

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203231Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

| | | |
|---|-----------------------------------|---|
| NDA # 203231 BLA # | NDA Supplement # N/A BLA STN # | If NDA, Efficacy Supplement Type: N/A |
| Proprietary Name: N/A Established/Proper Name: Zoledronic Acid Inj. Dosage Form: Injection; 4 mg per 100 mL | | Applicant: ACS DOBFAR INFO S.A. Agent for Applicant (if applicable): N/A |
| RPM: Kim J. Robertson | | Division: Oncology Products 1 |
| <p>NDA's: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> | | <p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA# 021223; Zometa (zoledronic acid) Injectable; IV (Infusion)</p> <p>Provide a brief explanation of how this product is different from the listed drug. The RLD's drug is contained within a Ready-to-Use Solution in a bottle. The (b)(2)'s drug is contained within a Ready-to-Use Solution in a bag. If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: July 22, 2013</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>August 03, 2013</u> | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) | | <input type="checkbox"/> None 1 st Cycle-Refuse to File; October 28, 2011; 2 nd Cycle-Tentative Approval (TA); November 09, 2012; 3 rd Cycle-Complete Response (CR), March 01, 2013 |

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

| | |
|---|---|
| <p>If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p> | <input type="checkbox"/> Received |
| <p>❖ Application Characteristics ²</p> | |
| <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p> | |
| <p>✓ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p> | <input type="checkbox"/> Yes, dates |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| <p>❖ Public communications (<i>approvals only</i>)</p> | |
| <ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • Press Office notified of action (by OEP) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated | <input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

| Exclusivity | |
|--|---|
| <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| <ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____ |
| ❖ Patent Information (NDAs only) | |
| <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| <ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input checked="" type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | <input type="checkbox"/> No paragraph III certification Date patent will expire 4939130*PED Patent Expired March 02, 2013 |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> | <input type="checkbox"/> N/A (no paragraph IV certification) <input checked="" type="checkbox"/> Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

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| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> |
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CONTENTS OF ACTION PACKAGE

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|--|---------------|
| Copy of this Action Package Checklist ³ | July 22, 2013 |
|--|---------------|

Officer/Employee List

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|---|--|
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |

Action Letters

| | |
|---|--|
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Action(s) and date(s) 1st Cycle-Refuse to File; October 28, 2011; 2nd Cycle-Tentative Approval (TA); November 09, 2012; 3rd Cycle-Complete Response (CR), March 01, 2013; 4 th Cycle-Approval August 02, 2013 |
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Labeling

| | |
|--|-----------------------------------|
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| <ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | February 20, 2013 |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | August 30, 2011; January 09, 2012 |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | N/A |

³ Fill in blanks with dates of reviews, letters, etc.

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|--|--|
| <ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) | <input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None |
| <ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | |
| <ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> • Most-recent draft labeling | October 24, 2012 (including overwrap) |
| <ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) | N/A |
| <ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) | <input checked="" type="checkbox"/> RPM March 22, 2012 <input checked="" type="checkbox"/> DMEPA October 19, 2012 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC October 02, 2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews |

Administrative / Regulatory Documents

| | |
|--|---|
| <ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) | March 22, 2012 <input type="checkbox"/> Not a (b)(2) September 24, 2012; January 30, 2013; July 08, 2013 <input type="checkbox"/> Not a (b)(2) July 23, 2013 |
| <ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <ul style="list-style-type: none"> • Applicant is on the AIP • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |
| <ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Application does not trigger PREA</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) | <input type="checkbox"/> Included |
| <ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) | <input checked="" type="checkbox"/> Verified, statement is acceptable |

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

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| Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) | Refer to Outgoing Communications tab in Action Package |
| ❖ Internal memoranda, telecons, etc. | January 20, 2012 |
| ❖ Minutes of Meetings | |
| • Regulatory Briefing (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> N/A or no mtg |
| • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| • EOP2 meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) | |
| ❖ Advisory Committee Meeting(s) | <input checked="" type="checkbox"/> No AC meeting |
| • Date(s) of Meeting(s) | |
| • 48-hour alert or minutes, if available (<i>do not include transcript</i>) | |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None August 02, 2013 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None July 31, 2013; October 19, 2012; October 05, 2012; July 31, 2013 |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input checked="" type="checkbox"/> None |
| Clinical Information⁵ | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) | N/A |
| • Clinical review(s) (<i>indicate date for each review</i>) | October 27, 2011 (filing review); October 18, 2012 |
| • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | None No Clinical studies were done |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> Not applicable |
| ❖ Risk Management | |
| • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) | N/A |
| • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) | <input type="checkbox"/> None |
| • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | |
| ❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) | <input checked="" type="checkbox"/> None requested |

⁵ Filing reviews should be filed with the discipline reviews.

| Clinical Microbiology <input checked="" type="checkbox"/> None | |
|--|--|
| ❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Clinical Microbiology Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Biostatistics <input checked="" type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Statistical Team Leader Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Statistical Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology Team Leader Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> None |
| Clinical Pharmacology review(s) (indicate date for each review) | <input type="checkbox"/> None March 08, 2012; September 19, 2012 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters) | <input checked="" type="checkbox"/> None |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> None |
| • Supervisory Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> None |
| • Pharm/tox review(s), including referenced IND reviews (indicate date for each review) | <input type="checkbox"/> None October 26, 2011; February 22, 2012; October 17, 2012 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review) | <input checked="" type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review) | <input checked="" type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | <input checked="" type="checkbox"/> None Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters) | <input checked="" type="checkbox"/> None requested |

| Product Quality | | <input type="checkbox"/> None |
|---|--|-------------------------------|
| ❖ Product Quality Discipline Reviews | | |
| <ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> | <input checked="" type="checkbox"/> None | |
| <ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> | <input type="checkbox"/> None November 01, 2011; February 22, 2012; March 09, 2012 | |
| <ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> | <input type="checkbox"/> None Biopharmaceutics; February 22, 2012; April 02, 2012; CMC: October 05, 2012; October 19, 2012; February 11, 2013; July 09, 2013 | |
| ❖ Microbiology Reviews | | |
| <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> | <input type="checkbox"/> Not needed February 17, 2012; July 24, 2012 | |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> | | |
| <input checked="" type="checkbox"/> None | | |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | | |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> | CMC Review; October 05, 2012; Page 125 | |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i> | N/A | |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i> | N/A | |
| ❖ Facilities Review/Inspection | | |
| <input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i> | Date completed: February 21, 2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable | |
| <input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i> | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation | |
| ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i> | | |
| <input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review) | | |

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Robertson, Kim

From: Robertson, Kim
Sent: Friday, October 19, 2012 4:31 PM
To: Jeff Scheithe (jscheithe@Sagentpharma.com)
Subject: NDA 203231-Zoledronic Acid Inj.--Additional DMEPA Comment

Importance: High

Hi Jeff:

With regard to Sagent's October 17, 2012 submission addressing our October 12, 2012 DMEPA comments regarding Carton and Container, please note that our DMEPA colleagues have a few more additional comments:

ADDITIONAL DMEPA COMMENTS:

NDA 203231
Zoledronic Acid Injection
4 mg/100 mL (0.04 mg/mL)
Container Label, Overwrap and Carton Labeling Comments

Container Label, Overwrap and Carton Labeling

1. Bold the infusion statement, **Infusion must not be less than ^{(b)(4)} minutes.**
*Note--Your proposed infusion time, ^{(b)(4)} 15 minutes, is still under review.
2. De-bold the storage information. Room temperature storage recommendations do *not* require bolding to alert practitioners.
3. De-bold the following statements:
Sterile, Nonpyrogenic, Preservative Free, DEHP-free, PVC-free. The container closure is not made of natural rubber latex.

Please provide us with updated Carton and Contain Labels no later than Tuesday, October 23, 2012.

Regards,
Kim

Kim J. Robertson

*Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
10/25/2012

Robertson, Kim

From: Robertson, Kim
Sent: Friday, August 24, 2012 3:16 PM
To: Jeff Scheithe (jscheithe@Sagentpharma.com)
Subject: NDA 203231; Zoledronic Acid--Container Label and Carton Labeling Comments

Importance: High

Hello Jeff:

Please note that during the review of Sagent Pharmaceuticals' NDA for Zoledronic Acid Injection 4mg/100mL (0.04 mg/mL), my DMEPA and CMC colleagues have ascertained the following comments:

CONTAINER LABEL AND CARTON LABELING COMMENTS:

A. General Comments

The container label and overwrap labeling are cluttered and require removal of unnecessary text to provide space to prominently display important information. Specifically, healthcare practitioners may experience difficulty locating the route of administration and warning to prevent mixing with calcium containing products. Furthermore, the infusion rate instructions are missing from the container label and carton labeling. In addition, the carton labeling lacks a prominent display of the route of administration, infusion rate, and warning to prevent mixing with calcium containing products.

