APPLICATION NUMBER:

204016Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)
Product Quality Microbiology Review

04 October 2012

NDA: 204-016/N-000

Drug Product Name
Proprietary: N/A
Non-proprietary: Zoledronic Acid Injection, 0.04mg/ml

Review Number: 1

Dates of Submission(s) Covered by this Review

<table>
<thead>
<tr>
<th>Submit</th>
<th>Received</th>
<th>Review Request</th>
<th>Assigned to Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 January 2012</td>
<td>31 January 2012</td>
<td>28 February 2012</td>
<td>29 February 2012</td>
</tr>
<tr>
<td>30 April 2012</td>
<td>30 April 2012</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>23 July 2012</td>
<td>23 July 2012</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>14 August 2012</td>
<td>14 August 2012</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Hospira, Inc.
Address: 275 North Field Dr.
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045

Representative: Khaled M Mohamed
Product Manager Regulatory Affairs
Telephone: 224-212-4909

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint.
Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** 505(b)(2)

2. **SUBMISSION PROVIDES FOR:** Marketing authorization

3. **MANUFACTURING SITE:**
   - Laboratorios Grifols, S.A.
   - Barcelona, Spain
   - FEI# 3002807257

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile solution, Intravenous injection, 4mg/100ml (0.04 mg/ml) packaged in a single port, 100ml intravenous infusion.

5. **METHOD(S) OF STERILIZATION:**

6. **PHARMACOLOGICAL CATEGORY:** Treatment of hypercalcemia of malignancy and for treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors.

B. **SUPPORTING/RELATED DOCUMENTS:** None

C. **REMARKS:**
   - The submission was provided in eCTD format and was available for review in EDR.
   - An ONDQA filing review was submitted on 09 March 2012. No specific questions were referred to OPS/NDMS. This reviewer's Filing Review was entered into DARRTS on 08 March 2012.
     - On 09 July 2012, a Microbiology Information Request was transmitted to the Applicant by the Project Manager. The Applicant replied to the information request on 23 July 2012. Those responses are incorporated into the body of this review.

Filename: N204016N000R1.doc
Executive Summary

I. Recommendations
A. Recommendation on Approvability - Recommend Approval
B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - Not Applicable

II. Summary of Microbiology Assessments
A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - The drug product is formulated and
B. Brief Description of Microbiology Deficiencies - None
C. Assessment of Risk Due to Microbiology Deficiencies - N/A

III. Administrative
A. Reviewer's Signature: _____________________________
   Robert J. Mello, Ph.D.
   Senior Microbiology Reviewer
B. Endorsement Block: _____________________________
   John W. Metcalfe, Ph.D.
   Senior Microbiology Reviewer
C. CC Block
   NDA 204016
Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE: The drug substance is not sterile.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product
- Description of drug product – Zoledronic acid, 4 mg/100 mL, is a sterile aqueous solution for intravenous infusion.
- Drug product composition – The composition of the drug product is provided below (copied from submission Section 3.2.P.1, Table 2, page 2/2):

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity per Milliliter (mL)</th>
<th>Strength: 4 mg/100mL Quantity per unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic Acid</td>
<td>0.04 mg</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Mannitol</td>
<td>2.2 mg</td>
<td>220 mg</td>
</tr>
<tr>
<td>Sodium Citrate</td>
<td>0.24 mg</td>
<td>24 mg</td>
</tr>
<tr>
<td>Sodium Chloride</td>
<td>0.0 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>q.s. to 1 mL</td>
<td>q.s. to 100 mL</td>
</tr>
<tr>
<td>Total Volume</td>
<td>1.00 mL</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

q.s. = Quantity sufficient
† Theoretical amount on an anhydrous basis

- Description of container closure system – The container closure system consists of a 100 mL bag with a twist-off cap. The bags are
P.2 Pharmaceutical Development
P.2.5 Microbiological Attributes:

- **Container-Closure and Package Integrity (CCI)** - On 14 August 2012, the applicant submitted an amendment for a minor change in the port tube dimensions. This would not affect the process but the container-closure testing would be affected. The applicant submitted updated test results (see below) using the new tube. (Note: the only changes in the tubing were fractional increases in dimension. Processes were unchanged.)

- Justification for not having a microbial limit specification for a non-sterile drug product - The drug product is sterile.

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT J MELLO
10/04/2012

JOHN W METCALFE
10/04/2012

I concur.
### PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 204-016  
**Applicant:** Hospira, Inc.  
**Letter Date:** 30 January 2012  
**Drug Name:** Zoledronic Acid Injection, 0.04mg/ml  
**NDA Type:** 505(b)(2)  
**Stamp Date:** 31 January 2012

The following are necessary to initiate a review of the NDA application:

<table>
<thead>
<tr>
<th>Content Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?</td>
<td>X</td>
<td></td>
<td>Module 3, Section 3.2.P.3.3</td>
</tr>
<tr>
<td>3 Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?</td>
<td>X</td>
<td></td>
<td>Module 3, Section 3.2.P.3.5</td>
</tr>
<tr>
<td>4 Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?</td>
<td>X</td>
<td></td>
<td>Container closure testing: Module 3, Section 3.2.P.2.5. Product is not preserved.</td>
</tr>
<tr>
<td>6 Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?</td>
<td>X</td>
<td></td>
<td>Module 3, Section 3.2.P.5.1</td>
</tr>
<tr>
<td>7 Has the applicant submitted the results of analytical method verification studies?</td>
<td>X</td>
<td></td>
<td>Module 3, Section 3.2.P.5.3</td>
</tr>
<tr>
<td>8 Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?</td>
<td>-</td>
<td>-</td>
<td>Not applicable</td>
</tr>
<tr>
<td>9 Is this NDA fileable? If not, then describe why.</td>
<td>X</td>
<td></td>
<td>The NDA is fileable from a microbiology product quality perspective.</td>
</tr>
</tbody>
</table>

**Additional Comments:** The drug product is formulated at 0.04mg/ml and packaged in 100ml bags having one tube with a twist-off administration cap.

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Robert J. Mello, Ph.D. (Senior Microbiology Reviewer)  
Date: 3/8/2012

Stephen E. Langille, Ph.D. (Senior Microbiology Reviewer)  
Date: 3/8/2012

Reference ID: 3099269
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT J MELLO
03/08/2012

STEPHEN E LANGILLE
03/08/2012