

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203231Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 203231	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Zoledronic Acid Injection Dosage Form: Aqueous Solution Strengths: 4 mg/100 mL		
Applicant: ACS Dobfar Info SA		
Date of Receipt: June 03, 2013		
PDUFA Goal Date: August 03, 2013		Action Goal Date (if different): N/A
Proposed Indications: <ul style="list-style-type: none">• Hypercalcemia of malignancy• Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 021223 Zometa (zoledronic acid) Injectable; IV (Infusion)	Safety and Efficacy findings based on the RLD's 4mg/5mL presentation.

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

An In-Vivo Bioavailability or Bioequivalence Waiver Request was submitted by the applicant; which was in turn granted by the biopharmaceutical discipline.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

N/A YES NO
If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

N/A YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Zometa (zoledronic acid) Injection	NDA 021223	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

- d) Discontinued from marketing?

YES NO

If “YES”, please list which drug(s) and answer question d) i. below.
If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?
YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This proposed drug product is a sterile injectable in a pre-mixed bag, as opposed to the RLD’s pre-mixed bottle.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)? **YES**

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

Note: The proposed product is pharmaceutically equivalent to the 4 mg/100 mL ready-to-use bottle of the Reference Listed Drug

*If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If “**YES**” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

N/A YES NO

If “**NO**”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): N021817, Zoledronic Acid Injectable; Intravenous Infusion, 5mL

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **NDA 021223**

4939130*PED-March 2, 2013;

7932241-February 5, 2028

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

N/A YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent numbers:

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number: 4939130
4939130* PED

Expiry date: September 2, 2012
March 2, 2013

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): 7932241; 8324189
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): April 02, 2012; January 09, 2013

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Note: The '189' patent was timely listed after submission of this application. A 30-month stay of approval is not applicable.

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
07/30/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 203231	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Zoledronic Acid Injection Dosage Form: Aqueous Solution Strengths: 4 mg/100 mL		
Applicant: ACS Dobfar Info SA		
Date of Receipt: January 9, 2012		
PDUFA Goal Date: November 9, 2012		Action Goal Date (if different): N/A
Proposed Indications: <ul style="list-style-type: none">• Hypercalcemia of malignancy• Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 021223 Zometa (zoledronic acid) Injectable; IV (Infusion)	Safety and Efficacy findings based on the RLD's 4mg/5mL presentation.

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

An In-Vivo Bioavailability or Bioequivalence Waiver Request was submitted by the applicant; which was in turn granted by the biopharmaceutical discipline.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

N/A YES NO
If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

N/A YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Zometa (zoledronic acid) Injection	NDA 021223	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

- d) Discontinued from marketing?

YES NO

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness? YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This proposed drug product is a sterile injectable in a pre-mixed bag, as opposed to the RLD’s pre-mixed bottle.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)? YES

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

Note: The proposed product is pharmaceutically equivalent to the 4 mg/100 mL ready-to-use bottle of the Reference Listed Drug

If “NO” to (a) proceed to question #11.

If “YES” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

N/A YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): N021817, Zoledronic Acid Injectable; Intravenous Infusion, 5mL

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): **NDA 021223**

4939130*PED-March 2, 2013;

7932241-February 5, 2028

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

N/A YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent numbers:

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number: 4939130
4939130* PED

Expiry date: September 2, 2012
March 2, 2013

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 7932241

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): April 2, 2012

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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
11/07/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling, and Packaging Review

Date: October 19, 2012

Reviewer: Jibril Abdus-Samad, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Zoledronic Acid Injection
4 mg/100 mL (0.04 mg/mL)

Application Type/Number: NDA 203231

Applicant: ACS Dobfar Info S.A.

OSE RCM #: 2012-480

*** This document contains proprietary and confidential information that should not be released to the public.***

** This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) which cannot be shared outside of the FDA. Users wanting this information must contact a designated individual in the Division of Medication Error Prevention who will gain approval from ISMP.**

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1 INTRODUCTION

This review evaluates the proposed single-port premixed bag, container label, carton, and insert labeling for Zoledronic Acid NDA 203231 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The Applicant proposes a single port premixed intravenous bag containing Zoledronic Acid 4 mg/100 mL. The reference listed drug (RLD) Zometa is currently available as a 4 mg/5 mL vial that requires dilution and a 4 mg/100 mL bottle ready for infusion. Additionally, the Zometa 4 mg/100 mL bottle design (RLD) allows for preparation of renally-adjusted doses by withdrawing solution utilizing a needle and syringe.

1.2 REGULATORY HISTORY

Zoledronic Acid NDA 203231 is the subject of a 505(b)2 application that notes Zometa (Zoledronic Acid) NDA 021223 as the reference listed drug (RLD). The original August 30, 2011 submission received a refusal to file. Subsequently, the Applicant resubmitted on January 9, 2012.

Previously, in OSE Review 2010-2370, dated January 5, 2011, for Zometa, we recommended the Applicant either provide a Zometa premixed bottle in strengths to accommodate the recommended renal dosages or provide detailed preparation instructions in the insert for healthcare practitioners so that they can safely prepare and administer this product in patients who are renally impaired. Subsequently in OSE Review 2011-408, dated June 3, 2011, we found the Applicant's proposed method of preparation of renally prepared doses error-prone. However, after much discussion, DMEPA aligned with DOP1 and ONDQA and provided recommendations to improve on the organization of the labeling and preparation instructions.

Another product Reclast (Zoledronic Acid) (NDA 021817 and NDA 022080) is available in a 5 mg/100 mL ready-to-use bottle. See Appendix B for a comparison of both Zoledronic Acid products.

1.3 PRODUCT INFORMATION

The following product information is provided in the January 9, 2012 submission that provides updated insert labeling.

- Active Ingredient: Zoledronic Acid
- Indication of Use:
 - Treatment of hypercalcemia of malignancy
 - Treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard anti-neoplastic therapy.
- Route of Administration: Intravenous
- Dosage Form: Injection

- Strength: 4 mg/100 mL (0.04 mg/mL)
- Dose and Frequency:
 - Hypercalcemia of malignancy : 4 mg intravenously over not less than 15 minutes.
 - Multiple Myeloma and Bone Metastases: 4 mg intravenously over not less than 15 minutes every 3 to 4 weeks for patients with creatinine clearance greater than 60 mL/minute.