B. Container Label

1. Revise the established name, ZOLEDRONIC ACID INJECTION, from all capital letters to Title Case and revise the strength, 4 mg/100 mL to include the concentration.
2. Revise the route of administration statement, (b) (4), to read, *For Intravenous Infusion*.
3. Add the infusion rate instructions, *Infusion time must not be less than 15 minutes*.
4. Revise the statement, (b) (4), to read, Single Use Only – Discard Unused Portion.
5. Relocate the route of administration, warning about calcium containing solutions, infusion rate, and single-use statements toward the upper portion of the label to appear below the strength statement. Thus, the principal display panel should appear as follows:

Zoledronic Acid Injection
4 mg/100 mL
(0.04 mg/mL)

For Intravenous Infusion

Do not mix with calcium-containing infusion solutions

Infusion time must not be less than 15 minutes

Single Use Only – Discard Unused Portion

6. Revise the statement, (b) (4), to read as follows:
See insert for dosage and administration.

Note the deletion of the word (b) (4) and use of lowercase letters for *dosage and administration* to remove clutter, create space, and improve readability of more important information.

7. Revise the storage information to read as follows:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

C. Overwrap Labeling

1. Improve the contrast between the black font strength statement and the blue background color to improve readability.
2. See comments from B1 through B7.

D. Carton Labeling

1. Revise the established name, ZOLEDRONIC ACID INJECTION, from all capital letters to Title Case and revise the strength, 4 mg/100 mL to include the concentration.
2. Revise the route of administration statement, (b) (4), to read, *For Intravenous Infusion*.
3. Add the infusion rate instructions, *Infusion time must not be less than 15 minutes*, to the principal display panel.
4. Revise the statement, (b) (4), to read, *Single Use Only – Discard Unused Portion*. Additionally, relocate this statement to the principal display panel.
5. The principal display panel should read as follows:

Zoledronic Acid Injection

4 mg/100 mL

(0.04 mg/mL)

For Intravenous Infusion

Do not mix with calcium-containing infusion solutions

Infusion time must not be less than 15 minutes

Single Use Only – Discard Unused Portion

6. Improve the contrast between the black font strength statement and the blue background color to improve readability.
7. Revise the statement, (b) (4), to read as follows:
See insert for dosage and administration.
8. Revise the storage information to read as follows:
Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

****We will require responses to these comments no later than Thursday, September 6, 2012!!****

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

*Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
08/24/2012

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, June 20, 2013 12:56 PM
To: 'Jeff Scheithe'
Cc: Tom Moutvic; Anne Renick
Subject: RE: NDA 203231; Zoledronic Acid Inj.

Hi Jeff:

Where might I find Sagent's latest C&C information? After we provided Sagent with DMEPA's comments, I'm certain Sagent provided us agreed upon C&C information, but I'm certain that was in 2012. C&C information is not in the February 20, 2013 submission, which means I would have to do as I indicated and have to check several submission locations in our database, as opposed to just referencing one location.

In the "Gratuitous Amendment", you stated you would submit, would you please add C&C, or hyperlinks to the C&C info. as well? As soon as I have what I need, the faster I can expedite my part of the NDA's review.

Thanks Jeff,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Thursday, June 20, 2013 10:38 AM
To: Robertson, Kim
Cc: Tom Moutvic; Anne Renick
Subject: RE: NDA 203231; Zoledronic Acid Inj.

Hi Kim,

Thank you for your response and the letter informing us that you have received the submission and are currently reviewing it.

Concerning the request to submit the current labeling, as I pointed out the most current and up to date labeling was submitted in Sequence 0027 which was submitted on February 20, 2013. This Sequence Number is following the numbering system required by FDA Guidance and should be accessible through your electronic review system.

We will submit a Gratuitous Amendment in which I will add a summary that contains hyperlinks to the current labeling that was submitted as part of the February 20, 2013 submission. I hope this will be helpful in your review of the file.

Thanks, Jeff

Jeff Scheithe
Associate Director of Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, June 19, 2013 4:18 PM
To: Jeff Scheithe
Subject: NDA 203231; Zoledronic Acid Inj.
Importance: High

Hi Jeff:

Please see the attached .pdf document, as it pertains to Sagent Pharmaceuticals, Inc. NDA submission re: Zoledronic Acid Injection.

The review of the NDA's re-submission is still ongoing; however, the CMC reviewer has notified me that she has all that she needs from Sagent to substantiate a complete review of the application from a CMC perspective. I however, would like to reiterate, per our last phone conversation, for ease of review, I still need Sagent to submit labeling (PI/C&C). I am aware that in Sagent's cover letter, it states that labeling has not been revised since its last submission; **Sequence 0027**. Please note however, that this numbering/sequence number means nothing to the Agency, as our numbering differs from that of our external customer. Having to look back and forth between the most recent and previous submissions in our database causes a disjointed review process and lost time for those reviewing Sagent's submission. Also, by submitting the most up-to-date labeling, **all** can ensure that it is consistent with the RLD labeling.

Please submit these materials right away.

Thanks,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441

Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
07/30/2013

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, May 30, 2013 3:49 PM
To: 'Jeff Scheithe'
Subject: RE: Additional Inquiries

Importance: High

Thank you Jeff.

Please be sure to include any updated Patent Information for us as well for this (b)(2). Sagent should refer to its CR letter for any additional materials we may need that would otherwise deem the information to be submitted suitable to be considered a Complete Response to the CR.

Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Thursday, May 30, 2013 9:10 AM
To: Robertson, Kim
Subject: RE: Additional Inquiries

Hi Kim,

Thanks for sending these inquires along to me. We will get working on these immediately. These inquires are not unexpected as they are really just asking us to answer the deficiencies already received which we planned to do of course in an amendment to the submission.

Thanks, Jeff

Have a nice day...

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, May 29, 2013 4:16 PM
To: Jeff Scheithe
Subject: RE: Additional Inquiries
Importance: High

Hi Jeff:

My CMC reviewers are in need of the following information from Sagent:

- Response to deficiency No. 2 in the Agency's Complete Response dated 01-Mar-2013 with supporting experimental data and complete scientific rationale, including, but not limited to, the formation and identity of the unknown peak revealed during the methods validation by FDA's Division of Pharmaceutical Analysis
- Any updated CMC information to address all three deficiencies as stated in the Agency's Complete Response dated 01-Mar-2013

Thank you for your patience Jeff.

Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Wednesday, May 29, 2013 3:33 PM
To: Robertson, Kim
Subject: Additional Inquiries

Hi Kim,

If at all possible, could you please try to deliver to us today any further issues that your team may have for the Zoledronic Acid submission. We are interested in getting all questions answered as soon as possible.

Thanks, Jeff

Jeff Scheithe
Associate Director of Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

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/s/

KIM J ROBERTSON
07/30/2013

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, May 22, 2013 1:17 PM
To: 'Jeff Scheithe'
Subject: RE: Zoledronic Acid NDA 203231, (b) (4)

Hi Jeff:

I have conveyed this information to my **primary** CMC reviewers. Would it be possible that Sagent will have the complete report of its investigation prior to next week? Or, at the very latest before next Tuesday, May 28th?

Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Wednesday, May 22, 2013 12:08 PM
To: Robertson, Kim; Kirby, Christina; Selvam, Mouna P; Bykadi, Gururaj
Cc: Tom Moutvic; Ravi Malhotra; Anne Renick; Jim Hussey
Subject: Zoledronic Acid NDA 203231, (b) (4)

Hello Kim, Christina, Gururaj and Mouna

With guidance from the New Drug FDA team and the St. Louis labs, we performed an investigation on an Unknown Peak that was seen in the St. Louis labs but had never been seen at our labs. Our investigation found that there was an Unknown Peak (b) (4)

Analysis was performed on Sagent's product and on a sample of the innovator's product and this same unknown peak was detected in both products at about the same level.

We will be making the slight modification to our HPLC method to reduce the pH of the mobile phase from 2.3 to 2.2 so that this peak will be resolved. We will also be monitoring this peak from this point on in both the 4mg/100mL (NDA 203231) (b) (4) products. Samples from all current lots of product will be retested, monitoring for this peak.

A complete report on our investigation should be available shortly. We will submit a copy of this report into both applications along with the updated HPLC method and results for retested sample data.

We are confident that with this information that we have complete control of product quality and have responded to concern's involving this unknown peak. Upon submission of the updated method and sample results we would like to ask for the consideration of the agency to approve these two products.

