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RESEARCH**

APPLICATION NUMBER:

203231Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	11/9/2012
From	Amna Ibrahim
Subject	Deputy Division Director Summary Review
NDA/BLA #	203231
Applicant Name	ACS Dobfar Info S.A.
Date of Submission	January 9, 2012
PDUFA Goal Date	November 9, 212
Proprietary Name / Established (USAN) Name	Zoledronic Acid Injection
Dosage Forms / Strength	Intravenous formulation/ 4mg/100mL
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Hypercalcemia of malignancy 2. 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 <p>Important limitation of use: The safety and efficacy of Zoledronic Acid Injection has not been established for use in hyperparathyroidism or nontumor-related hypercalcemia</p>
Action for NME:	Tentative Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Geoff Kim MD
Pharmacology Toxicology Review	Wei Chen PhD
CMC Review/OBP Review	Joyce Crich PhD
Clinical Pharmacology Review	Pengfei Song PhD
DDMAC	Marybeth Toscano PharmD
CDTL Review	Nallaperum Chidambaram PhD
OSE/DMEPA	Jibril Abdus-Samad, PharmD

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

CDTL=Cross-Discipline Team Leader

1. Introduction

Zometa (NDA 21223) is approved for hypercalcemia of malignancy and for patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. It is available as a single ready-to-use bottle (4 mg/100 mL) and a single-use vial of concentrate (4 mg/5 mL). Dosage is reduced for patients with renal impairment. NDA 203231 for zoledronic acid has been submitted using the 505(b)(2) pathway, relying listed drug Zometa 4 mg/5 mL (NDA 21223).

2. Background

Per sponsor, “on June 17, 2011, a new RLD was approved and listed in the Orange Book as Zometa® (Zoledronic Acid) Injection, 4mg /100mL (NDA 021223; Novartis Pharmaceuticals Corporation) however, as this product is not available on the market and this product has a modified formulation, we are submitting this application based on the 4mg/5mL RLD presentation.” This NDA was submitted previously but received a refuse to file letter due to insufficient of stability data.

There were some major issues for this NDA. The first one arose because the single-use bag did not allow for dose reduction [REDACTED] ^{(b) (4)}

[REDACTED] After discussions with the sponsor, the label was modified to clarify that this drug product is intended for patients with a normal kidney function (for whom dose reduction of zoledronic acid is not required). Another issue was regarding the patent of Zometa. The sponsor submitted a Paragraph III / Paragraph IV patent certification in this NDA. Beth Duval in an email dated 9/28/2012 informed this division that the patent was addressed by paragraph IV certification.

Please see review by CDTL Nallaperum Chidambaram PhD for details.

3. CMC/Device

The CMC reviewer Joyce Crich PhD, states in her review that “from the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.” Her review was co-signed by CDTL Nallaperum Chidambaram, PhD on 10/19/2012. No phase 4 commitments or requirements were recommended.

CMC review also states that “include the following language in the approval letter: Based on the provided stability data, a 12-month expiration dating period is granted for Zoledronic Acid Injection 4 mg/100mL in the proposed commercial container closure system when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).”

Per Zedong Dong PhD, ONDA biopharmaceutics reviewer, “the Applicant’s request for a waiver of the CFR requirement to provide in vivo bioequivalence data to support the approval of their proposed product under NDA 203- 231 is acceptable and the biowaiver for Zoledronic Acid Injection is granted.” He recommended the approval of Zoledronic Acid from the Biopharmaceutics viewpoint.

According to the CDTL review, the Office of Compliance issued an overall acceptable recommendation for this application on 2/21/2012.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 12 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Wei Chen PhD stated in her review that no nonclinical studies are needed to support the approval of the proposed zoledronic acid product at this time. No changes to the Reference Listed Drug’s package insert were recommended in sections containing nonclinical data. There are no issues from the Pharmacology/Toxicology discipline that would preclude approval of this zoledronic acid product for the proposed indications. Her review was co-signed by Todd Palmby PhD, Pharmacology/Toxicology team leader on 10/17/2012.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Pengfei Song, Ph.D. in his review dated 9/17/2012 states that “There is no bioequivalent study nor clinical study submitted in this application. The Applicant is relying on the findings of safety and effectiveness for Zometa to support the approval of the proposed product. The only clinical pharmacology related issue is that drug interaction information with thalidomide should be consistent with the latest labeling language of the RLD.” He also states that “this NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language”

6. Clinical Microbiology

Stephen E. Langille, Ph.D. in his review dated 7/24/2012 recommended approval.