Co-administer oral calcium supplements of 500 mg and a multiple vitamin containing 400 International Units of vitamin D daily



- How Supplied: 4 mg/100 mL single-use ready-to-use flexible container
- Storage: Store at temperatures not exceeding 30°C (86°F). Protect from freezing.
- Container and Closure System: The container closure system consists of three components: a (b) (4) bag with one tube, a twist-off administration cap, and a clear overwrap.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS and ISMP^{***} databases for Zoledronic Acid medication error reports. We also reviewed the Zometa labels and labeling submitted by the Applicant.

^{***} This document contains proprietary data from the Institute for Safe Medication Practices (ISMP), which cannot be shared outside of the FDA. Users wanting this information must contact a designated individual in the Division of Medication Error Prevention who will gain approval from ISMP.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) and requested a search of the ISMP databases using the strategy listed in Table 2 and 3, respectively. The search date of December 8, 2010 was used because our last search covered the time period prior to that date in OSE Review 2010-2370, dated January 5, 2011.

Table 2: AERS Search Strategy	
Date	December 8, 2010 to June 14, 2012
Drug Names	Zoledronic Acid (active ingredient) Zometa, Reclast (trade name) Zoled%, Zom%, Recl% (verbatim term)
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues (HLT) Product Label Issues (HLT) Product Quality Issues (NEC) HLT

Table 3: ISMP MERP** and Quantros MedMarx Search Strategy**	
Time period	December 8, 2010 to June 14, 2012
Drug Names	“Zome*” “Reclast “Zole*”
Search Strategy	Medication prescribed (Medication error specific field) Medication administered (Medication error specific field) Suspect Medication (ADRs specific field) Event Description

The AERS database searches identified 102 reports. Each report was reviewed for relevancy and duplication. After individual review, 85 reports were not included in the final analysis for the following reasons:

- Adverse drug reactions unrelated to a medication error
- Practice based errors that do not provide causality such as wrong patient errors or dose omission errors

** This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) which cannot be shared outside of the FDA. Users wanting this information must contact a designated individual in the Division of Medication Error Prevention who will gain approval from ISMP.

- Foreign cases involving (b) (4), the internationally marketed version of Reclast because the labels and labeling may be different than U.S. However, U.S. cases involving Reclast were evaluated.

Additionally, the ISMP database searches identified 46 reports. Each report was reviewed for relevancy and duplication. After individual review, 18 reports were not included in the final analysis for the following reasons:

- Adverse drug reactions unrelated to a medication error
- Wrong patient errors
- Dose omission errors
- Wrong administration time errors

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on June 29, 2012 for additional cases and actions concerning Zometa (Zoledronic Acid). Two ISMP Newsletters note Zoledronic Acid was listed as one of the primary suspect drugs for reported serious events reported to FDA (1542 cases in 2010 and 287 cases in quarter 3 of 2009).^{1,2} There were no further details provided as to the nature of these serious events and if they were related to medication errors.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,³ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted August 25, 2011 (Appendix C)
- Overwrap Labeling submitted August 25, 2011 (Appendix D)
- Carton Labeling submitted August 25, 2011 (Appendix E)
- Insert Labeling submitted March 30, 2012

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the RLD Zometa (Zoledronic Acid) and we looked at the reviews to ensure the proposed Zoledronic Acid labels and labeling were in concurrence with our previous recommendations. The significant Zometa medication errors documented in OSE Review 2010-2370 included wrong drug, wrong dose, wrong frequency of administration, and wrong rate of administration errors. We concluded the proposed Zometa bottle did not appear to pose a greater risk in causing these types of errors compared to the 4 mg/5 mL vial.

¹ ISMP Medication Safety Alert, Acute Care. October 6, 2011

² ISMP Medication Safety Alert, Acute Care. February 25, 2010

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

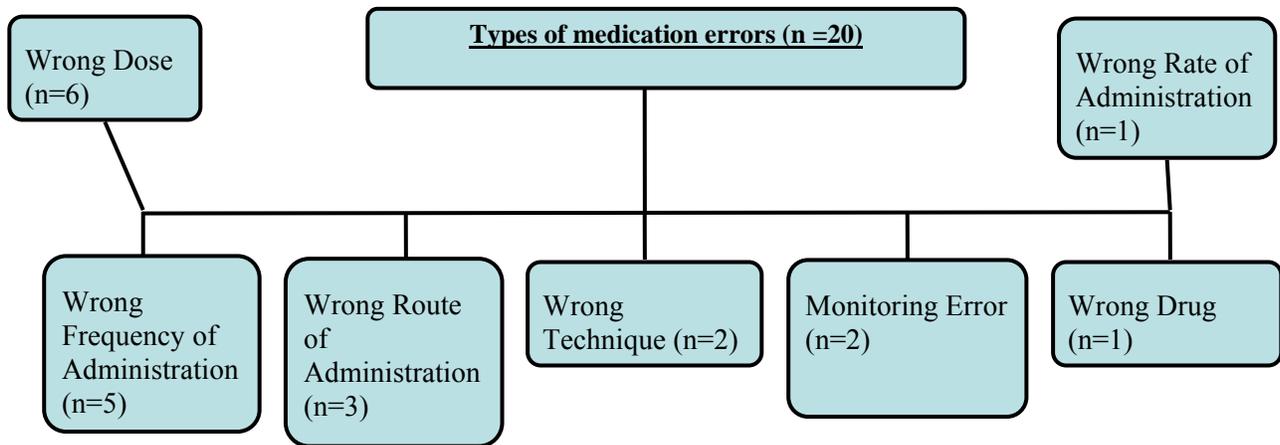
3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS, ISMP MERP, and Quantros MedMarx searches and the risk assessment of the Zometa product design as well as the associated label and labeling.

3.1 AERS MEDICATION ERROR CASES

Following exclusions as described in section 2.1, seventeen (n=17) Zoledronic Acid medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter⁴. We note the number of medication error types (n=20) is greater than the number of cases (n= 17) because 3 cases contained more than one type of error, hence the discrepancy. Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix F contains a more detailed listing of the cases.