Thanks for everyone's assistance with these products,
Jeff Scheithe

Jeff Scheithe
Associate Director of Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

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/s/

KIM J ROBERTSON
07/30/2013

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, April 30, 2013 2:01 PM
To: 'Jeff Scheithe'
Subject: RE: Zoledronic Acid Teleconference

Hi Jeff:

The CMC reviewer wanted to know if Sagent could provide us its test data/results obtained using the modified method suggested to Sagent by our St. Louis Lab colleagues, per our last discussions, prior to our upcoming t-con?

Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Tuesday, April 30, 2013 8:21 AM
To: Robertson, Kim
Subject: Zoledronic Acid Teleconference

Good Morning Kim,

If possible, could you please send us any information you might have on tomorrow's teleconference so that we might be best prepared for the discussion.

Thanks, Jeff

Jeff Scheithe
Associate Director of Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

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/s/

KIM J ROBERTSON
07/30/2013

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, March 28, 2013 5:23 PM
To: 'Jeff Scheithe'
Cc: Trehy, Michael
Subject: RE: Zoledronic Samples

Importance: High

| Tracking: | Recipient | Read |
|------------------|------------------|-------------------------|
| | 'Jeff Scheithe' | |
| | Trehy, Michael | Read: 3/28/2013 6:22 PM |

Hi again Jeff:

I would like to **confirm** that what you have outlined in your e-mail with regard to what we need from Sagent is correct.

We do however, require additional information as well:

- We would like to have the same sample that Sagent analyzed and reported in its document that was sent to us on 3/27/13; "Chroms for Discussion.docx"
- Several vials of "Placebo for Standard Solution"

Please note that we have begun our re-examination of the samples that we currently have from the NDA method validation, and have already measured several chromatograms using the column Sagent sent for the method validation. We still see the additional peak, and we've formulated some hypotheses regarding its origin. We will test those hypotheses tomorrow. We are prepared to begin working on Sagent's samples as soon as they arrive.

Please forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael L. Trehy, Ph.D.
1114 Market Street, Room 1002
St. Louis, MO 63101

Thanks Jeff,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Thursday, March 28, 2013 8:52 AM
To: Robertson, Kim; Trehy, Michael
Subject: Zoledronic Samples

Hello Kim, Michael,

At the conclusion of yesterday's teleconference concerning Zoledronic Acid Injection, NDA 203231, we were asked to send samples to be retested at the FDA's labs. What I believe is needed would be a sample of each of the three ZA batches already tested by the agency and a sample from a recently produced batch. This would give the agency both very old samples (30 months) and a fresh sample (1-2 months).

Is there anything else the agency would need? Where should we send these samples. We are preparing to send these out today as soon as we can get an answer to these questions.

Thanks again for all your help with this very important product,
Jeff

Jeff Scheithe
Senior Manager of Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

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/s/

KIM J ROBERTSON
07/30/2013

From: Tilley, Amy
Sent: Wednesday, July 03, 2013 4:25 PM
To: 'jscheithe@Sagentpharma.com'
Cc: Robertson, Kim
Subject: Additional CMC Information request - NDA 203231

Importance: High
Jeff,

I am covering today for Kim Robertson. The CMC Review Team has the following Information Request.

Please replace the phrase of (b) (4) with the phrase of (b) (4) in your Amendment SN0031 to reflect the nature of this peak, and submit the revised amendment as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

Never doubt that a small group of thoughtful, committed people can change the world; indeed, it's the only thing that ever has.

--Margaret Mead, The Wagon and the Star

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/s/

AMY R TILLEY
07/03/2013

From: Venugopal.Rajesh
To: ["jscheithe@Sagentpharma.com"](mailto:jscheithe@Sagentpharma.com)
Cc: Alebachew.Elleni
Subject: CMC Information request - NDA 203231
Date: Monday, July 01, 2013 3:42:16 PM

Hello Mr. Scheithe:

On behalf of Ms. Kim Robertson, I am sending you the following information request from our CMC reviewers for your NDA:

Please include the following information in the tables of your proposed drug product regulatory specifications in related sections (e.g.3.2.P.5.1 and 3.2.P.8.1)

For your future batch analysis, please report the amount of this peak accordingly in your annual reports.

| Test | Release Acceptance Criteria | Proposed Shelf Life Acceptance Criteria | Reference Method | ACS Info Internal Method |
|---|------------------------------------|--|-------------------------|---------------------------------|
| (b) (4) (Note: it is generated by the chromatographic system and it is not considered as an impurity). | (b) (4) | (b) (4) | HPLC Internal Method | MCP429.USP-8 |

We kindly request a response by close of business Wednesday, July 3 2013.

Regards,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
07/01/2013



NDA 203231

**ACKNOWLEDGE --
CLASS 1 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:

We acknowledge receipt on January 08, 2013, of your January 08, 2013, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zoledronic Acid Injection, 4mg per 100 mL.

We consider this a class 1 response to our November 09, 2012, action letter. Therefore, the user fee goal date is March 08, 2013.

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

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology
Products
Center for Drug Evaluation and Research

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/s/

KIM J ROBERTSON
02/08/2013

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Monday, October 22, 2012 3:57 PM
To: 'jscheithe@Sagentpharma.com'
Cc: Robertson, Kim
Subject: FDA Information Request - Revised Labeling NDA 203231, Zoledronic Acid Injection

| | | |
|------------------|------------------------------|-------------------------------|
| Tracking: | Recipient | Delivery |
| | 'jscheithe@Sagentpharma.com' | |
| | Robertson, Kim | Delivered: 10/22/2012 3:57 PM |

Good Afternoon Jeff,

Please provide a response by return e-mail and official submission to the attached labeling by COB, Wednesday, 10/24/12



10/22/2012 3:57 PM
From: Sagentpharma.com...

Thank you,
Frank (for Kim Robertson)

Frank H. Cross, Jr., MA, MT (ASCP)
Captain, USPHS Commissioned Corps
Chief, Project Management Staff
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
White Oak Bldg 22, Room 2110
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0876 (office)
(301) 796-9845 (fax)
frank.crossjr@fda.hhs.gov

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

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/s/

FRANK H CROSS
10/22/2012



NDA 203231

**METHODS VALIDATION
MATERIALS RECEIVED**

SAGENT Pharmaceuticals, Inc.
Attention: Jeff Scheithe
1901 N. Roselle Road
Suite 700
Schaumburg, IL 60195-3176

Dear Jeff Scheithe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zoledronic Acid Injection, 4 mg/100 mL and to our September 25, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on October 22, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
10/22/2012

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Monday, October 22, 2012 3:57 PM
To: 'jscheithe@Sagentpharma.com'
Cc: Robertson, Kim
Subject: FDA Information Request - Revised Labeling NDA 203231, Zoledronic Acid Injection

| Tracking: | Recipient | Delivery |
|------------------|------------------------------|-------------------------------|
| | 'jscheithe@Sagentpharma.com' | |
| | Robertson, Kim | Delivered: 10/22/2012 3:57 PM |

Good Afternoon Jeff,

Please provide a response by return e-mail and official submission to the attached labeling by COB, Wednesday, 10/24/12



10/22/2012 3:57 PM
From: Sagentpharma.com...

Thank you,
Frank (for Kim Robertson)

Frank H. Cross, Jr., MA, MT (ASCP)
Captain, USPHS Commissioned Corps
Chief, Project Management Staff
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
White Oak Bldg 22, Room 2110
10903 New Hampshire Avenue
Silver Spring, MD 20993
(301) 796-0876 (office)
(301) 796-9845 (fax)
frank.crossjr@fda.hhs.gov

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/s/

FRANK H CROSS
10/22/2012

Robertson, Kim

From: Robertson, Kim
Sent: Friday, October 12, 2012 3:21 PM
To: Jeff Scheithe (jscheithe@Sagentpharma.com)
Subject: NDA 203231; Additional DMEPA Comments

Importance: High

Hi Jeff:

Please see below some additional DMEPA comments, as they pertain to NDA 203231, Zoledronic Acid Injection and its Carton and Container presentations:

NDA 203231
Zoledronic Acid Injection
4 mg/100 mL (0.04 mg/mL)
Container Label, Overwrap and Carton Labeling Comments

A. Container Label, Overwrap and Carton Labeling

1. Delete the (b) (4) graphics that surround the established name and strength statements, Zoledronic Acid Injection 4 mg per 100 mL (0.04 mg per mL). There should be no intervening matter between the established names and strength. Additionally, the blue color surrounding the established name provides poor color contrast between with black colored font.
2. Revise the established name, Zoledronic Acid Injection, so that the font is of equal size and weight. Currently, *Zoledronic* is more prominent than the other portion of the established name, *Acid Injection*.
3. Delete the large number 4, as it is the most prominent information on the label. We suspect this represents the strength, 4 mg, but we are unsure. However, the strength, 4 mg, appropriately appears on the labels and labeling.
4. Relocate the statement, *This product is not intended for use with patients with reduced renal function*, to appear below the infusion time statement.