7. Clinical/Statistical-Efficacy

Dr Geoffrey Kim in his review, dated 10/18/2012 and co-signed by Dr Amy McKee, states that “no new clinical data were submitted in support of this application. This application relies on the clinical studies of safety and efficacy used to support the reference listed product

Zometa (NDA 021223) which have been previously reviewed and have been found to have an acceptable risk-benefit profile. Therefore, the medical reviewer recommends approval for all of the above indications.” He also states that “Since the single-use bags do not allow for dose reductions, the dosage and administration section [REDACTED] (b) (4) include the statement: “This premixed ready-to-use bag is intended only for patients with normal renal function (creatinine clearance greater than 60 mL/min). The statement: “This product is not intended for patients with reduced renal function” is also included on the carton and container labels and on the ready-to-use-bag.”

8. Safety

See the Efficacy section above.

9. Advisory Committee Meeting

None conducted.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

- DSI Audits: not done
- Financial Disclosure: not applicable
- DDMAC: Marybeth Toscano, PharmD stated in her review that OPDP had no comments on the draft labeling or carton and container labeling.
- DMEPA: Jibril Abdus-Samad, PharmD stated in his review that “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.” In an addendum on 11/9/2012, the reviewer stated that DMEPA finds the Applicant’s revisions to the labels and labeling acceptable.

There are no other unresolved relevant regulatory issues

12. Labeling

All labeling issues were resolved.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**
A tentative approval action is recommended based on the risk-assessment assessment below as well as the pediatric exclusivity on the patent.
- **Risk Benefit Assessment**
This is a 505b2 application based on the listed drug Zometa. No review reported any deficiencies. The labeling has been reviewed by all disciplines and found acceptable.
- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**
None.
- **Recommendation for other Postmarketing Requirements and Commitments**
None.

Amna Ibrahim MD
Deputy Division Director
DOP1

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/s/

AMNA IBRAHIM
11/09/2012

Cross-Discipline Team Leader Review #2

DATE	2-NOV-2012
From	Nallaperumal Chidambaram, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	203231
Applicant	ACS Dobfar Info. S.A.
Date of Submission	06-JAN-2012
PDUFA Goal Date	09-NOV-2012
Proprietary Name/ Established (USAN) names	Zoledronic Acid Injection
Dosage forms / Strength	4 mg/100 mL
Proposed Indication(s)	Multiple treatment of: <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
Recommendation:	Approval

1. Introduction

NDA 203231 was initially submitted to the Agency on 30-AUG-2011. The Agency subsequently undertook a "Refuse to File" action on 28-OCT-2011 based on limited stability data to support a commercially viable shelf-life. The Applicant resubmitted the NDA on 06-JAN-2012, and the Agency conveyed the fileability determination in a 23-MAR-2012 letter.

The two pending issues that were noted in the CDTL memo dated 19-OCT-2012 related to (1) minor labeling changes, and (2) the impact of pending Novartis patent for infusion time on the approvability of this application. The above two issues were satisfactorily resolved. The applicant agreed to the Agency's recommendation with regard to minor labeling revisions and also to revert back to not less than 15 minutes of infusion time as provided in the RLD. The input from ORP with regard to pending Novartis patent was that this will not have an impact if the Novartis patent is still pending on the date an approval action is taken for this application. It is this reviewers understanding that the above patent is still pending.

This CDTL memo serves to summarize the critical issues noted in all review disciplines and recommends an “**approval**” action for this application. All individual discipline reviews may be found in DARRTS. Additional information can be located in the previous CDTL memo dated 19-OCT-2012.

2. Background

The Reference Listed Drug for this submission is Zometa® (zoledronic acid) Injection (NDA 21-233), single-use ready-to-use bottle and is currently marketed by Novartis. The proposed drug product is a sterile, ready-to-infuse solution of zoledronic acid (4 mg/100 mL of 0.9% NaCl solution) in a 100 mL flexible (b) (4) infusion bags equipped with one (b) (4) tube and twist off port (b) (4) which are placed in aluminum over-pouches.