Figure 1: Zoledronic Acid medication error cases categorized by type of error (n=20)



Wrong Dose (n=6)

Five of the six cases involved patients with renal impairment receiving Zoledronic Acid without renal adjustments. The first case involved a patient that received Zometa 4 mg despite requiring a renal dose adjustment. No outcome or causality was reported. The second case involved a patient with renal impairment (Cr 4.63 mg/dL) that received Zometa 4 mg in 10 mL (wrong technique error). This patient was found dead in his bed the next morning with cause of death determined as chronic renal insufficiency accompanied with acute progress of micturition disorder. The third case involved a patient with renal impairment that received Reclast, which is contraindicated in patients

⁴ The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed September 25, 2012.

with CrCl < 35 mL/min. No causality or outcome was reported. The fourth case involved a patient with chronic renal failure that received a reduced dose of Reclast. Reclast is contraindicated for patients with chronic renal failure. The patient experienced a hip fracture and died in the hospital. The fifth case involved a patient that Zometa 4 mg despite requiring a renal dose adjustment. The patient experience anuria, however no causality was reported. The sixth case of wrong dose error that involved a nurse administering 4 mg instead of the prescribed dose of 3 mg. The outcome and casualty were not reported.

Wrong Frequency of Administration (n=5)

The first case reported a patient received Zometa daily for 4 days instead of every three to four weeks. This resulted in fever, pancytopenia, hypocalcaemia, and abnormal electrolytes. No causality was reported. The second case involved a patient that received Reclast 2 months after the initial dose instead of the 12 months dosing frequency. The patient required emergency room treatment for vomiting, fever, knee bends, and dehydration. No causality was reported. The third case involved a patient that received her second Reclast after 14 months, missed her next dose. The patient fell and suffered a broken femur requiring hospitalization and surgery. No causality was reported. The fourth case involved a patient that received her second dose of Reclast 2 years after the first. The patient experienced fractures in both left and right femurs. No causality was reported. The last case involved a patient that received her second dose of Reclast after 2 months. The patient died 5 months later however, Reclast was not attributed to the death.

Wrong Route of Administration (n=3)

The first case involves a patient that received Zometa intramuscularly in her right buttock instead of intravenously. The patient experienced a tumor of 2 cm to 3 cm in diameter, indurated, and painful. The formulation of Zometa was not reported. The causality was not reported. The second case involved another patient that received Zometa intramuscularly. The report notes the patient died, however the cause of death was not reported. No causality was reported. The third report involved a patient that received Reclast 5 mg subcutaneously. No causality was reported. The patient did experience fractured femurs related to wrong frequency of administration errors previously noted.

Wrong Technique (n=2)

The case involved a patient that received Reclast and experienced extravasation. The reports states that during administration, the nurse missed the vein and put it into the skin at the injection site. The patient experienced pain, panic attacks and paralysis. The patient reported the skin fell off and got infected. There was no causality reported. The second case of wrong technique involved a patient that received Zometa 4 mg that was diluted in 10 mL instead of 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection. This case also involved a monitoring error in which the patient did not receive a renally dose adjustment that was previously noted above. This patient was found dead in his bed the next morning with cause of death determined as chronic renal insufficiency accompanied with acute progress of micturition disorder.

Monitoring Errors (n=2)

The first case involved a patient the received concomitant bisphosphonate therapy while receiving both Zometa (zoledronic acid) and Aredia (disodium pamidronate). The patient experienced severe osteonecrosis of the jaw, pain, infection and disfigurement. The last case involved a patient that received Zometa 4 mg from December 2002 to July 2005 despite declining renal function

Wrong Drug (n=1)

There was one case of wrong drug error in which a patient was ordered Zoledronic Acid 4 mg IV every 4 weeks. The pharmacist dispensed Aclasta 5 mg/100 mL. The nurse drew up 1 mg/20 mL and infused the remaining 4 mg/80 mL. No outcome was provided for this event. The report does state the pharmacist assumed the order was for Aclasta infusion.

Wrong Rate of Administration (n=1)

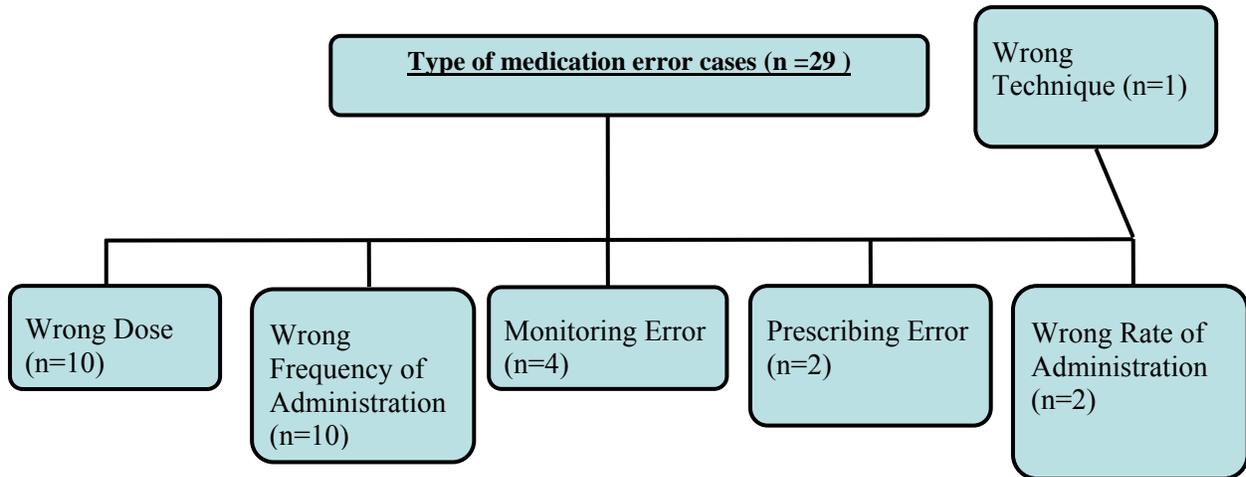
The case of wrong rate of administration involves a patient in France that received Zometa 4 mg over 5 minutes for the first 18 months of treatment. The report states the speed of the Zometa perfusions was considered a predisposing factor for the patient's renal insufficiency. No causality was reported.

