

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203231Orig1s000

OTHER ACTION LETTERS



NDA 203231

COMPLETE RESPONSE

ACS Dobfar Info SA
Attention: Thomas J. Moutvic
Vice President, Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195

Dear Mr. Moutvic:

Please refer to your New Drug Application (NDA) dated January 06, 2012, received January 09, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zoledronic Acid Injection, 4 mg per 100 mL.

We acknowledge receipt of your amendments dated January 24, and February 20, 2013.

We also acknowledge receipt of your amendment dated January 08, 2013, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The following deficiencies were noted during method validation, and the following methods have been determined to be unacceptable for regulatory purposes. Due to these deficiencies, the Agency is not able to confirm the strength, identity, quality, purity and potency of the proposed drug product as required under 21 CFR 314.50(d)(1).

1. HPLC Method for Assay (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-7), is not acceptable for quality control and regulatory purposes, due to (i) inadequate System Suitability, as the resolution between (b)(4) did not pass because of (b)(4) due to sample overloading, and (ii) using an unacceptable system suitability placebo solution which causes shifts in retention time of the (b)(4) (b)(4) comparing the standard solution placebo.

2. HPLC Method for Unknown Impurities (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-8.2), is not acceptable for quality control and regulatory purposes, due to the same reason as described in 1 above.
3. HPLC Method for Known Impurities (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-8.1), is not acceptable for quality control and regulatory purposes, due to (i) the incorrect description of buffer preparation which caused unrepeatable chromatograph results, and (ii) an incorrect calculation formula which is not in agreement with the standard solution preparation per the method.

In order to address these deficiencies, redevelop and revalidate your regulatory methods for assay, unknown and known impurities, and provide updated regulatory specifications for drug product as well as updated batch analysis data and stability data.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials 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/clinical trials 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

If you have any questions, call Kim J. Robertson, Regulatory Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
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/

AMNA IBRAHIM
03/01/2013



NDA 203231

TENTATIVE APPROVAL

ACS Dobfar Info SA
Attention: Thomas J. Moutvic
Vice President, Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195

Dear Mr. Moutvic :

Please refer to your New Drug Application (NDA) dated January 06, 2012, received January 09, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zoledronic Acid Injection, 4 mg per 100 mL.

We acknowledge receipt of your amendments dated February 08, 2012; March 05 and 30, 2012; April 16, 2012; May 29, 2012, June 27, 2012; July 19, 2012(2); September 06, 2012(3); September 20, 2012; October 05, 10, 15, 17, and 24, 2012.

This NDA provides for the use of Zoledronic Acid Injection, 4 mg per 100 mL for the treatment of:

- Hypercalcemia of malignancy
- Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the package insert, overwrap, carton and immediate container labels). This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

Please note that your submitted data does not support a requested 24 months of shelf-life but it does support a 12-month expiration dating period. When you submit your amendment prior to the expiration of the patent or exclusivity as described below, please either provide additional stability data to support your requested 24 month shelf life or accept a 12-month expiry.

The listed drug upon which your application relies is subject to a period of patent and/or exclusivity protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

To obtain final approval of this application, submit an amendment two or six months prior to the: 1.) expiration of the patent and/or exclusivity protection or 2.) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as “**REQUEST FOR FINAL APPROVAL**”. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and Risk Evaluation and Mitigation Strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not deemed approved.

Please note that this drug product may not be marketed in the United States without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d).

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. See the guidance for industry titled, “Contents of a Complete Submission for the Evaluation of Proprietary Names”, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

If you have any questions, call Kim J. Robertson, Regulatory Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
Overwrap
Carton and Container Labeling

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

AMNA IBRAHIM
11/09/2012