Thus, the principal display panel should appear as follows:

Zoledronic Acid Injection
4 mg/100 mL
(0.04 mg/mL)

For Intravenous Infusion

Do not mix with calcium-containing infusion solutions

Infusion time must not be less than 15 minutes

This product is not intended for patients with reduced renal function

Single Use Only – Discard Unused Portion

B. Carton Labeling

1. Delete [REDACTED] ^{(b) (4)} to reduce clutter.
2. Increase the space between the statements on the principal display panel that appear below the strength. Thus, the statements on the principal display panel should appear as follows:

For Intravenous Infusion

Do not mix with calcium-containing infusion solutions

Infusion time must not be less than 15 minutes

This product is not intended for patients with reduced renal function

Single Use Only – Discard Unused Portion

Please provide us with updated Carton and Container Information by Wednesday, October 17, 2012; Noon.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
10/12/2012

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, October 11, 2012 4:56 PM
To: Jeff Scheithe (jscheithe@Sagentpharma.com)
Subject: NDA 203231; Zoledronic Acid Inj.--PI with FDA Revisions/Comments

Importance: High

Hi Jeff:

Please see the attached Word .doc, as it is the Zoledronic Acid Inj. PI that contains our FDA revisions and/or comments.

We have another labeling meeting scheduled for **October 16, 2012** to continue discussions for this label. **It is imperative that Sagent provides us with a return label no later than Monday, October 15, 2012; Noon.** Without a return label, there can be no meeting for us.

Regards,
Kim



11/10/2012
Zoledronic: Inven...

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
10/12/2012

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, September 13, 2012 7:13 PM
To: 'Jeff Scheithe'
Cc: Cross Jr, Frank H
Subject: RE: NDA 203231; Zoledronic Acid Inj.--DMEPA Information Request; Tcon Request

This is an excellent question Jeff. Given that I still haven't received the latest CMC comments to convey to you, I understand Sagent's concern. I am going to be away for a few days; returning on Sept. 20th. Unless the Proj. Mgr. covering me in my absence is given specific instructions for Sagent to attend to, we may actually propose another date, during the t-con, when we would want an updated PI from Sagent.

For now, **with regard to the PI**, Sagent may hold on the Sept. 19th response date. Please reply to the other IRs by the requested date.

Thanks,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Thursday, September 13, 2012 11:57 AM
To: Robertson, Kim
Subject: RE: NDA 203231; Zoledronic Acid Inj.--DMEPA Information Request; Tcon Request

Hello Kim,

Thank you for sending over the latest requests concerning labeling. We have a question though.

Currently we are being asked to make some changes to the package Insert by Sept 19th per the DMEPA request below. There are also some requested changes per the CMC Track Changes document, a teleconference meeting set up for Sept 21st that might result in some PI labeling changes and indication that there are more CMC comments expected. Wouldn't be more productive for Sagent and for your reviewers, to have Sagent address all of these changes, as a whole, in one package insert change instead of 2 to 4 amendments?

Thanks, Jeff

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, September 12, 2012 2:59 PM
To: Jeff Scheithe

Subject: NDA 203231; Zoledronic Acid Inj.--DMEPA Information Request; Tcon Request

Importance: High

Hi Jeff:

Per our phone conversation, please see the attached Word .doc, as it is Sagent's PI for Zoledronic Acid Inj. We have made some minor edits in tracked changes to the PI for your consideration. Please review and include Sagent's concurrence, and/or any comments/revisions. Please remember to implement any Sagent provisions in THIS PI and indicate any Sagent provisions with tracked changes.

Secondly, the division is requesting a t-con with Sagent. We have a tentative date/time of **September 21, 2012; 1pm-2pm (eastern)**. I will confirm this date/time, as soon as I have a majority acceptance from of the meeting from my colleagues.

Finally, please see below another DMEPA Request for Information:

DMEPA REQUEST FOR INFORMATION:

[Redacted content] (b) (4)

[Redacted content] (b) (4)

Please provide a response to the DMEPA request by September 19, 2012. Please note that additional CMC comments are forthcoming.

The attached .pdf document is an excerpt of Sagent's Deficiency Response Summary to DMEPA.

Regards,

Kim

Kim J. Robertson

Regulatory Health Project Manager

Office of Hematology and Oncology Products

Division of Oncology Products 1

E-mail: kim.robertson@fda.hhs.gov

Phone: (301) 796-1441

Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
10/04/2012

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, September 26, 2012 5:15 PM
To: 'Jeff Scheithe'
Subject: RE: NDA 203231; Zoledronic Acid Inj.--CMC Request for Information

Hi Jeff:

My CMC reviewer went to the Module you cited in your e-mail, and she informed me that the information contained therein is **not** what she is asking for. What she saw were three Executed Batch Records (for the three primary drug product batches) with their English translations; however, the provided Executed Batch Records are NOT the Master Batch Record, which is the detailed blank form that future commercial batches will be manufactured and controlled accordingly. Please refer to 21 CFR 211.186.

She is still in need of this information.

Thanks,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Wednesday, September 26, 2012 8:31 AM
To: Robertson, Kim
Subject: RE: NDA 203231; Zoledronic Acid Inj.--CMC Request for Information

Good Morning Kim,

I received your request for the Master Batch Record and wanted to inform you that the Master Batch Records and the English translations were included in the original submission sequence (0000) and are located in Module 3.2.R.1.P.1 Executed Batch Record for Drug Product in the Regional Section.

If there is anything else your reviewer require I will be glad to get it to them.

Thanks, Jeff

Jeff Scheithe
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195

Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, September 25, 2012 4:09 PM
To: Jeff Scheithe
Subject: NDA 203231; Zoledronic Acid Inj.--CMC Request for Information

Hello Jeff:

Please see the following CMC request for information:

- Please provide the Master Batch Record (MBR) for Zoledronic Acid Injection 4 mg/100 mL and its corresponding English translation.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
09/26/2012



NDA 203231

**REQUEST FOR METHODS
VALIDATION MATERIALS**

SAGENT Pharmaceuticals, Inc.
Attention: Jeff Scheithe
1901 N. Roselle Road
Suite 700
Schaumburg, IL 60195-3176

Dear Jeff Scheithe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zoledronic Acid Injection, 4 mg/100 mL.

We will be performing methods validation studies on Zoledronic Acid Injection, 4 mg/100 mL, as described in NDA 203231. In addition to the reference standards and columns requested in my letter of September 17, 2012 we will also require samples of your drug product.

Samples

- 20 samples of a current batch Zoledronic Acid Injection, 4 mg/100 mL
- 10 samples of batch no 00390, 00391, and 00339 that were stored at 25°C/40% RH
- 10 samples of batch no 00390, 00391, and 00339 that were stored at 40°C/15% RH
- 10 samples of blank samples (no API) both aged and freshly prepared

Please include the MSDSs for the samples. The aged samples will assist us in evaluating the method for unknown impurities.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael L. Trehy, Ph.D.
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
09/25/2012

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, September 20, 2012 4:34 PM
To: Jeff Scheithe
Subject: RE: Zoledronic Conference Call

Importance: High

Hello Jeff:

I have returned to the office and as you can imagine, I have a lot of work to catch up on. This application is at the top of my list of projects, so I started with Sagent first. We had an internal meeting today to discuss some issues involving the Zoledronic Acid Inj. application, and I was asked to provide Sagent with one additional CMC comment to accompany the four previously conveyed comments that Ms. Amy Tilley provided Sagent on September 20, 2012. Please see below:

ADDITIONAL CMC COMMENT:

- Based on provided stability data, we recommend that you tighten the regulatory specification for assay from (b) (4) % to (b) (4) %. Provide an updated specification table to reflect the revision.

I'm certain that Amy confirmed the attendance of our DMEPA colleagues at the t-con; however, I thought I would re-confirm.....they will be in attendance.

If you have not done so, would you please provide us with a call-in number for tomorrow's t-con?

Thanks Jeff,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Friday, September 14, 2012 11:44 AM
To: Tilley, Amy
Cc: Robertson, Kim
Subject: Zoledronic Conference Call

Hello Amy,

I have been working with Kim on Zoledronic Acid for Injection 4mg/100mL (203231). Kim has set up a teleconference meeting between Sagent and the CMC reviewers for next Friday, Sept 21 from 1 to 2pm eastern time.

I had emailed Kim to ask her if she could also have a representative from DMEPA attend the meeting as it might be very helpful to resolve concerns on the labeling from both the CMC reviewers and DMEPA together at the same meeting.