3.2 ISMP MERP^{*} AND QUANTROS MEDMARX^{®***} MEDICATION ERROR CASES**

Following exclusions as described in section 2.1, twenty-eight (n=28) Zoledronic Acid medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Of note, these MedMarx cases did not provide outcomes. Additionally, we note the number of medication error types (n=29) is greater than the number of cases (n=28) because 1 report contained more than one type of error, hence the discrepancy. Figure 2 provides a stratification of the number of cases included in the review by type of error. Appendix G contains a more detailed listing of the cases.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Figure 2: Zoledronic Acid medication error cases categorized by type of error (n=29)



Wrong Dose (n=10)

The first case involved a patient that received Zometa 4 mg instead of his normal dose renally-adjusted dose of 3.5 mg. The second case involved a pharmacist notifying a physician that the patient’s creatinine level was high, resulting in the physician adjusting the dose. The third case involved a physician that ordered 3.2 mg dose instead of the correct adjusted dose of 3.5 mg. The fourth case involved a pharmacist that contacted a physician to decrease the Zometa dose due to the patient’s low creatinine clearance. The fifth case and sixth cases involved pharmacists that notified physicians to decrease the dose of Zometa to 3.3 mg due to the patient’s creatinine clearance. In the seventh and eighth cases, the physician was notified to renally dose Zometa 4 mg to 3.3 mg. The ninth case involved a patient that was ordered Zometa 3.5 mg, however the dose required further reduction to 3.3 mg due to renal function. The last case involved in pharmacist that notified the physician assistant to reduce the dose of Zometa 4 mg to 3.5 mg

Wrong Frequency of Administration (n=10)

The first case involved a patient that was ordered Zometa along with chemotherapy despite receiving Zometa the previous day. The second case involved a pharmacy technician that entered a Zometa order in the computer incorrectly resulting in Zometa being scheduled for the patient to receive daily for 2 days. The error was caught by the pharmacist on the second day and the patient did not receive the second dose. The third case involved a patient that received Zometa 2 weeks after the previous dose. The patient received a partial infusion before the error was caught. The fourth case involved a patient that received Zometa 2 consecutive weeks. The fifth case involved an order for Zometa that was too early based on the previous administration date. No other details were provided. The sixth case involved an order for Zometa 10 days after the last dose. No other details were provided. The seventh case involved Zometa being ordered on an incorrect date. No further details were provided. The eighth case involved a patient that received Zometa monthly, however should have received Zometa every 3 months for

hypercalcemia. The ninth case involved Zometa ordered into the computer incorrectly resulting in Zometa being scheduled for the patient to receive daily for 3 days. The patient received 2 doses prior to the error being discovered. The last case involved a Zometa dose that was ordered a day early.

Monitoring Errors (n=4)

The first case involved a patient that was taking Fosamax (alendronate) when receiving Reclast despite being told by her physician to stop Fosamax. No outcome or causality was reported. The second case involved a pharmacist that noticed a patient was receiving concomitant Xgeva and Zometa. The Zometa was discontinued. The third case involved a patient with renal impairment that received Reclast. The infusion was stopped early. No adverse events were reported. The fourth case involved a patient that received Zometa without current renal function lab tests. No patient harm was identified.

Prescribing Error (n=2)

The first case involved a pharmacist that noticed a Zometa 6 mg order. The order was clarified to Zometa 4 mg. The second case involved an order for Reclast 4 mg IV. The pharmacist dispensed Reclast 5 mg and to infuse over 15 hours (wrong rate of administration error also).

Wrong Rate of Administration (n=2)

Zometa was ordered to be infused over 30 minutes (200 mL/hr) however the label on the bag stated 400 mL/hr. The second case involved a Reclast order that was labeled to infuse over 15 hours.

Wrong Technique (n=1)

The case involved a patient that received Zometa through the same intravenous site as all other meds instead of a separate IV line.

3.3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

3.3.1 Medication Error Case Summary

We find the labeling for the proposed Zoledronic Acid adequately address the medication errors (monitoring errors, wrong frequency of administration, wrong route of administration, wrong technique, wrong drug, wrong dose, wrong rate of administration, and prescribing errors) that occurred with the RLD Zometa. Additionally, we did not find any medication error cases specifically related to preparation of renally-adjusted doses with the currently marketed Zometa premixed bottle. Therefore, the medication errors with Zometa did not note any labeling issues that should be revised for the proposed product labeling.

3.3.2 Impact of Physical Design

The proposed single-port pre-mixed bag is designed for administration of Zoledronic Acid 4 mg via connection to an intravenous infusion set. The Applicant proposed a 4 mg strength only and did not propose the other dose renal dose recommendations for Zoledronic Acid (3.5 mg, 3.3 mg, and 3 mg). Additionally, the proposed product design does not allow for preparation of renally-adjusted doses unlike the currently marketed

Zometa (Zoledronic Acid) 4 mg/100 mL bottle design, which allows for adjustment of the dose using a standard syringe and needle.

Currently in the marketplace, manufacturers of similarly designed single-port premixed bags provide multiple strengths to accommodate these doses. Examples of these products include Gentamicin (60 mg, 80 mg, 100 mg, 120 mg), Vancomycin (500 mg, 750 mg, 1 g) and Ceftriaxone (1 g and 2 g) premixed bags. In pharmacy practice, if a drug that is available in a premixed formulation is prescribed but there is no premixed formulation available in the strength prescribed, the dose must be compounded by the pharmacy using a vial. Currently, there is a Zoledronic Acid 4 mg/5 mL vial currently marketed for pharmacy compounding.

We requested the Applicant address renal dose preparation and administration along with a request from DOP1 and ONDQA for verification from the Applicant that the single-port on the intravenous bag was not designed for withdrawal or addition of fluid into the intravenous bag (Appendix H). (b) (4)

[Redacted]

[Redacted] (b) (4)

3. 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 (b) (4)

[Redacted] Additionally, this information should also be noted on a sticker over the tube and twist-off cap portion of the pre-mixed bag 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.

[Redacted] (b) (4)

3.3.3 Container Label, Overwrap and Carton Labeling

The container label and overwrap labeling submitted August 25, 2011 are cluttered and require the 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. These revisions were communicated to the Applicant on August 24, 2012 (Appendix K).

