), or muscle spasms. Patients should consult their physician immediately if they develop these symptoms. (See ADVERSE REACTIONS.)

Physicians should inform their patients that there have been reports, primarily in patients treated with bisphosphonates for other illnesses, of persistent pain and/or non-healing sore of the mouth or jaw. If patients experience these symptoms they should tell their physician or dentist.

Drug Interactions

In vitro studies indicate that zoledronic acid is approximately 22% bound to plasma proteins. *In vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug. However, no *in vivo* drug interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This has not been reported in zoledronic acid clinical trials. Caution should also be exercised when zoledronic acid is used in combination with loop diuretics due to an increased risk of hypocalcemia. Caution is indicated when zoledronic acid is used with other potentially nephrotoxic drugs.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Two-year oral carcinogenicity studies were conducted in mice and rats. Rats were given daily oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg. No increased incidence of tumors was observed (at doses $\leq$0.1 times the human intravenous dose of 5 mg, based on a comparison of relative body surface areas). Mice were given daily oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses $\geq$0.002 times the human intravenous dose of 5 mg, based on mg/m2 comparison). Rats were given daily oral doses of zoledronate of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses $\leq$0.1 times the human intravenous dose of 5 mg, based on mg/m2 comparison).

Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the in vivo rat micronucleus assay.

Female rats were given daily subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (equivalent to human systemic exposure following a 5 mg intravenous dose, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group and high-dose group (0.3 to 1 times human systemic exposure following a 5 mg intravenous dose, based on

AUC comparison) included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

Pregnancy Category D

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous vs oral) on this risk has not been established.

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups ($\geq$0.3 times the human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison). Adverse maternal effects were observed in all dose groups ($\geq$0.1 times the human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given daily subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg during gestation, adverse fetal effects were observed in the mid- and high-dose groups (about 2 and 4 times human systemic exposure following a 5 mg intravenous dose, based on AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (about 1.2 times the anticipated human systemic exposure, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given daily subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg during gestation (at doses $\leq$0.4 times human systemic exposure following a 5 mg intravenous dose, based on mg/m2 comparison) no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses $\geq$0.04 times the human 5 mg intravenous dose, based on mg/m2 comparison). Adverse maternal effects were associated with drug-induced hypocalcemia. (See CONTRAINDICATIONS and WARNINGS.)

Labor and Delivery

Reclast should not be administered to women during labor and delivery.

Nursing Mothers

It is not known whether Reclast is excreted in human milk. Because many drugs are excreted in human milk, and because Reclast binds to bone long-term, Reclast should not be administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Reclast in pediatric patients have not been established.

Geriatric Use

Phase 3 studies of Reclast in the treatment of Paget's disease of bone included 132 Reclast-treated patients who were at least 65 years of age, while 68 Reclast-treated patients were at least 75 years old. No overall differences in efficacy or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

In the Paget's disease trials, two 6-month, double-blind, comparative, multinational studies of 349 men and women aged > 30 years with moderate to severe disease and with confirmed Paget's disease of bone, 177 patients were exposed to Reclast® (zoledronic acid) Injection and 172 patients exposed to risedronate. Reclast was administered once as a single 5-mg dose in 100 mL solution infused over at least 15 minutes. Risedronate was given as an oral daily dose of 30 mg for 2 months.

The incidence of serious adverse events was 5.1% in the Reclast group and 6.4% in the risedronate group. The percentage of patients who withdrew from the study due to adverse events was 1.7% and 1.2% for the Reclast and risedronate groups, respectively. Consistent with intravenous administration of bisphosphonates.

Adverse reactions occurring in at least 2% of the Paget's patients receiving Reclast (single 5-mg IV infusion) or risedronate (30-mg oral daily dose for 2 months) over a 6-month study period are listed by system organ class in Table 1.

