

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-817**

**APPROVABLE LETTER**



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 500 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.

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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

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/s/

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Mary Parks  
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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.,  $\leq 1.90$  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 \_\_\_\_\_  
\_\_\_\_\_ take 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.

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.

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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

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David Orloff  
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