Subsequent to our recommendations, the Applicant submitted updated container label, overwrap and carton labeling on October 2, 2012 (Appendices L to N). The label and labeling in this submission required revisions to improve the prominence of the established name, strength on the principal display panel, and relocation of the warning that alerts healthcare practitioners that this product is not intended for use with patients with reduced renal function. The Applicant placed this warning at the lower portion of

the container label, and overwrap and carton labeling since it would be closer to the single port on the premixed bag. However, this information can be easily overlooked. These revisions were communicated to the Applicant on October 12, 2012 (Appendix O). We await the Applicant's response to our container label, overwrap and carton labeling comments.

4 CONCLUSIONS

The proposed single-port premixed bag of Zoledronic Acid 4 mg/100 mL does not allow for preparation of renal impairment dosages. Doses for renally impaired patients must be prepared from the currently marketed Zometa (Zoledronic Acid) 4 mg/5 mL vial or 4 mg/100 mL premixed bottle. Other premixed drug products are generally provided in multiple strengths to accommodate all the recommended dosages for their product, but the Applicant has not proposed to manufacture the other renal impairment dosages (3.5 mg, 3.3 mg, and 3 mg) in a premixed bag. We find the Applicant's proposal acceptable to mitigate the risk of errors with this packaging configuration by revising the container label, carton and insert labeling to communicate that the product is not intended for use with patients with renal impairment. We provided comments to the labels and labeling to the Applicant on October 12, 2012. At the time this review was completed, we have yet to receive the final version of the labels and labeling.

If you have further questions or need clarifications, please contact Francis Fahnbulleh, project manager, at 301-796-0942.

4.1 COMMENTS TO THE DIVISION

Since this product is not intended for patients with renal impairment, the insert labeling requires revision to the Dosage and Administration section to alert practitioners that this product is for only patients with creatinine clearance greater than 60 mL/min. Additionally, there are dangerous abbreviations and symbols that require revision.

A. Dosage and Administration – Section 2

The Dosage and Administration section contains trailing zeros. Trailing zeros have led to ten-fold overdoses.⁵ As part of national campaign to eliminate the use of dangerous abbreviations and dose designations, FDA agreed to remove such abbreviations from the approved labels and labeling. Therefore, we request all trailing zeros be deleted.

B. Dosage and Administration, Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors – Section 2.2

1. The Dosage and Administration section contains the abbreviation, (b) (4) has been misinterpreted as (b) (4). As part of national campaign to eliminate the use of dangerous abbreviations and dose designations, FDA agreed to remove such abbreviations from the approved labels and labeling. Therefore, we request the abbreviation, (b) (4) be replaced with the words, (b) (4).
2. In Table 1, replace the symbol, -, with the word, to.

⁵ <http://www.ismp.org/Tools/errorproneabbreviations.pdf> Last accessed September 25, 2012, 2012

C. Dosage Forms and Strengths –Highlights and Section 3
Preparation of Solution – Section 2.3
How Supplied – Section 16

Revise the statement, (b) (4) single use bag, to read, 4 mg/100 mL
single-use premixed bag.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ITCH EBB](#)) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

ISMP Databases

Quantros MEDMARX Database

MEDMARX® is a national, Internet-accessible database that hospitals and health care systems use to track and trend adverse drug reactions and medication errors. Hospitals and health care systems participate in MEDMARX voluntarily and subscribe to it on an annual basis. MEDMARX is a quality improvement tool, which facilitates productive and efficient documentation, reporting, analysis, tracking, trending, and prevention of adverse drug events.

OSE Reviews

Baugh, Denise. OSE Review 2011-408: Label and Labeling Review for Zometa, June 3, 2011

Baugh, Denise. OSE Review 2010-2370: Label and Labeling Review for Zometa, January 5, 2011

Appendix B: Zoledronic Acid Product Comparison

Product	Zoledronic Acid Injection (proposed product)	Zometa (Zoledronic Acid) Injection	Reclast (Zoledronic Acid)
NDA	204016	021223, 021386	021817, 022080
Strength	4 mg/100 mL injection	4 mg/5 mL vial 4 mg/100 mL	5 mg/100 mL
Recommended Dose	4 mg	4 mg	5 mg
Renal Adjustment	*3.5 mg for CrCl 50 mL/min to 60 mL/min, 3.3 mg for CrCl 40 mL/min to 49 mL/min, 3 mg for CrCl 30 mL/min to 39 mL/min	*3.5 mg for CrCl 50 mL/min to 60 mL/min, 3.3 mg for CrCl 40 mL/min to 49 mL/min, 3 mg for CrCl 30 mL/min to 39 mL/min	Contraindicated in CrCl < 35 mL/min

* Renal adjustment is only for the indications of Multiple Myeloma and Bone metastasis from solid tumors

Appendix C: Container Label submitted August 25, 2011



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

Appendix F: Details of Medication Error Cases retrieved from AERS involving Zometa and Reclast

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
7332585, 3/4/2011, age unknown, US	Wrong Dose	not reported	not reported	Pt received Zometa 4 mg despite needing renal dose adjustment
7370273, 3/23/2011, 62 y/o, US	Wrong Dose Wrong Technique	not reported	Death	Pt presented with a Scar value = 4.63 mg/dl Zometa 4 mg infusion started via a permanent catheter, in addition, Zometa concentrate had been diluted in 10 ml instead of 100 ml of 0.9% Sodium chloride or 5% glucose solution. On the next day morning, the patient was found dead in his bed
7905008, 11/9/2012, 58 y/o female, US	Wrong Dose	not reported	not reported	Pt with Cr 1.6 mg/dL received treatment with Reclast (zoledronic acid) for osteoporosis, on (b) (6). The patient received 3.5 mL of Reclast before the physician decided to stop infusion due to slight decreased in renal function.
8389195, 5/12/2011, 61 y/o , Japan	Wrong Dose	not reported	anuria	The patient received Zometa (zoledronic acid) for an unspecified indication at a 4 mg per administration as IV drip, without any adjustment of dose related to renal function, from an unknown date.
7244432, 1/25/2011. elderly man, US	Wrong Dose Wrong Rate of Administration	not reported	renal insufficiency, osteonecrosis and osteitis of jaw and mandibula	Patient received Zometa 4 mg within 45 minutes despite decreasing renal function. CrCl 22 mL/min
7693314, 8/19/2011	Wrong Dose	not reported	not reported	nurse administered by mistake Zometa 4 mg instead of the prescribed dose of 3 mg
7378831, 3/28/2011, 35 y/o man, DE	Wrong Frequency of Administration	not reported	fever, pancytopenia in form of thrombocytopenia and leukocytopenia, hypocalcaemia and abnormal electrolytes	Pt treated with Zometa (zoledronic acid) 4 mg daily for metastatic prostate cancer since 08 Mar 2011.
7491404, 5/19/2011, 52 y/o female, US	Wrong Frequency of Administration	not reported	vomiting, fever, knee bends and dehydration	Patient received Reclast (zoledronic acid) for an unknown indication on an unspecified date in Dec 2009 and then in Feb 2010.
8162491, 2/24/2012, 82 y/o woman	Wrong Frequency of Administration	not reported	left and right femur fracture	Reclast History: First dose: Feb. 25, 2009 Second dose: March 2, 2011 **NOTE: 2 years in between doses**