Might you be able to see if this can be arranged in Kim's absence.

Thanks, Jeff

Jeff Scheithe
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

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/s/

KIM J ROBERTSON
09/20/2012



NDA 203231

**REQUEST FOR METHODS
VALIDATION MATERIALS**

SAGENT Pharmaceuticals, Inc.
Attention: Jeff Scheithe
1901 N. Roselle Road
Suite 700
Schaumburg, IL 60195-3176

Dear Jeff Scheithe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zoledronic Acid Injection, 4 mg/100 mL.

We will be performing methods validation studies on Zoledronic Acid Injection, 4 mg/100 mL, as described in NDA 203231.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

| | |
|----------------|------------------------------------|
| MCP429.USP-7 | HPLC Method for assay |
| MCP429.USP-8.2 | HPLC Method for unknown impurities |
| MCP429.USP-8.1 | HPLC Method for known impurities |

Samples and Reference Standards

| | |
|--------|--|
| 500 mg | zoledronic acid monohydrate reference standard |
| 200 mg | (b) (4) reference standard |
| 200 mg | (b) (4) reference standard |

Equipment

- 1 Atlantis dC18, 250 x 4.6, 5 µm column
- 1 Phenomenex Luna 5 µm Phenyl-Hexyl, 250 x 4.6

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Michael L. Trehy, Ph.D.
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
09/17/2012

From: Tilley, Amy
Sent: Friday, September 14, 2012 4:53 PM
To: 'jscheithe@Sagentpharma.com'
Cc: Robertson, Kim; Adkins, Yolanda
Subject: NDA 203231 Zoledronic Acid Inj - CMC Comments
Jeff,

On behalf of Kim Robertson below are CMC Comments for NDA 203231 Zoledronic Acid Injection.

CMC Comments to NDA 203231 responses needed prior to 9-21-12 Tcon.

1. The proposed tests for Degradation Products (e.g. Specified Unidentified Degradation Products with (b)(4)) in the revised regulatory drug product specifications are not acceptable. All degradates (individual and total) must be calculated as the percentage (%) of API Zoledronic Acid in the drug product (e.g. peak area comparison with zoledronic acid if there is no reference standard available for a degradants), regardless the origin of degradation products.

- Revise the test method and test description for degradation products in the drug product specifications accordingly.
- Submit adequate analytical test method and method validation for degradation products (individual and total).
- Provide updated specification table

2. The reprocessed stability data submitted in amendments SN013 and SN017 are not acceptable. Any reprocessing of raw data is not acceptable. Resubmit observed batch data and stability data as recommended in comment No.1.

3. Confirm whether the long term stability data that was submitted initially (refer to SN 000 dated 30-Aug-2012 and SN 006 dated 06-Jan-2012) was based on observed data and that the levels of degradation products/impurities (individual and total) were calculated as the percentage of API, Zoledronic Acid in the drug product.

4. (b)(4)

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products
1,

CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,
MD 20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
09/14/2012

Robertson, Kim

From: Robertson, Kim
Sent: Friday, September 07, 2012 6:28 PM
To: Jeff Scheithe (jscheithe@Sagentpharma.com)
Subject: FW: NDA Zoledronic Acid Inj.-Revised DMEPA Info. Request

Hi Jeff:

Please refer to Sagent's August 29, 2012 e-mail consisting of proposals in response to the division's August 24, 2012 e-mail re: DMEPA's Requests. Upon further review, my DMEPA colleagues have revised their recommendations and propose the following:

-Your August 29, 2012 response to our August 24, 2012 Information Request is not acceptable because a healthcare practitioner reading this insert labeling may erroneously conclude Zoledronic Acid does not require renal dose adjustments. However, in addition to the two options presented to you previously on August 31, 2012, we have an additional option for your consideration. This option below communicates to healthcare practitioners that Zoledronic Acid requires renal dose adjustments; however, your Zoledronic Acid 4 mg/100 mL premixed bag should not be used for these patients.

- Revise the container label, carton, and package insert labeling to communicate this product is not intended for use with patients that require renal dose adjustments and therefore these patients must receive a different Zoledronic Acid product. Additionally, this information should also be noted on a sticker over the tube and twist-off port, so that healthcare practitioners note this warning prior to administration. The length of the statement may require a sticker that has a flap or flange to allow additional space.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Robertson, Kim
Sent: Friday, August 31, 2012 1:46 PM
To: 'Jeff Scheithe'
Subject: RE: NDA Zoledronic Acid Information Requests

Hi Jeff:

Would you please clarify for me what you mean when you say, "What is the PDUFA date for **this filling**". Are you referring to the submission of the due date for the DMEPA information that we are asking for? If so, then I would have to check with my DMEPA colleagues with regard to **their** internal deadlines, as I am not certain what detriment this could have for the application if their deadline is not met. Please be aware though that the DMEPA issue has caused concern for the **entire** Zoledronic Review Team. I would have to defer to my DMEPA colleagues on the matter of a possible missed September 06th due date.

If Sagent cannot meet the September 06th DMEPA deadline, could you provide me with a date as to **when** Sagent would comply, so I can inform them? I will have to check on the acceptability of a Sagent proposed date and provide you with feedback, once I hear from DMEPA.

Lastly, an applicant not being able to meet certain deadlines does not stop any clocks. Depending upon the time and the type of data submitted, it could either extend the clock (major amendment-at the discretion of the division), **OR**, if reviewers feel that they do not have adequate time to review the newly submitted materials in the current review cycle, a Complete Response (CR) will be issued to the application.

Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Friday, August 31, 2012 12:58 PM
To: Robertson, Kim
Subject: RE: NDA Zoledronic Acid Information Requests

Hi Kim,

I have a couple of general questions stemming from the response.

With the response, the reviewer is requiring us to either have a (b) (4) and because of this there would be some additional lab testing to be performed. What is the PDUFA date for this filling and what is the protocol if we are not able to complete the testing soon enough for agency review to meet this date? Does the clock stop and then start again once we supplied the data for review?

Thanks, Jeff

Jeff Scheithe

Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, August 31, 2012 11:33 AM
To: Jeff Scheithe
Subject: RE: NDA Zoledronic Acid Information Requests

You are most welcome Jeff. You enjoy your weekend as well.
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Friday, August 31, 2012 12:23 PM
To: Robertson, Kim
Subject: RE: NDA Zoledronic Acid Information Requests

Kim,
Thank you for your reply. We will move ahead with our responses as soon as possible.

Have a nice holiday weekend,
Jeff

Jeff Scheithe
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, August 31, 2012 11:17 AM
To: Jeff Scheithe
Cc: Tom Moutvic; Elizabeth Dunlap; Lindsey Thomas; Mary Anne Anderson; Elena.Longhi@acsdobfar.net; Sergio Dusci
Subject: RE: NDA Zoledronic Acid Information Requests

Hello Jeff et al:

Per my previous e-mail to you Jeff, I will implement our FDA responses directly under Sagent's original request. Please see below:

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

From: Jeff Scheithe [<mailto:jscheithe@Sagentpharma.com>]
Sent: Wednesday, August 29, 2012 5:50 PM
To: Robertson, Kim
Cc: Tom Moutvic; Elizabeth Dunlap; Lindsey Thomas; Mary Anne Anderson; Elena.Longhi@acsdobfar.net; Sergio Dusci
Subject: NDA Zoledronic Acid Information Requests

Hello Kim

Per our conversation, I am writing to you with a couple of requests for clarifications concerning both a DMEPA request for information and a CMC request for information.

DMEPA's Request:

In an email received August 24, 2012, DMEPA had some comments on Sagent's proposed draft labeling concerning (b) (4)

(b) (4)

(b) (4)

2.2 Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors

The recommended dose of Zoledronic Acid Injection in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance greater than 60 mL/min is 4 mg infused over **no less than 15 minutes** every 3-4 weeks. The optimal duration of therapy is not known.

(b) (4)

During treatment, serum creatinine should be measured before each Zoledronic Acid Injection dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

For patients with normal baseline creatinine, increase of 0.5 mg/dL

For patients with abnormal baseline creatinine, increase of 1.0 mg/dL

In the clinical studies, Zoledronic Acid Injection treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zoledronic Acid Injection should be reinitiated at the same dose as that prior to treatment interruption.

Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

CMC Information Request

In an email received August 24, 2012, the CMC Reviewer found it unacceptable that we proposed excluding any degradation products originating from other components that go into the formulation. We would like clarification on whether the reviewer is referring to the two impurities that we tracked during exhibit batch stability studies; Impurity (b) (4) and Impurity (b) (4). If so we will respond with justification on why we would not report these impurities.