Table 1: Adverse Reactions Reported in at Least 2% of Paget's Patients Receiving Reclast (Single 5-mg IV Infusion) or Risedronate (Oral 30 mg Daily for 2 Months) Over a 6-Month Follow-Up Period

	5 mg IV Reclast®	30 mg/day x 2 Months risedronate
System Organ Class	% (N = 177)	% (N = 172)
Infections and Infestations		
Influenza	7	5
Metabolism and Nutrition Disorders		
Hypocalcemia	3	1
Anorexia	2	2
Nervous System Disorders		
Headache	11	10
Dizziness	9	4
Lethargy	5	1
Paraesthesia	2	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	5	1
Gastrointestinal Disorders		
Nausea	9	6
Diarrhea	6	6
Constipation	6	5
Dyspepsia	5	4
Abdominal distension	2	1
Abdominal pain	2	2
Vomiting	2	2
Abdominal pain upper	1	2
Skin and Subcutaneous Tissue Disorders		
Rash	3	2
Musculoskeletal, Connective Tissue and Bone Disorders		
Arthralgia	9	11

Bone Pain	9	5
Myalgia	7	4
Back pain	4	7
Musculoskeletal stiffness	2	1
General Disorders and Administrative Site Conditions		
Influenza-Like Illness	11	6
Pyrexia	9	2
Fatigue	8	4
Rigors	8	1
Pain	5	4
Peripheral edema	3	1
Asthenia	2	1

Laboratory Findings

In the Paget's disease trials, early, transient decreases in serum calcium and phosphate levels, were observed. Approximately 21% of patients had serum calcium levels <8.4 mg/dL 9-11 days following Reclast administration.

Renal Dysfunction

Treatment with intravenous bisphosphonates has been associated with renal dysfunction manifested as deterioration in renal function (i.e., increased serum creatinine) and in rare cases, acute renal failure. Renal dysfunction has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or additional risk factors (e.g., oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration, etc), the majority of whom received a 4-mg dose every 3-4 weeks, but it has been observed in patients after a single administration. In clinical trials in Paget's disease there is no evidence of renal deterioration following a single 5-mg 15-minute infusion.

Acute Phase Reaction

Reclast has been associated with the signs and symptoms of acute phase reaction, influenza-like illness, pyrexia, myalgia, arthralgia, and bone pain. Symptoms usually occur within the first 3 days following Reclast administration. One or more of these events which were suspected to be related to drug were reported in 25% of patients in the Reclast-treated group compared to 8% in the risedronate-treated group. The majority of these symptoms resolved within 4 days of onset.

Ocular Adverse Events

Cases of iritis/uveitis/episcleritis have been reported in patients treated with bisphosphonates, although no cases were reported in the Paget's disease clinical studies. Conjunctivitis has been reported in patients treated with Reclast.

Injection Site Reactions

Local reactions at the infusion site such as redness, swelling and/or pain has been observed infrequently following the administration of zoledronic acid. No cases were reported in the Paget's disease clinical trials.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw has been reported with Reclast (see PRECAUTIONS).

Bronchoconstriction in Aspirin Sensitive Asthma Patients

While not observed in clinical trials with Reclast there have been previous reports of bronchoconstriction in aspirin sensitive patients receiving bisphosphonates.

OVERDOSAGE

There is no experience of acute overdose with Reclast® (zoledronic acid) Injection . Patients who have received doses higher than those recommended should be carefully monitored. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

Single doses of Reclast should not exceed 5 mg and the duration of the intravenous infusion should be no less than 15 minutes. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

DOSAGE AND ADMINISTRATION

Treatment of Paget's Disease of Bone

The recommended dose is 5 mg of Reclast® (zoledronic acid) Injection in 100 mL ready to infuse solution administered intravenously via a vented infusion line.

Patients must be appropriately hydrated prior to administration of Reclast, this is especially important for patients receiving diuretic therapy (see PRECAUTIONS). Reclast can be dosed without regard to meals.

The infusion time must not be less than 15 minutes (see WARNINGS) given over a constant infusion rate.