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
8196830, 3/9/2012, 63 y/o female	Wrong Frequency of Administration	not reported	not reported	The patient received Reclast (zoledronic acid) 5 mg/100 mL IV infusion, for unknown indication on 16 Dec 2010. This patient also received Reclast on 28 Feb 2011.
8212148, 3/15/2012, 52 y/o female	Wrong Frequency of Administration Wrong Route of Administration	not reported	left femur fracture	This poly medicated patient received Reclast (zoledronic acid) (dose: 5 mg once yearly) by SQ (subcutaneous) route, for the treatment of an osteoporosis on 10 Mar 2009 and 06 May 2010.
7598342, 7/8/2012, 63 y/o female, MX	Wrong Route of Administration	misuse by physician	tumor of 2-3 cm of diameter, indurated and painful	Patient received Zometa (zoledronic acid) to reduce her pain and bone loss on (b) (6) at a dose of 1 application (4 mg/ 5 mL) single dose, but was applied in her right buttock by mistake.
7956613, 12/5/2011, 60 y/o male, US	Wrong Route of Administration	not reported	Death, cause not reported	The patient received treatment with Zometa (zoledronic acid) 4 mg monthly, intramuscular, for bone metastases, from an unknown date.
7992461, 12/19/2011, 78 y/o female, US	Monitoring Error	not reported	hip fracture suspected to be due to Reclast	Patient with chronic renal failure received Reclast 2.5 mg/50 mL
8444028, 6/18/2012, male of unknown age, US	Monitoring Error	not reported	severe osteonecrosis of the jaw, including pain, infection and disfigurement	Patient was infused with Zometa (zoledronate) and Aredia (disodium pamidronate) for an unspecified indication on an unspecified date
7472976, 5/11/2011, female, unknown age, US	Wrong Technique	performance error	extravasation, pain, panic attacks, paralysis	Patient received Reclast infusion (zoledronic acid). During administration, the nurse missed the vein and put it into the skin. The patient's vein opened up and she developed an infection.
8130262, 2/10/2012, female, unknown age, US	Wrong Drug	not reported	diarrhea, vomiting	After verification of script with pharmacy, it stated zoledronic acid 4 mg IV every 4 weeks. The pharmacist assumed it was an Aclasta infusion. Nurse was provided Aclasta 5 mg/100 mL, she draw up 1 mg/20 mL and infused 4 mg

Appendix G: Details of Medication Error Cases retrieved from ISMP MERP*** and Quantros MedMarx*** involving Zometa and Reclast

Report ID, Date Received, Age and Gender,	Type of Error	Narrative
18272163, 80 y/o M	Wrong Dose	The physician ordered Zometa 4 mg. IVPB however the patient has only been receiving 3.5 mg. in the past due to kidney problems.
18312278, 64 y/o M	Wrong Dose	When the Pharmacist was verifying the medication order she noticed that the patient's Creatinine was high and notified the Physician. Physician reduced the Zometa dosage.
18400791, 82 y/o M	Wrong Dose	Patient needed a dose modification due to a creatinine clearance level on a clinical trial. Dose should have been modified to 3.5 mg but was entered as 3.2 mg and administered.
18677690, 65 y/o F	Wrong Dose	When the Pharmacist was reviewing the medications he discovered that the patient's Creatinine was low and there needed to be a decrease in dosage from 4 mg. to 3.5 mg. Physician was notified and the order was changed.
18810360, 74 y/o M	Wrong Dose	When the pharmacist was verifying the order she noticed that the dose needed to be adjusted due to creatinine clearance. Physician was notified and the order was change to Zometa 3.3 mg. IVPB time once
18881862, 74 y/o M	Wrong Dose	When the Pharmacist was verifying the medication order she discovered that the dose of Zometa needed to be reduced due to the patient's creatinine clearance value. Physician was notified and a new dose entered.
19665405, 69 y/o F	Wrong Dose	Zometa 4 mg IV ordered for patient with CrCl of 48.8 ml/min. It was recommended to the physician to renally dose the medication to 3.3 mg IV of Zometa.
20638910, 77 y/o F	Wrong Dose	Pt. was ordered Zometa 4 mg, but has a CrCl of 44.6 ml/min. The med was renally dosed to 3.3 mg IV X 1.
21335917, 76 y/o M	Wrong Dose	Patient was here for 4th dose of Zometa. Zometa was prescribed with a 3.5 mg. dose, but the pt. has a CrCl of 38.5 mL/min and SCr of 1.5. The recommended dose for the patient is 3 mg. IV. The order was changed to the recommended dose of 3 mg.
21445445, 71 y/o M	Wrong Dose	Patient ordered Zometa 4 mg and the pt's CrCl was 51.9 and SCr 1.20 on (b) (6), today's labs not received yet. Pharmacist notified Physician Assistant and order was clarified to Zometa 3.5 mg.