FDA Response-CMC (August 31, 2012): Yes, we are referring any degradation products originating from other components that go into the formulation, including degradation

products with (b) (4) and (b) (4) from the blank ((b) (4) as the applicant claimed). Even though you have already provided justification for not reporting these degradation products (or impurities) in the amendment SN 013, CMC does not accept such justification.

As Sagent has missed the August 29, 2012 deadline, we will require responses to address ALL of our outstanding issues no later than September 06, 2012!!

Regards,
Kim

Thank you,
Jeff

Jeff Scheithe
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

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/s/

KIM J ROBERTSON
09/07/2012

Robertson, Kim

From: Robertson, Kim
Sent: Friday, August 31, 2012 12:17 PM
To: 'Jeff Scheithe'
Cc: Tom Moutvic; Elizabeth Dunlap; Lindsey Thomas; Mary Anne Anderson; Elena.Longhi@acsdobfar.net; Sergio Dusci
Subject: RE: NDA Zoledronic Acid Information Requests

Hello Jeff et al:

Per my previous e-mail to you Jeff, I will implement our FDA responses directly under Sagent's original request. Please see below:

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

From: Jeff Scheithe [mailto:jscheithe@Sagentpharma.com]
Sent: Wednesday, August 29, 2012 5:50 PM
To: Robertson, Kim
Cc: Tom Moutvic; Elizabeth Dunlap; Lindsey Thomas; Mary Anne Anderson; Elena.Longhi@acsdobfar.net; Sergio Dusci
Subject: NDA Zoledronic Acid Information Requests

Hello Kim

Per our conversation, I am writing to you with a couple of requests for clarifications concerning both a DMEPA request for information and a CMC request for information.

DMEPA's Request:

In an email received August 24, 2012, DMEPA had some comments on Sagent's proposed draft labeling concerning (b) (4)

(b) (4)

(b) (4)

2.2 Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors

The recommended dose of Zoledronic Acid Injection in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance greater than 60 mL/min is 4 mg infused over **no less than 15 minutes** every 3-4 weeks. The optimal duration of therapy is not known.

During treatment, serum creatinine should be measured before each Zoledronic Acid Injection dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dL
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dL

In the clinical studies, Zoledronic Acid Injection treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zoledronic Acid Injection should be reinitiated at the same dose as that prior to treatment interruption.

Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

CMC Information Request

In an email received August 24, 2012, the CMC Reviewer found it unacceptable that we proposed excluding any degradation products originating from other components that go into the formulation. We would like clarification on whether the reviewer is referring to the two impurities that we tracked during exhibit batch stability studies; Impurity (b) (4) and Impurity (b) (4). If so we will respond with justification on why we would not report these impurities.

FDA Response-CMC (August 31, 2012): Yes, we are referring any degradation products originating from other components that go into the formulation, including degradation products with (b) (4) and (b) (4) from the blank ((b) (4) as the applicant claimed). Even though you have already provided justification for not reporting these degradation products (or impurities) in the amendment SN 013, CMC does not accept such justification.

As Sagent has missed the August 29, 2012 deadline, we will require responses to address ALL of our outstanding issues no later than September 06, 2012!!

Regards,
Kim

Thank you,
Jeff

Jeff Scheithe
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195
Ph: 847-908-1625
Fax: 847-901-1601
Email: jscheithe@sagentpharma.com

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/s/

KIM J ROBERTSON
08/31/2012

Robertson, Kim

From: Robertson, Kim
Sent: Friday, August 24, 2012 3:29 PM
To: Jeff Scheithe (jscheithe@Sagentpharma.com)
Subject: NDA 203231; Zoledronic Acid Injection--DMEPA Comments re: Renal (b) (4)
Dose/Pre-mix Bag

Hello again Jeff:

Please see below additional DMEPA comments, as they pertain to Sagent Pharmaceuticals' NDA for Zoledronic Acid Injection, 4mg/100mL (0.04 mg/mL):



****Please provide us with responses to these comments no later than Friday, August 31, 2012**.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845

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/s/

KIM J ROBERTSON
08/24/2012

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, June 13, 2012 6:15 PM
To: Jeff Scheithe (jscheithe@Sagentpharma.com)
Subject: NDA 203231; Zoledronic Acid Injection--Info. Request

Importance: High

Hello again Jeff:

If you have not already done so, please submit updated labeling for Zoledronic Acid Injection on behalf of ACS Dobfar Info SA as soon as possible, given that the innovator has had a recent supplemental approval (March 14, 2012) of their label.

Thank you,
Kim

Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
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/s/

KIM J ROBERTSON
06/13/2012

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, June 13, 2012 5:58 PM
To: Jeff Scheithe (jscheithe@Sagentpharma.com)
Subject: NDA 203231; Zoledronic Acid Inj. --Info. Request-CMC and P/T

Importance: High

Hello Jeff:

With regard to ACS Dobfar Info SA's NDA for Zoledronic Acid Injection, the CMC and Pharmacology/Toxicology reviewers of the application have the following request for information:

I. CMC Comments:

1. Revise the proposed drug product specification to include:
 - (a) A listing of degradation products with appropriate acceptance criteria, as recommended in ICH Q3B (R2) Section V. Note: the term "Related Substances" in your proposed drug product specification is not appropriate for degradation products.
 - (b) An analytical method identification number for each test. It appears that the provided method numbers marked as "ACS Info Internal Method" MCP429.USP and MPF088 do not specifically refer to the analytical methods for each test.

For detailed guidance regarding drug product specifications, refer to related sections in ICH Q6A.

2. Tighten the acceptance criteria for degradation products (specified identified, specified unidentified, unspecified, and total) in the proposed regulatory drug product specifications (shelf life specifications), based on complete scientific rationale, batch data, stability data, and non-clinical study results (refer to Pharmacology/Toxicology comment below).

3. Re-submit all batch analysis data (both at release and on shelf life) based to the revised drug product specification. Include a code number or an appropriate descriptor [e.g. relative retention time (RRT)] for each degradation product. Refer to ICH Q3B (R2), Section IV.

4. Provide a detailed summary of degradation products and impurity profile observed during manufacturing, stability studies and forced degradation studies for Zoledronic Acid Injection (4 mg/100 mL). Include supporting HPLC chromatograms and a list of relative retention times (RRTs) for impurities/degradation products. Refer to ICH Q3B (R2), Section II.

5. Provide analytical method number for each test in sections 3.2.P.5.2 and 3.2.P.5.3 Refer to comment No.1.

6. The validation or the validation report for HPLC method for assay in section 3.2.P.5.3 is incomplete. Perform validation and submit the validation results for the following:

- (a) Linearity established with a minimum of five concentrations from 80% to 120% of the test concentration.
- (b) Precision (intermediate precision)
- (c) Robustness

Refer to ICH Q2B for analytical method validation for assay.

7. Your HPLC method validation or validation reports for known and unknown impurities are incomplete (refer to section 3.2.P.5.3). Perform validation and submit the validation results for the following:

- (a) The range of linearity covering from the reporting level of an impurity to 120% of the specification. Refer to ICH Q2B (R2), Section IV.
- (b) Specificity for degradation products/impurities which standards are not available. Refer to ICH Q2B (R2), Section II (2).
- (c) Accuracy. Refer to ICH Q2B (R2) Section V (B & C).
- (d) Precision (intermediate precision). Refer to ICH Q2B (R2) Section VI.

8. Provide Certificate of Analysis from the proposed potential alternate suppliers for each component of the container closure system. Provide data from extractable/leachable studies and compatibility studies with the alternate “equivalent” components from these suppliers as stated in Section 3.2.P.7.

9. Justify the variations observed in the level of “single unknown impurity” in your stability study report. Include following in your justification:

- Adequacy of the analytical method for impurities (e.g. specificity, precision, accuracy, linearity, range, LOD, and LOQ etc).
- Possibility of unknown impurities and degradation products being further degraded during storage.

Data in the stability study report shows the level of “single unknown impurity” decreases or varies significantly during storage. For example, reported results for batch 00390 are: 0 mo. (b)(4)%, 1 mo. (b)(4)%, 3 mo. (b)(4)%, and 6 mo. (b)(4)% at accelerated conditions. Similar results are also observed for batches 00391 and 00391. Explain why levels of impurities increase over time then decrease at later time points.

10. Revise the test intervals in the proposed post-approval stability protocol for annual batches (refer to section 3.2.P.8.1.2.3) to be the same as the stability study protocol for the first three commercial batches (refer to section 3.2.P.8.1.2.2), as recommended in ICH Q1A (R2).

