CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200795Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 200795

COMPLETE RESPONSE

Hospira, Inc.
Attention: Khaled M. Mohamed
275 North Field Dr.
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045-5046

Dear Mr. Mohamed:

Please refer to your New Drug Application (NDA) dated December 11, 2009, received December 11, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Gemcitabine Injection, 200 mg/5.3 mL, 1 g/26.3 mL, and 2 g/52.6 mL.

We acknowledge receipt of your amendments dated January 19, 2009, April 1 and 19, 2010, June 23, 2010, August 3, 5, 16 and 20, 2010, September 9, 2010, October 29, 2010, and December 6, 2010.

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

PRODUCT QUALITY

Method Number (Method No. 6.320 for Chromatographic Purity Test) is not adequately validated for linearity, accuracy, and precision. Accordingly, it is not possible to confirm actual levels of the following impurities in supporting and primary drug product batches: (b) (4)

MICROBIOLOGY

Microbiological studies in support of the 24 hour post-dilution/penetration storage time for Gemcitabine Injection as stated in the proposed labeling, have not been provided. Provide risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions proposed. In lieu of these data, the product labeling should recommend that the post-constitution storage period is not more than 4 hours at room temperature or 24 hours if refrigerated. Reference is made to *Guidance for Industry: ICH Q8 Pharmaceutical Development*, Section II.E and *Guidance for Industry*: *ICH Q1A(R2) Stability Testing of New Drug Substances and Products*, Section 2.2.7.

The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution. The time

point at which the initiation of growth is clearly evident should be identified. Sufficient replicates should be done to be able to identify when the titer is rising above the testing error of the no growth points. It is generally accepted that growth is evident when the population increases more than 0.5 Log_{10}. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label-recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.

NONCLINICAL

Provide justification for the impurity levels within lot U022750RA, the lot used in the Study 1632-08668. This justification should adequately address accuracy and precision of previous reported measures to allow for setting of specifications for (b) (4)

Should new analytical methods indicate that substantial differences exist between information submitted previously to qualify impurities or should a justifiable bridge between analytical procedures previously used and those to be developed are not be capable of being established, specifications may need to be lowered to below qualification thresholds or an additional non-clinical study may be necessary to support specifications

LABELING

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

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

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

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

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

If you have any questions, call Amy Tilley, Regulatory Project Manager, at 301-796-3994.

Sincerely,

{See appended electronic signature page}

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

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

/s/

AMNA IBRAHIM
01/11/2011
For Dr Robert Justice