Report ID, Date Received, Age and Gender,	Type of Error	Narrative
16792398, 70 y/o F	Monitoring Error	Reclast dispensed and hung. Patient creatinine is "borderline" per pharmacy after med hung. Infusion stopped after 44 mL administered.
16464860, 39 y/o F	Monitoring Error	Pt received Zometa with no current BUN or Creatinine
17138724, 88 y/o F	Monitoring Error	More than 50% of the way through the Reclast infusion, patient stated that she was glad her pharmacy worked out her insurance issues so that she could still take her fosamax.
18946653, 66 y/o M	Monitoring Error	The Pharmacist was verifying the medications ordered and discovered that Xgeva and Zometa were ordered for the patient. Zometa was discontinued and the patient received Xgeva.
16464860, 64 y/o F	Wrong Frequency of Administration	Zometa to be infused however patient had received Zometa the previous week. Nurse notified physician and order for Zometa was discontinued.
17465942, 62 y/o M	Wrong Frequency of Administration	Order written by physician for Zometa 4 mg to be given 1x on 4/5. Order entry tech selected correct product but did not change default frequency from 1 month to 1x. When scheduled qmonth, the administration time defaults to the next day (b) (6) at 1000. Changing it to a 1x med defaults the time to today. The pharmacist did not catch error on order entry and verified order. A label printed, the drug was mixed and sent on (b) (6) at 1800. The administration was handwritten on the MAR and documented as given. Because the order was not modified to 1x, the dose appeared on (b) (6) MAR preprinted to be given. The nurse called for the med, but the pharmacist working on (b) (6) saw that the dose was entered incorrectly, asked the nurse to check the prior day's MAR for documentation of administration. The nurse looked and saw that the patient had received the med. The patient was spared receiving a second dose.
17659599, 48 y/o M	Wrong Frequency of Administration	Pt scheduled to receive Zometa 4 mg IV monthly. Dose last administered 4/8; ordered 4/22 compounded and partially infused prior to error being identified.
18000163, 68 y/o F	Wrong Frequency of Administration	Patient received Zometa 4 mg IV 2 consecutive weeks per physicians order.
18125319, 73 y/o M	Wrong Frequency of Administration	Care plan was entered which included Zometa, order was signed by physician and released by triage nurse to be prepared and dispensed by pharmacy too early based on previous administration date.

Report ID, Date Received, Age and Gender,	Type of Error	Narrative
19582509, 79 y/o F	Wrong Frequency of Administration	Zometa order signed and released to pharmacy. Patient's last dose was 12-6. Dose not due today 12-16.
20781695, 64 y/o M	Wrong Frequency of Administration	Medication due on 6/25 but order was signed and released on 4/27. Dose not given on this date and care plan to be corrected for future date.
20863208, 75 y/o F	Wrong Frequency of Administration	Pt to clinic for mad visit and faslodex injection. Upon checking to see when pt is due for next Zometa infusion, found that pt received Zometa monthly on 2/22 and then on 3/21. Pt should be on q 3 month schedule. Pt calcium level on 4/18 is normal 9.6 and creatinine normal at 1.1.
20968120, 63 y/o M	Wrong Frequency of Administration	Patient was ordered Zometa 4 mg iv "today" on 11/10 order was profiled in emar for daily by pharmacy and then signed off by RN. Dose was given that day and was also given on 11/11. Dr. was notified on 11/12. The pharmacist that entered the med on pt profile did not remove the auto stop of 3 days that pops up on the med orders. This automatically scheduled med for three day dose.
21381606, 56 y/o F	Wrong Frequency of Administration	Staff person entered the dose for this date which was administered as ordered but it really was not due till the next day.
18387715, 62 y/o F	Wrong Rate of Administration	Zometa was ordered to be infused over 30 minute period which would be 200 cc/hour indicated on iv label to infuse at 400 cc/hr.
19215439, 60 y/o M	Wrong Technique	Pt was administered Zometa at 1615 - Medication is to be given through a separate IV site from other meds. Med was given through same site as all other IV meds.

Appendix H: August 24, 2012 IR regarding renal dose reductions and single port bag functionality



(b) (4)

Appendix I: August 31, 2012 DMEPA IR detailing options to accommodate safe preparation for renally-adjusted doses

We find the Applicant's proposal to remove the renal dose recommendation unacceptable. This proposal is error-prone because a healthcare practitioner looking at this insert labeling may erroneously conclude Zoledronic Acid does not require renal dose adjustments. (b) (4)



3. 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 cap, 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.

Appendix J: DMEPA IR to further evaluate (b) (4) September 21, 2012



(b) (4)

Appendix K: Container Label and Carton Labeling Comments sent August 24, 2012

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 (b) (4) 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 (b) (4) 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 (b) (4) 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 (b) (4) 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].

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

Appendix O: Container Label and Carton Labeling Comments sent August 24, 2012

A. Container Label, Overwrap and Carton Labeling

1. Delete the [REDACTED] (b) (4) 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 [REDACTED] (b) (4) minutes

This product is not intended for patients with reduced renal function

Single Use Only – Discard Unused Portion

B. Carton Labeling

1. Delete the [REDACTED] (b) (4) intravenous bag 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 [REDACTED] (b) (4) minutes

This product is not intended for patients with reduced renal function

Single Use Only – Discard Unused Portion

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

/s/

JIBRIL ABDUS-SAMAD
10/19/2012

SCOTT M DALLAS
10/19/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Prescription Drug Promotion (DPDP)

******Pre-decisional Agency Information******

Memorandum

Date: October 2, 2012

To: Kim Robertson, Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
OPDP

Subject: OPDP comments on draft product labeling for Zoledronic Acid
Injection 4 mg/100 mL
NDA 203231

In response to your consult request dated February 22, 2012, OPDP has reviewed the draft labeling (Package Insert and carton and container labels) for Zoledronic Acid Injection. OPDP's comments are based on the proposed, substantially complete version of the PI, and on the carton and container labels submitted by the applicant, available in the EDR at <\\CDSESUB1\EVSPROD\NDA203231\203231.enx>

OPDP has no comments on the draft labeling.

OPDP has no comments on the carton and container labels.

If you have any questions, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov.

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/s/

MARYBETH TOSCANO
10/02/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 203231

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

Applicant: ACS Dobfar Info S.A.