II. Pharmacology/Toxicology Comment:

The proposed acceptance limit for “single unknown impurity” in the drug product specification may not be acceptable for genotoxic or carcinogenic impurities. Therefore, you may choose to evaluate genotoxic potential of unknown impurities, or reduce the limit for “single unknown impurity” to NMT (b)(4)%, at which the daily exposure would be (b)(4) mcg/day with the recommended dose of 4 mg/day.

We need a response to these requests no later than Thursday, June 28, 2012.

Regards,
Kim

*Kim J. Robertson
Regulatory Health Project Manager
Office of Hematology and Oncology Products
Division of Oncology Products 1
E-mail: kim.robertson@fda.hhs.gov
Phone: (301) 796-1441
Fax: (301) 796-9845*

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/s/

KIM J ROBERTSON
06/13/2012



NDA 203231

FILING COMMUNICATION

ACS Dobfar Info S.A.
Attention: Thomas Moutvic
Vice President, Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195-3176

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, 4mg/100mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 9, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 12, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. There should be no white-space between the 'HIGHLIGHTS OF PRESCRIBING INFORMATION' and the Highlights Limitation Statement

2. The drug product title must be bolded and in all upper case letters
3. In the product title, remove (b) (4), and replace it with “for intravenous use”.
4. Avoid using “IV”, as it is commonly mistaken for Roman numeral IV. Instead, use “intravenous”. Spell out “intravenous” for the acronym in the entire label.
5. Ensure that each summarized statement references the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. There are at least 3 summarized sections that do not have references under ‘Dosage and Administration’
6. Only “adverse reactions” should be included in the PI. Avoid using terms, such as “adverse events”. Please ensure this is corrected in the entire label
7. Bold your Revision Date at the end of HL
8. In the Table of Contents, in the ‘Contraindications’ section, remove the subsection number “4.1”.
9. Avoid using terms, such as “rare” and “very rare”. Remove them and re-word the label as appropriate
10. Under ‘Warnings and Precautions’; Section 5.5 Pregnancy, please elaborate why you have the statement, “(b) (4)” in all caps and why it is located here. Explain why this should not be a contraindication
11. The subtitle heading for ‘Adverse Reactions’, 6.1, should read, “Clinical Trials Experience”; not “(b) (4)” as presently stated
12. Remove the Revision Date at the end of the label. It is not needed when it is at the end of HL

We request that you resubmit labeling that addresses these issues by April 2, 2012. The resubmitted labeling will be used for further labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

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

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
03/23/2012



NDA 203231

**ACKNOWLEDGE RESUBMISSION
AFTER REFUSE-TO-FILE**

ACS Dobfar Info S.A.
Attention: Thomas Moutvic
Vice President, Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195-3176

Dear Mr. Moutiv:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act in response to our October 28, 2011, refusal to file letter for the following:

Name of Drug Product: Zoledronic Acid Injection; 4mg/100mL

Review Priority Classification: Standard

Date of Application: January 06, 2012

Date of Receipt: January 09, 2012

Our Reference Number: NDA 203231

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 09, 2012, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 09, 2012.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KIM J ROBERTSON

02/23/2012

Ack. Letter NDA 203231 Zoledronic Acid Inj.; Sagent Pharmaceuticals

MEMORANDUM OF TELECON

DATE: December 15, 2011

APPLICATION NUMBER: NDA 203231

BETWEEN:

Name: Jeff Scheithe, Senior Manager of Regulatory Affairs
Thomas M. Moutvic, V.P. of Regulatory Affairs

Phone: PHONE # [REDACTED] (b) (6) Access Code: [REDACTED] (b) (6)

Representing: Sagent Pharmaceuticals, Inc.

AND

Name: Sarah Pope Miksinski, Ph.D., CMC Branch Chief, ONDQA
Haripada Sarker, Ph.D., CMC PAL, ONDQA
Joyce Crich, Ph.D., CMC Reviewer, ONDQA
Kim J. Robertson, Regulatory Project Manager, DOP 1

Division of Oncology Products 1, HFD-150, FDA

SUBJECT: Type C Meeting to Discuss the Refusal to File letter for NDA 203231
Zoledronic Acid Injection, 4mg/100mL

On August 29, 2011, Sagent Pharmaceuticals, Inc. submitted a 505(b)(2) NDA application for Zoledronic Acid Injection, 4mg/100mL. During the first 60-days into the review cycle of the application, it was noted that the applicant's submission contained a proposed drug product shelf-life of 24 month based upon only 6 months of long term and accelerated stability data. Thereby, this resulted in the determination that the application was incomplete, given that insufficient stability data was provided and a commercially viable shelf life could not be established. Sagent Pharmaceuticals, Inc. was ultimately issued a Refuse to File Letter from the Agency on October 28, 2011.

On November 11, 2011, Sagent Pharmaceuticals, Inc. submitted a Type C meeting request to discuss the Refusal to File Letter with Agency. The applicant wanted to know if the Agency would accept their filing based upon 6 months of long term and accelerated stability data under the provisions of the Q1C ICH Guidelines. The CMC reviewer team reiterated to the applicant that according to the Q1C ICH Guidance, "...Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time (e.g., 6 months accelerated and 6 months long term data from

ongoing studies) may be acceptable in **certain justified cases.**” Sagent was told that their application did not fit that justification. The review team further explained the assessment of fileability in that it is consistent in similar determinations for other 505(b)(2) applications.

It was recommended to the applicant that they follow the ICH Q1A Guidance as they move forward. The applicant agreed. The applicant further decided in the meeting to resubmit their application in its entirety (with additional stability data) for the Agency to review and that they would be able to do so within a matter of days.

Sarah Pope Miksinski, Ph.D.
CMC Branch Chief, ONDQA

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/s/

SARAH P MIKSINSKI
01/20/2012

FAX

FOOD AND DRUG ADMINISTRATION
DIVISION OF ONCOLOGY PRODUCTS 1
10903 New Hampshire Avenue
Silver Spring, Maryland 20903



| | | | |
|--|-----------------------------------|---------|----------------------------------|
| To: | <u>NAME</u> : Jeff Scheithe | From: | <u>Kim J. Robertson</u> |
| FAX: | (847) 908-1601 | FAX: | <u>301-796-9845</u> |
| E-mail: | <u>jscheithe@Sagentpharma.com</u> | E-mail: | <u>kim.robertson@fda.hhs.gov</u> |
| Phone: | <u>(847) 908-1625</u> | Phone: | <u>301-796-1441</u> |
| Pages, including cover sheet: | <u>2</u> | Date: | <u>December 6, 2011</u> |
| RE: <u>Meeting Request Granted (NDA 203231) Type C; T-con</u> | | | |

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address below by mail. Thank you.

Dear Mr. Scheithe:

In response to Sagent's November 11, 2011 meeting request for a Type C, NDA meeting re: the Zoledronic Acid Injection, 4mg/100mL application, we have a tentative date of **Thursday, December 15, 2011 2:30PM-3:30PM, EST** to discuss its Refusal to File status.

We will conduct our meeting to center around your question, i.e., we don't generally have presentations since all the needed information has been presented in your preparation package. Below you will find the list of FDA attendees/invitees for the meeting.

Thank you,
Kim J. Robertson
Regulatory Project Manager

FDA Attendees/Invitees for t-con:

Richard T. Lostritto, Ph.D., CMC Division Director
Sarah Pope-Miksinski, Ph.D., CMC Branch Chief
Haripada Sarker, Ph.D., CMC PAL
Joyce Crich, Ph.D., CMC Primary Reviewer
Kim J. Robertson, Regulatory Project Manager

Robert L. Justice, M.D., M.S., Division Director (invited)
Amna Ibrahim, M.D., Division Deputy Director (invited)
V. Ellen Maher, M.D., Medical Team Leader (invited)
Geoffrey Kim, M.D., Medical Reviewer (invited)
Anne Pilaro, Ph.D., Pharmtox Supervisor (invited)
Wei Chen, Ph.D., Pharmtox Reviewer (invited)
Qi Liu, Ph.D., Clinpharm Team Leader (invited)
Pengfei Song, Ph.D., Clinpharm Reviewer (invited)

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/s/

KIM J ROBERTSON

12/06/2011

06December11 Meeting Request Granted; Type C; Zoledronic Acid Inj., 4mg/100mL; Sagent Pharmaceuticals, Inc.