The inactive ingredients in the proposed product and the RLD product are (b) (4) the same and they are present in the following quantities: 900 mg of sodium chloride, USP, 220 mg of mannitol, USP, 100 mL water for injection and sodium citrate to adjust pH.

Dosing Regimen and Administration

The recommended dose of Zoledronic acid Injection is as follows:

Hypercalcemia of malignancy

- 4 mg as a single-use intravenous infusion over no less than (b) (4) minutes
- 4 mg as retreatment after a minimum of 7 days

Multiple myeloma and bone metastasis from solid tumors

- 4 mg as a single-use intravenous infusion over no less than (b) (4) minutes every 3 to 4 weeks for patients with creatinine clearance of greater than 60 mL/min.
- This premixed ready-to-use bag is intended only for patients with normal renal function (creatinine clearance greater than 60 mL/min.)

3. CMC

NDA 203231 was submitted on 30-AUG-2011 as a 505(b)(2) application. The original submission was refused to file on 28-OCT-2011 because requested 24 months of shelf-life based on 6 months of long term and accelerated stability data is not sufficient to support a commercially viable shelf-life. The applicant resubmitted this application on 6-JAN-2012 with 12 months of long-term and 6 months of accelerated stability data.

General product quality considerations

The CMC reviewer (Dr. Joyce Crich) recommended approval in her review #2 of this NDA dated 19-OCT-2012. (b) (4)

The drug substance is a small molecule synthesized in (b) (4) steps. The manufacturing and controls information is cross-referenced to a DMF. This DMF was found to be adequate (Refer to Dr. D. Chowdhury's review dated 16-AUG-2012).

Zoledronic Acid Injection is a clear, colorless, sterile solution for intravenous infusion and is available in 4 mg/100 mL dosage strength. The formulation contains zoledronic acid monohydrate as the active pharmaceutical ingredient equivalent to 4 mg of zoledronic acid anhydrous, 0.9% Sodium Chloride USP, Mannitol USP, Sodium Citrate (b) (4) USP and Water for Injection USP. The drug product is filled in (b) (4) 100 ml bags equipped with one (b) (4) tube (b) (4) and twist off port (b) (4) which are then placed in aluminum (b) (4) over pouches to protect the product from light and water permeation.

Updated stability data up to 18 months was provided during the review cycle. Due to inconsistencies noted in the level of degradation products between stability data submitted in the resubmission and updated stability data, longer shelf-life than 12 months can not be considered.

ONDQA Biopharm review

The Biopharm reviewer (Dr. Z. Dong) noted in his review dated 02-APR-2012 that before the initial submission of this NDA, the Orange Book listed Zometa Injection (4 mg/100 mL) as a new RLD. However, the applicant indicated that they were using currently approved 4 mg/5 mL strength as the RLD. The applicant therefore requested a waiver of evidence for *in vivo* BA/BE as per 21 CFR §320.22 (b)(1)(i) & (ii).

The reviewer noted that all excipients fall below the FDA Inactive Ingredient Guide (IIG) limits for intravenous administration. The 4 mg/5 mL RLD concentrated solution when diluted in 100 mL of sterile 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP prior to use will result in slightly larger volume than the proposed zoledronic acid injection. The reviewer further noted that this slight difference in the concentrations of active and inactive ingredients between the RLD and the proposed zoledronic acid injection is unlikely to affect the bioavailability and bioequivalence of the proposed product and the requested biowaiver for zoledronic acid injection was granted.

Facilities review/inspection

The Office of Compliance issued an overall acceptable recommendation for this application on 21-FEB-2012.

Microbiology

The microbiology reviewer (Dr. S. Langille) identified no deficiencies based on the information provided in the application and had recommended approval of this NDA in his review dated 24-JUL-2012.

Other notable issues (resolved or outstanding): None

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer (Dr. W. Chen) in her review dated 17-OCT-2012 noted that no nonclinical studies were submitted and none are needed to support the approval of zoledronic acid injection. In addition, no changes to RLD's package insert were proposed and none recommended.