To reduce the risk of hypocalcemia, all patients should receive 1500 mg elemental calcium daily in divided doses (750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D daily, particularly in the 2 weeks following Reclast administration. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of hypocalcemia. (See PRECAUTIONS.)

Reclast solution for infusion must not be allowed to come in contact with any calcium-containing solutions, and should be administered as a single intravenous solution through a separate vented infusion line.

The recommended dose in patients with creatinine clearance >35mL/min is 5 mg of Reclast (zoledronic acid) infused over no less than 15 minutes at a constant infusion rate. (See WARNINGS, PRECAUTIONS, Renal Insufficiency.)

Re-treatment of Paget's Disease

After a single treatment with Reclast in Paget's disease an extended remission period is observed. Specific re-treatment data are not available. However, re-treatment with Reclast may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, or in those patients who failed to achieve normalization of their serum alkaline phosphatase, or in those patients with symptoms, as dictated by medical practice.

HOW SUPPLIED

Reclast® (zoledronic acid) Injection, solution for intravenous infusion, is available as a sterile solution at a pH between 6.0 to 7.0. Each plastic bottle contains 5.330 mg zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis, 4950 mg of mannitol, USP, and 30 mg of sodium citrate, USP, and 100mL water for injection, USP.

5 mg/100 mL Bottle.....NDC 0078-0435-61

After opening, the solution is stable for 24 hours at 2 – 8 °C (36 - 46°F).

If refrigerated, allow the refrigerated solution to reach room temperature before administration.

Note: **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

Storage

Store at 25°C (77°F); excursions permitted to 15 -30°C (59 -86°F) [see USP Controlled Room Temperature].

For more information visit www.reclast.com or call 1-866-732-5278.

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

April 2007 T2007-52

PATIENT INFORMATION
Reclast®
(zoledronic acid) Injection

Solution for Intravenous Infusion

(pronounced RE-klast)

Rx only

Read this information carefully before you get Reclast Injection. Because there may be new information, read the patient leaflet each time you get another dose. This leaflet does not replace talking with your doctor. Only your doctor can prescribe Reclast Injection for you. If you have any questions about Reclast Injection, ask your doctor.

What is the most important information I should know about Reclast?

Reclast contains the same active ingredient (zoledronic acid) found in Zometa® Injection. If you are already being treated with Zometa Injection, you should not receive Reclast Injection.

It is important to drink fluids before getting Reclast, and to take 1500 mg of calcium and 800 IU of vitamin D daily, especially during the first 2 weeks after getting Reclast.

Patients with severe kidney problems should not receive Reclast Injection.

What is Reclast?
Reclast is a medicine to treat adults with Paget's disease of bone.

What is Paget's disease of bone?
Normally bone breaks down and is replaced by new bone. In Paget's disease, bone breaks down too much and the new bone made is not normal. Bones affected by Paget's like the skull, spine, and legs, become deformed and weaker than normal. This can cause problems like bone pain and the bones can bend or break. Paget's disease may be discovered by X-ray examination or blood tests.

How does Reclast work?
Reclast attaches to bone and keeps it from breaking down too much. A single dose works fast and keeps working to make your bones stronger again.

Who should not get Reclast?
You should not get Reclast if:
- Your blood calcium level is too low.
- You have severe kidney problems
- You are pregnant or plan to become pregnant. Reclast may harm your unborn baby.
- You are breast-feeding. It is not known if Reclast could pass through your breast milk into your baby.
- You are allergic to anything in Reclast (the active ingredient is zoledronic acid), or other ingredients in Reclast. There is a list of inactive ingredients in Reclast at the end of this leaflet.

What should I tell my doctor before getting Reclast?
Tell your doctor about all your medical conditions. It is important to tell your doctor if:
- You have kidney problems.
- You have a history of low blood calcium
- You are unable to take daily calcium and vitamin D supplements.
- You had parathyroid or thyroid surgery (these glands are located in your neck).
- You have a malabsorption syndrome
- You had sections of your intestine removed.
- You have asthma (wheezing) from taking aspirin.