NDA 203231

REFUSAL TO FILE

ACS Dobfar Info S.A.
Attention: Thomas Moutvic
Vice President, Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195-3176

Dear Mr. Moutvic:

Please refer to your August 29, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zoledronic Acid Injection, 4 mg/100 mL.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reason:

The proposed drug product shelf-life of 24 months based on 6 months of long term and accelerated stability data are not sufficient to support a commercially viable shelf-life. Also note that as per GRMPs, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

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

Sincerely yours,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
10/28/2011

From: Robertson, Kim
Sent: Friday, October 28, 2011 12:54 PM
To: Justice, Robert
Subject: FW: CMC Deficiency for Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)

From: Sarker, Haripada
Sent: Friday, October 28, 2011 10:20 AM
To: Robertson, Kim
Cc: Patel, Hasmukh B; Pope Miksinski, Sarah; Lostritto, Richard T; Crich, Joyce; Cross Jr, Frank H
Subject: RE: CMC Deficiency for Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)

Filling Issue.

Thanks---hari

From: Robertson, Kim
Sent: Thursday, October 27, 2011 4:29 PM
To: Sarker, Haripada
Cc: Patel, Hasmukh B; Pope Miksinski, Sarah; Lostritto, Richard T; Crich, Joyce; Cross Jr, Frank H
Subject: RE: CMC Deficiency for Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)

Hari, I need a point of clarification please.....what do you mean by "**deficiency**"? Is this a review issue, or a filing issue? I presume it's not a filing issue, unless CMC's position has changed since the filing meeting.....

Please clarify.

Thanks,
Kim

From: Sarker, Haripada
Sent: Thursday, October 27, 2011 2:02 PM
To: Robertson, Kim
Cc: Patel, Hasmukh B; Pope Miksinski, Sarah; Lostritto, Richard T; Crich, Joyce
Subject: RE: CMC Deficiency for Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)

Ok.

Thanks---Hari

From: Robertson, Kim
Sent: Thursday, October 27, 2011 2:02 PM
To: Sarker, Haripada
Cc: Patel, Hasmukh B; Pope Miksinski, Sarah; Lostritto, Richard T; Crich, Joyce
Subject: RE: CMC Deficiency for Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)

Actually, the filing letter is issued on day 60.....so, I can put this

deficiency in the 60-day letter.

Thanks everyone,
Kim

From: Sarker, Haripada
Sent: Thursday, October 27, 2011 1:45 PM
To: Robertson, Kim
Cc: Patel, Hasmukh B; Pope Miksinski, Sarah; Lostritto, Richard T; Crich, Joyce; Sarker, Haripada
Subject: CMC Deficiency for Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)

Kim:

Please Find the following CMC deficiency comment for 74-day filling letter.

1. The proposed drug product shelf-life of 24 months based on 6 months of long term and accelerated stability data are not sufficient to support a commercially viable shelf-life. Also note that as per GRMPs, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

Thanks---hari

From: Lostritto, Richard T
Sent: Thursday, October 27, 2011 1:39 PM
To: Sarker, Haripada
Cc: Patel, Hasmukh B; Pope Miksinski, Sarah
Subject: RE: Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)/ Clinical:(Kim); CMC(?); RPM:(Robertson)

Hari,

This takes care of all filing issues? If so, please move it forward to Kim.

From: Sarker, Haripada
Sent: Thursday, October 27, 2011 9:55 AM
To: Lostritto, Richard T
Cc: Patel, Hasmukh B; Pope Miksinski, Sarah
Subject: RE: Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)/ Clinical:(Kim); CMC(?); RPM:(Robertson)

Rik:

The NDA is not fileable due to following CMC issue. Find my following draft CMC deficiency comment for 74-day filling letter.

1. The proposed drug product shelf-life of 24 months based on 6 months of long term and accelerated stability data are not sufficient to support **a** commercially viable shelf-life. Also note that as per GRMPs, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Information

submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

Please revise as appropriate.

Thanks---hari

From: Pope Miksinski, Sarah
Sent: Wednesday, October 26, 2011 4:04 PM
To: Sarker, Haripada
Cc: Patel, Hasmukh B; Lostritto, Richard T
Subject: RE: Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)/ Clinical:(Kim); CMC(?); RPM:(Robertson)

OK - if it needs to be signed off before Monday, you may need to get Hasmukh or Rik to sign. Hasmukh is acting on Friday, but Rik needs to be apprised of any RTFs.

From: Sarker, Haripada
Sent: Wednesday, October 26, 2011 3:50 PM
To: Pope Miksinski, Sarah
Subject: RE: Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)/ Clinical:(Kim); CMC(?); RPM:(Robertson)

Sarah:

Tomorrow, I will compose the standard CMC filing issue due to inadequate DP stability data for your input.

Thanks---hari.

From: Pope Miksinski, Sarah
Sent: Wednesday, October 26, 2011 3:46 PM
To: Sarker, Haripada
Cc: Lostritto, Richard T
Subject: RE: Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)/ Clinical:(Kim); CMC(?); RPM:(Robertson)

Hi Hari,

I think this is definitely a filing issue, particularly since this is an injectable product and since there is no clinical urgency. Deviations from assay and impurity specs are not trivial failures, in my opinion.

I copy Rik on all filing issues, so am doing so here.

Sarah

From: Sarker, Haripada
Sent: Wednesday, October 26, 2011 3:40 PM
To: Pope Miksinski, Sarah
Subject: FW: Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)/ Clinical:(Kim); CMC(?); RPM:(Robertson)
Importance: High

Sarah:

In yesterday's filling meeting CMC has one filling issue regarding 6 months DP long term stability data. As per your request, I checked the accelerated stability data as following.

Based on 6 months of stability data on 3 batches at long term and at accelerated conditions, shelf life of 24 months is proposed.

DP accelerated stability studies (b) (4) are conducted. DP is found stable in all conditions, except (b) (4) stability, where the DP assay and impurity slightly deviates from specification.

Please let me know if this a filling issue.

The issue of b2 vs J is ongoing.

Thanks---hari

From: Robertson, Kim
Sent: Wednesday, September 28, 2011 7:45 PM
To: Justice, Robert; Ibrahim, Amna; Maher, Virginia E.; Kim, Geoffrey; Pilaro, Anne; Chen, Wei; Pope Miksinski, Sarah; Sarker, Haripada; Liu, Qi (CDER); Song, Pengfei; Dorantes, Angelica; Jenney, Susan; Robertson, Kim
Cc: Mesmer, Deborah; Murgu, Anthony; Jenney, Susan; Fedenko, Katherine; Liberatore, Mark; Ramanadham, Mahesh; CDER-DDMAC-RPM; Kim, Tamy; CDER SEALD Labeling
Subject: Filing/Planning Mtg-N203231; Zoledronic Acid Inj. 505(b)(2)/ Clinical:(Kim); CMC(?); RPM:(Robertson)
When: Tuesday, October 25, 2011 11:00 AM-12:00 PM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER 150 Calendar; CDER OODP Meeting Calendar; CDER WO 2201 conf rm Bldg22

When: Tuesday, October 25, 2011 11:00 AM-12:00 PM (GMT-05:00) Eastern Time (US & Canada).

Where: CDER 150 Calendar; CDER OODP Meeting Calendar; CDER WO 2201 conf rm Bldg22

Note: The GMT offset above does not reflect daylight saving time adjustments.

~~*~*~*~*~*~*~*~*

505(b)(2) NDA Filing/Planning Meeting

Product(s): Zoledronic Acid Injection; 4 mg/100mL

Indication: Treatment of hypercalcemia of malignancy. Multiple myeloma, bone mets. from solid tumors in conjunction with standard antineoplastic therapy. Prostate cancer should

have progressed after treatment with at least one hormonal therapy.

--Decide fileability. On its face, is the application sufficiently complete to permit a substantive review? Reviewers should have their discipline filing review templates completed, so they can be DARRTS archived after the filing meeting

-- Identify Significant Review Issues for the Filing Communication Letter

-- Determine Review Priority; (Standard or Priority)

--Plan the review process

Filing Due Date=Sunday, October 30, 2011; technically Friday, October 28, 2011

EDR Location: \\CDSESUB1\EVSPROD\NDA203231\203231.enx

OFFICE/DIVISION: OHOP/DOP1

ATTENDEES: TBD

A/V ASSISTANCE: NONE

KJR/9-28-11

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

/s/

KIM J ROBERTSON
10/28/2011



NDA 203231

NDA ACKNOWLEDGMENT

ACS Dobfar Info S.A.
Attention: Thomas Moutvic
Vice President, Regulatory Affairs
Sagent Pharmaceuticals, Inc.
1901 N. Roselle Road, Suite 700
Schaumburg, IL 60195-3176

Dear Mr. Moutvic:

We have received your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Zoledronic Acid Injection; 4mg/100mL

Date of Application: August 29, 2011

Date of Receipt: August 30, 2011

Our Reference Number: NDA 203231

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 28, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Regulatory Project Manager
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/

KIM J ROBERTSON

09/22/2011

NDA Acknowledgment Letter/N203231; Zoledronic Acid Injection; ACS Dobfar Info S.A.;
Mr. Thomas Moutvic