The CMC reviewer requested input for the proposed acceptance criterion for "Single Unknown Impurity" in the drug product of (b) (4) % at release and no more than (NMT) (b) (4) % for shelf-life. The Pharmacology reviewer initially determined that the proposed limit for single unknown impurity may not be acceptable for genotoxic or carcinogenic impurities and recommended reducing to NMT (b) (4) %, at which the daily exposure would be (b) (4) with a recommended dose of 4 mg/day. The applicant responded that in their assessment of the manufacturing process for zoledronic acid, they did not identify any genotoxic alerts and that the proposed specification is consistent with ICH Q3B. Based on the above, the pharmacology reviewer found the proposed limit of (b) (4) % for single unknown impurity acceptable.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer (Dr. Pengfei Song) in his review dated 17-SEPT-2012 indicated that no bioequivalent study or clinical study was submitted in this application and that the applicant was relying on the findings of safety and efficacy for Zometa to support the approval of their application. The only concern expressed was that drug interaction information with thalidomide in the proposed labeling should be consistent with the latest labeling language of the RLD. According to Pengfei (e-mail to the review team dated 19-OCT-2012), the labeling revisions related to this section were forwarded and accepted by the applicant. The reviewer found the information acceptable.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The clinical reviewer (Dr. Geoffrey Kim) in his review dated 18-OCT-2012 indicated that no new clinical data were submitted in support of this application and that this application relies on the clinical studies of safety and efficacy used in support of the reference listed product Zometa (N21-233). The RLD was previously reviewed and have been found to have an acceptable risk-benefit profile. Based on the above, the medical reviewer recommends approval for the indications noted above.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Not applicable

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP): This application is not in the AIP list.

Exclusivity or patent issues of concern: None.

Financial disclosures: The application did not contain financial disclosure form.

Other GCP issues: None

DSI audits: Not applicable

Other discipline consults: DDMAC/DMEPA/Micro/Biopharm/
Methods Validation

The DMEPA reviewer (Dr. Jibril Abdus-Samad) in his review dated 19-OCT-2012 recommended changes to container, carton and overwrap labeling. The applicant provided their responses on 24-OCT-2012. The DMEPA reviewer found the responses to be acceptable (refer to Dr. Jibril Abdus-Samas's e-mail dated 24-OCT-2012).

Any other outstanding regulatory issues: None

12. Labeling

All issues were resolved satisfactorily. Please refer to

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

This reviewer recommends approval of this NDA

Risk Benefit Assessment

The review of this NDA is based primarily on chemistry, manufacturing and controls data. All Chemistry, manufacturing and controls deficiencies are resolved and the application has received an overall acceptable recommendation from the Office of Compliance. Therefore, the Applicant has adequately supported the commercialization of the proposed drug product.

Recommendation for Postmarketing Risk Management Activities

This does not apply to this NDA.

Recommendation for other Postmarketing Study Commitments

None

Recommended Comments to Applicant

Based on provided stability data, a 12-month expiration dating period is granted for Zoledronic acid injection 4 mg/100 mL in the proposed container closure system and when stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

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/s/

NALLAPERUM CHIDAMBARAM
11/05/2012

Cross-Discipline Team Leader Review

DATE	19-OCT-2012
From	Nallaperumal Chidambaram, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	203231
Applicant	ACS Dobfar Info. S.A.
Date of Submission	06-JAN-2012
PDUFA Goal Date	09-NOV-2012
Proprietary Name/ Established (USAN) names	Zoledronic Acid Injection
Dosage forms / Strength	4 mg/100 mL
Proposed Indication(s)	Multiple treatment of: <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
Recommended:	Approval pending (1) resolution of minor labeling issues, and (2) Patent issue related to time of infusion

1. Introduction

NDA 203231 was initially submitted to the Agency on 30-AUG-2011. The Agency subsequently undertook a “Refuse to File” action on 28-OCT-2011 based on limited stability data to support a commercially viable shelf-life. The Applicant resubmitted the NDA on 06-JAN-2012, and the Agency conveyed the fileability determination in a 23-MAR-2012 letter. This CDTL memo serves to summarize the critical issues noted in all review disciplines and recommends “approval” pending resolution of minor labeling issues and a patent issue with respect to the time for infusion. All individual discipline reviews may be found in DARRTS.