Labeling Reviewed

Submission Date: January 06, 2012

Receipt Date: January 09, 2012

Background and Summary Description

Sagent Pharmaceuticals, Inc., on behalf of ACS Dobfar Info S.A., has submitted a 505(b)(2) New Drug Application (NDA) for Zoledronic Acid Injection; N203231 that provides for the treatment of Hypercalcemia of malignancy, patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy. This dossier was originally submitted on August 30, 2011 and received a Refusal to File determination from the Agency, based upon insufficient stability data. The applicant has collected the requested 12-months of data and has re-submitted the application on January 09, 2012. The application was filed on February 22, 2012 and it will receive a Standard Review Designation; thereby making the PDUFA Date November 09, 2012.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

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” and put it beside the product name. Correct this 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) (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

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by April 2, 2012. The resubmitted labeling will be used for further labeling discussions.

Kim J. Robertson

March 21, 2012

Regulatory Project Manager

Date

Frank H. Cross, Jr.

March 22, 2012

Chief, Project Management Staff

Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

• General comments

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
RPM Comment: The applicant was missing some reference numbers in the HL of their 'Dosage and Administration' section.

- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)

• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

RPM Comment: The drug product name was not in all upper case letters and there was extra white-space between the limitation statement and the “**Highlights of Prescribing Information**” title.

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

RPM Comment: The drug product name was not in all upper case letters

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.

- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

RPM Comment: The revision date was not bolded as it should be.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.

- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

RPM Comment: The applicant will be informed that the correct title should be “Clinical Trials Experience”, as opposed to “(b) (4)”, which is what they have stated in their PI.

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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

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/s/

KIM J ROBERTSON
03/22/2012

FRANK H CROSS
03/22/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203231	NDA Supplement #:N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: None Established/Proper Name: Zoledronic Acid Dosage Form: Aqueous Solution Strengths: 4mg/100mL		
Applicant: ACS Dobfar Info SA Agent for Applicant (if applicable): Sagent Pharmaceuticals, Inc.		
Date of Application: January 06, 2012 Date of Receipt: January 09, 2012 Date clock started after UN: N/A		
PDUFA Goal Date: November 09, 2012	Action Goal Date (if different): N/A	
Filing Date: February 23, 2012	Date of Filing Meeting: February 22, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Hypercalcemia of malignancy, multiple myeloma with documented bone metastases in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input checked="" type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): N/A				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid</p> <p><input type="checkbox"/> Exempt (orphan, government)</p> <p><input type="checkbox"/> Waived (e.g., small business, public health)</p> <p><input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears</p> <p><input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>N021223</td> <td>Zometa (zoledronic acid) Injection</td> <td>PED</td> <td>March 2, 2013</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	N021223	Zometa (zoledronic acid) Injection	PED	March 2, 2013									<p>X</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
N021223	Zometa (zoledronic acid) Injection	PED	March 2, 2013																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>X</p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		X		Patent Information submitted, but not on FDA Form 3542a. Not required in that this is not a new drug that would normally have new associated patents.
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?		X		Applicant has requested waiver of the requirement for <i>in-vivo</i> bioequivalence testing
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is</i>				

<i>included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>			X	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>		X		
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>		X		
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) Vial Label/bag comparison			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 22, 2012

BLA/NDA/Supp #: 203231

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Zoledronic Acid Injection

DOSAGE FORM/STRENGTH: 4mg/100mL

APPLICANT: ACS Dobfar Info SA

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Hypercalcemia of malignancy, multiple myeloma with documented bone metastases in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

BACKGROUND: Sagent Pharmaceuticals, Inc., on behalf of ACS Dobfar Info S.A., has submitted a 505(b)(2) New Drug Application (NDA) for Zoledronic Acid Injection; N203231 that provides for the treatment of Hypercalcemia of malignancy, patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy. This dossier was originally submitted on August 30, 2011 and received a Refusal to File determination from the Agency, based upon insufficient stability data. The applicant has collected the requested 12-months of data and has re-submitted the application on January 09, 2012. The application was filed on February 22, 2012 and it will receive a Standard Review Designation; thereby making the PDUFA Date November 09, 2012.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim J. Robertson	
	CPMS/TL:	Frank Cross, Jr.	
Cross-Discipline Team Leader (CDTL)	Haripada Sarker, Ph.D.		
Clinical	Reviewer:	Geoffrey Kim, M.D.	
	TL:	V. Ellen Maher, M.D.	
Social Scientist Review <i>(for OTC)</i>	Reviewer:	N/A	

<i>products)</i>	TL:		
	Reviewer:	N/A	
OTC Labeling Review (<i>for OTC products)</i>	TL:		
	Reviewer:	N/A	
Clinical Microbiology (<i>for antimicrobial products)</i>	TL:		
	Reviewer:	N/A	
Clinical Pharmacology	TL:	Qi Liu, Ph.D.	
	Reviewer:	Pengfei Song, Ph.D.	
Biostatistics	TL:		
	Reviewer:	N/A	
Nonclinical (Pharmacology/Toxicology)	TL:	Anne Pilaro, Ph.D.	
	Reviewer:	Wei Chen, Ph.D.	
Statistics (carcinogenicity)	TL:		
	Reviewer:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements)</i>	TL:		
	Reviewer:	N/A	
Product Quality (CMC)	TL:	Haripada Sarker, Ph.D.	
	Reviewer:	Joyce Crich, Ph.D.	
Quality Microbiology (<i>for sterile products)</i>	TL:		
	Reviewer:	Stephen Langille, Ph.D.	
CMC Labeling Review	TL:		
	Reviewer:	N/A	
Facility Review/Inspection	TL:		
	Reviewer:		
OSE/DMEPA (proprietary name)	TL:		
	Reviewer:	TBD	

OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers (Biopharm)	Reviewer: Zedong Dong, Ph.D. TL: Angelica Dorantes, Ph.D.		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: (b)(2)</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: (b)(2); this drug is not the first in its class.

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Robert L. Justice, M.D., M.S.	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	<ul style="list-style-type: none"> • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
X	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Kim J. Robertson

February 21, 2012

Regulatory Project Manager

Date

Frank Cross, Jr.

February 22, 2012

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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

03/22/2012

RPM Filing Review Form N203231 Zoledronic Acid Inj. Sagent Pharmaceuticals for
ACS Dobfar Info S.A.

FRANK H CROSS

03/22/2012