Tell your doctor about all the medicines you take, including prescription and nonprescription drugs, herbal remedies, and vitamins. Keep a list of them to show your doctor.

Your doctor needs to know if you are taking any drugs that could harm your kidneys. Give your doctor a list of all your medicines. Your doctor will know if any of your medicines could harm your kidneys.

Your doctor needs to know if you are taking Zometa (zoledronic acid). If you are taking Zometa, you should not take Reclast

You may have experienced side effects to other bisphosphonates such as headache, upset stomach, etc. These are not considered allergic reactions. Consult with your physician if you have questions regarding allergies and side effects.

How will I get Reclast?
- To prevent low blood calcium, it is important to take calcium and vitamin D supplements (for example, tablets) as directed by your doctor. After getting Reclast all patients with Paget's disease should take 1500 mg of calcium a day in divided doses (for example, 750 mg two times a day, or 500 mg three times a day) and 800 IU vitamin D a day to keep your blood calcium at a healthy level. It is especially important to take the calcium and Vitamin D supplements during the first 2 weeks after getting Reclast.
- On the day of your treatment, you should eat and drink normally, which includes drinking at least 2 glasses of fluid (such as water), as directed by your doctor before receiving Reclast.
- Reclast is given intravenously (in your vein) by a nurse or doctor. It takes at least 15 minutes to get your medicine.
- Because Reclast works for a long time, you may not need another dose of Reclast for a year or longer.

How do I know Reclast is still working?

Your doctor can check Paget's disease with a simple blood test.

What are the possible side effects of Reclast?

Patients may get one or more side effects. The most common side effects are mild to moderate and happen within 3 days after you get Reclast. They usually go away within 4 days after they start and could include:

- fever and chills
- pain in your muscles, bones or joints
- nausea
- fatigue
- headache

Skin reactions such as redness, swelling and/or pain at the infusion site may occur. Bisphosphonates (the group of drugs that Reclast belongs to) may cause swelling, redness and itching to the eyes or eye sensitivity to light.

If you have questions about these side effects, talk to your doctor.

Some patients may experience low blood calcium after getting Reclast. Symptoms of low blood calcium may include numbness or tingling sensations (especially in the area around the mouth) or muscle spasms. Contact your doctor immediately if you notice any of these symptoms after getting Reclast.

There have been reports, primarily in patients treated with bisphosphonates for other illnesses, of persistent pain and/or non-healing sore of the mouth or jaw. If you experience these symptoms tell your doctor or dentist.

Inactive ingredients: mannitol, USP, sodium citrate, USP, and water for injection, USP.

General information about Reclast

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. This leaflet is a summary of the most important information about Reclast.

For more information, ask your doctor or visit www.reclast.com or call 1-866-732-5278

APRIL 2007 PRINTED IN U.S.A T2007-51

NOVARTIS

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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.

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

/s/

Theresa Kehoe
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 ≥ ——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 hypocalemia (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.

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

/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

Table of Contents

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 [redacted]. To 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.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zoledronic acid, trade named Zometa and proposed trade name Reclast, is a bisphosphonic acid which acts 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 deterioration 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 trials 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 [redacted] 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]
Trial 2304 No. (%) patients with therapeutic response	85/88 97%	60/82 73%	24% (12%, 35%) p<.0001
Trial 2305 No. (%) patients with therapeutic response	84/88 95%	67/89 75%	20% (9%, 31%) p=.0002
Pooled studies 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 ration 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	----------	----------
Bradyarrhythmia	3 (0.1)	2 (0.0)	----------	----------
Bradycardia	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.

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 ≥ 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

N	Zoledronate 3862	Placebo 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

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)		
	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

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

/s/

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

Eric Colman
4/16/2007 07:23:49 AM
MEDICAL OFFICER

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

Table of Contents

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 suppmental 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.