2. Background

The Reference Listed Drug for this submission is Zometa® (zoledronic acid) Injection (NDA 21-233), single-use ready-to-use bottle and is currently marketed by Novartis. The proposed drug product is a sterile, ready-to-infuse solution of zoledronic acid (4 mg/100 mL of 0.9% NaCl solution) in a 100 mL

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- This premixed ready-to-use bag is intended only for patients with normal renal function (creatinine clearance greater than 60 mL/min.)

3. CMC

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The CMC reviewer (Dr. Joyce Crich) recommended approval in her review #2 of this NDA dated 19-OCT-2012. (b) (4)

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The reviewer noted that all excipients fall below the FDA Inactive Ingredient Guide (IIG) limits for intravenous administration. The 4 mg/5 mL RLD concentrated solution when diluted in 100 mL of sterile 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP prior to use will result in slightly larger volume than the proposed zoledronic acid injection. The reviewer further noted that this slight difference in the concentrations of active and inactive ingredients between the RLD and the proposed zoledronic acid injection is unlikely to affect the bioavailability and bioequivalence of the proposed product and the requested biowaiver for zoledronic acid injection was granted.

Facilities review/inspection

The Office of Compliance issued an overall acceptable recommendation for this application on 21-FEB-2012.

Microbiology

The microbiology reviewer (Dr. S. Langille) identified no deficiencies based on the information provided in the application and had recommended approval of this NDA in his review dated 24-JUL-2012.

Other notable issues (resolved or outstanding): None

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer (Dr. W. Chen) in her review dated 17-OCT-2012 noted that no nonclinical studies were submitted and none are needed to support the approval of zoledronic acid injection. In addition, no changes to RLD's package insert were proposed and none recommended.

The CMC reviewer requested input for the proposed acceptance criterion for "Single Unknown Impurity" in the drug product of (b) (4) % at release and no more than (NMT) (b) (4) % for shelf-life. The Pharmacology reviewer initially determined that the proposed limit for single unknown impurity may not be acceptable for genotoxic or carcinogenic impurities and recommended reducing to NMT (b) (4) %, at which the daily exposure would be (b) (4) with a recommended dose of 4 mg/day. The applicant responded that in their assessment of the manufacturing process for zoledronic acid, they did not identify any genotoxic alerts and that the proposed specification is consistent with ICH Q3B. Based on the above, the pharmacology reviewer found the proposed limit of (b) (4) % for single unknown impurity acceptable.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer (Dr. Pengfei Song) in his review dated 17-SEPT-2012 indicated that no bioequivalent study or clinical study was submitted in this application and that the applicant was relying on the findings of safety and efficacy for Zometa to support the approval of their application. The only concern expressed was that drug interaction information with thalidomide in the proposed labeling should be consistent with the latest labeling language of the RLD. According to Pengfei (e-mail to the review team dated 19-OCT-2012), the labeling revisions related to this section were forwarded and accepted by the applicant. The reviewer found the information acceptable.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The clinical reviewer (Dr. Geoffrey Kim) in his review dated 18-OCT-2012 indicated that no new clinical data were submitted in support of this application and that this application relies on the clinical studies of safety and efficacy used in support of the reference listed product Zometa (N21-233). The RLD was previously reviewed and have been found to have an acceptable risk-benefit profile. Based on the above, the medical reviewer recommends approval for the indications noted above.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Not applicable

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP): This application is not in the AIP list.

Exclusivity or patent issues of concern: Based on Novartis patent for infusion time, input from ORP on this issue is pending.

Financial disclosures: The application did not contain financial disclosure form.

Other GCP issues: None

DSI audits: Not applicable

Other discipline consults: DDMAC/DMEPA/Micro/Biopharm/
Methods Validation

Any other outstanding regulatory issues: None

12. Labeling

All issues resolved except for minor DMEPA recommendation.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

This reviewer recommends approval pending (1) satisfactory resolution of minor labeling issues, and (2) Patent issue related to time of infusion.

Risk Benefit Assessment

The review of this NDA is based primarily on chemistry, manufacturing and controls data. All Chemistry, manufacturing and controls deficiencies are resolved and the application has received an overall acceptable recommendation from the Office of Compliance. Therefore, the Applicant has adequately supported the commercialization of the proposed drug product.

Recommendation for Postmarketing Risk Management Activities

This does not apply to this NDA.

Recommendation for other Postmarketing Study Commitments

None

Recommended Comments to Applicant

Based on provided stability data, a 12-month expiration dating period is granted for Zoledronic acid injection 4 mg/100 mL in the proposed container closure system and when stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

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/s/

NALLAPERUM CHIDAMBARAM
10/19/2012

CLINICAL REVIEW

Application Type NDA 505(b)(2)
Application Number(s) NDA 203231
Priority or Standard Standard

Submit Date(s) January 06, 2012
Received Date(s) January 09, 2012
PDUFA Goal Date November 09, 2012
Division / Office DOP1/OHOP

Reviewer Name(s) Amy McKee, MD (CTL)
Geoffrey Kim, MD
Review Completion Date 10/17/12

Established Name Zoledronic Acid
(Proposed) Trade Name Zoledronic Acid for Injection
Therapeutic Class Bisphosphonate
Applicant ACS Dobfar

Formulation(s) Aqueous Solution, single-use,
ready-to-use bag for
intravenous infusion
Dosing Regimen Multiple
Indication(s) treatment of:
• Hypercalcemia of
Malignancy
• Patients with multiple
myeloma and patients with

documented bone
metastases from solid tumors

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

No new clinical data were submitted in support of this application. This application relies on the clinical studies of safety and efficacy used to support the reference listed product Zometa (NDA 021223) which have been previously reviewed and have been found to have an acceptable risk-benefit profile. Therefore, the medical reviewer recommends approval for all of the above indications.

1.2 Risk Benefit Assessment

Please refer to NDA 021223. No new clinical data were submitted with this application.

Zoledronic Acid Injection, Ready-to-Infuse Solution is a 'pre-mix' or 'ready-to-infuse' solution presentation containing 4 mg zoledronic acid packaged in 100 mL flexible plastic (b) (4) infusion bags equipped with one (b) (4) Tube and Twist Off Port (b) (4) which are placed in aluminum over-pouches. These single-use infusion bags were not designed to accommodate safe withdrawal of excess drug product for dose reductions or modifications. In patients with multiple myeloma and with mild to moderate renal impairment, a dose reduction of Zometa is recommended (Table 1). Since the single-use bags do not allow for dose reductions, the dosage and administration section (b) (4) (b) (4) include the statement: "This premixed ready-to-use bag is intended only for patients with normal renal function (creatinine clearance greater than 60 mL/min). The statement: "This product is not intended for patients with reduced renal function" is also included on the carton and container labels and on the ready-to-use-bag. These (b) (4) labels and package insert were deemed to be adequate by the medical reviewer and the reviewers from the Division of Medical Error Prevention and Analysis.

Table 1: Reduced Doses for Patients with Baseline CrCl less than or equal to 60 mL/min

Baseline Creatinine Clearance (mL/min)	Zometa Recommended Dose*
greater than 60	4 mg
50 – 60	3.5 mg
40 – 49	3.3 mg
30 – 39	3 mg

*Doses calculated assuming target AUC of 0.66(mg·hr/L) (CrCl = 75 mL/min)

Clinical Review
{Insert Reviewer Name}
{Insert Application Type and Number}
{Insert Product Trade and Generic Name}

1.3 Summary of Presubmission Regulatory Activity Related to Submission

This application was initially submitted on August 29, 2011. The application was initially deemed to be insufficient for the following reason: The proposed drug product shelf-life of 24 months based on 6 months of long term and accelerated stability data are not sufficient to support a commercially viable shelf-life. Also note that as per GRMPs, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

The application was resubmitted on January 06, 2012 and no additional filing issues were identified.

1.4 Labeling Recommendations

Please refer to the package insert.

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

/s/

GEOFFREY S KIM
10/18/2012

AMY E MCKEE
10/18/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2x Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			x	
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			x	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34.	Are all datasets to support the critical safety analyses available and complete?			x	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			x	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			x	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Geoffrey Kim	10/21/11
<hr/>	
Reviewing Medical Officer	Date
V. Ellen Maher	10/27/11
<hr/>	
Clinical Team Leader	Date

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

/s/

GEOFFREY S KIM
10/27/2011