CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200795Orig1s000

MEDICAL REVIEW(S)

Memorandum

To: NDA 200-795

From: Haripada Sarker, Ph.D. Date: 7/27/2011

Re: CDTL Memo Update - Addendum

Reference is made to the 28-Dec-2010 original CDTL memo by Dr. Sarah Pope Miksinski. The purpose of this addendum is to evaluate the updated HPLC method validation information to ascertain the impurity levels of drug as following, and to provide an updated recommendation of approval from a CMC perspective

A brief description of the drug substance and the drug product can be found in the original CMC review conducted by Dr. Joyce Crich (dated 12/15/2010) in DARRTS. No deficiencies were identified for the drug substance. For the drug product, the major CMC information such as formulation composition, manufacturing process and control, drug product specification, batch analysis data, stability studies and data, packaging configuration were determined to be acceptable by the first CMC reviewer. However, the following deficiency was identified by Dr. Joyce Crich (dated 12/15/2010) and was communicated to the sponsor through a CR letter dated 1/11/2011.

> *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)

On June 10, 2011 the applicant resubmitted the NDA along with the details of the analytical method (chromatographic purity test, method #6.320). The sponsor has revalidated this method for linearity, accuracy, and precision at the proposed limits and at the higher concentrations of impurities (b) (4) (b) (4) utilized in the non-clinical toxicology studies. The details of the individual validation including test method, criteria and data are discussed in the later part of this review. The level of the impurities that were used in the non-clinical study for qualification purposes were previously questionable due to the fact that sufficient analytical method validation information was not submitted in the original submission. Resubmission of this application has provided enough information on the validation of the HPLC method thereby demonstrating that the method is specific, accurate, linear, sensitive and precise over the ICH range of QL to 120% of specification. Additionally, the validation testing was also conducted over an extended range (beyond the ICH guideline) to accommodate the batches with high levels of these impurities used in the toxicological studies. This assessment was conducted in the current review cycle and is captured in the Chemistry Review by Dr. AKM Khairuzzaman dated 7/15/2011, which recommends approval from a CMC perspective.

The results demonstrated that the method is accurate, precise and linear over the extended range. Therefore, the qualification level of these impurity derived from the non clinical studies are found to be acceptable. Please see the Chemistry Review by for further details.

There were no other deficiencies identified for this NDA (see CDTL memo dated 28-Dec-2010). Outstanding CMC and Pharmacology/Toxicology deficiencies are resolved in this review cycle, also Office of Compliance issued an acceptable recommendation. This application is recommended for approval from a CMC perspective, and therefore, the application is also recommended for approval overall.

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/s/

HARIPADA SARKER
07/27/2011

SARAH P MIKSINSKI
07/27/2011

Summary Review for Regulatory Action

Date	1/11/2011
From	Amna Ibrahim MD
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 200795 000
Applicant Name	Hospira, Inc
Date of Submission	12/11/2009
PDUFA Goal Date	1/11/2011 (after major amendment)
Proprietary Name / **Established (USAN) Name**	Gemcitabine Injection Gemcitabine
Dosage Forms / Strength	Sterile solution for injection/ 38 mg/mL
Proposed Indication(s)	1. In combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy. 2. In combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated. 3. In combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer. 4. As first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine injection is indicated for patients previously treated with 5-FU.
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Martin Cohen MD/ John Johnson MD
Pharmacology Toxicology Review	Robert Dorsam PhD/Sandi L Verbois PhD
CMC Review/OBP Review	Joyce Crich PhD/Sarah P Miksinski PhD
Microbiology Review	Stephen Langille PhD/
Clinical Pharmacology Review	Stacy Shord PhD/Qi Liu PhD
CDTL Review	Sarah P Miksinski PhD
OSE/DRISK	Latonia Ford
PMHS	Jeanine Best
DMEPA	Yelena Maslov

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
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Background

Hospira Inc. submitted NDA 200795 on 12/11/2009 based on previously approved NDA 20-509 for Gemzar (Eli Lilly and Co) as a 505b2 submission. Per applicant, the active ingredients and excipients are the same as Gemzar except for mannitol and sodium acetate.

2. CMC/Device

According to CMC primary review by Joyce Crich PhD dated 12/14/2010, cosigned by Sarah Miksinski PhD, "The application cannot be recommended for approval from a chemistry, manufacturing, and controls (CMC) standpoint until the following deficiency is satisfactorily resolved:"

"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)

"Additionally, the Office of Compliance has issued an overall withhold recommendation (06-DEC-2010) for this application. This application cannot be recommended for approval until the above deficiency and any cGMP-related deficiencies are satisfactorily resolved."

In the microbiology review by Stephen E Langille PhD dated, 11/29/2010 cosigned by James L McVey on 12/2/2010, it is stated that "microbiological studies in support of the 24 hour post-dilution/penetration storage time for Gemcitibine Injection (as stated in the proposed labeling) have not been provided. Please provide a 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." Dr Miksinski recommends that this labeling deficiency related to the proposed post-dilution storage time be included in the action letter.

Dr Sarah Miksinski does not recommend approval of this NDA in her CDTL review. She states that "as per the Chemistry review and final Pharmacology/Toxicology memo dated 15-DEC-2010, acceptable resolution of the outstanding CMC and Pharmacology/Toxicology deficiencies is required before an overall approval recommendation can be made for the NDA. Additionally, an overall acceptable recommendation must be received from the Office of Compliance before this product can be recommended for approval from a CMC perspective."

I concur with the conclusions reached by the chemistry reviewer and CDTL regarding the acceptability of the manufacturing of the drug product and drug substance.

3. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology studies were provided in this submission. Sandi L Verbois PhD in her review dated 12/8/2010 states that she agrees with Dr. Robert Dorsam's conclusion that the sponsor should 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 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.

I concur with the conclusions reached by the pharmacology/toxicology reviewer. The sponsor should provide justification for the impurity levels.

4. Clinical Pharmacology/Biopharmaceutics

Stacy Shord, PhD in her review states that based on the comparison to the listed drug (Gemzar® for Injection; Eli Lilly and Company, Inc.), Hospira is requesting a waiver of in vivo bioequivalence for Gemcitabine Injection® in accordance with 21 CFR 320.22(b). Clinical studies are not included in the current 505(b)2 application and the application relies on the Agency's finding of safety and effectiveness for the approved drug-Gemzar® for Injection (NDA 20-509), as the active ingredient, route of administration (i.v. infusion) and indications for the Hospira drug product are the same as the listed drug product." And that "the Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 200-795/S-000. This application is acceptable from a clinical pharmacology perspective.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

Per Martin Cohen MD, clinical reviewer, there were no clinical studies submitted and no financial disclosures were needed. Clinical review was not required for this NDA.

7. Safety

Not applicable

8. Advisory Committee Meeting

Not applicable.

9. Pediatrics

Pediatric and Maternal Health Staff were consulted regarding whether protected pediatric use information that appears in Gemzar labeling can be carved-out of this 505(b)(2) gemcitabine labeling. PMHS preferred that all drugs with data on the safe and effective use in the pediatric population be labeled with such information, especially when that information was obtained under legislation intended to provide evidence based labeling. However, because the pediatric legislation did not anticipate the conditions of 505(b)(2) applications, and because the pediatric data in gemcitabine

labeling does not pose a tangible safety risk if omitted, PMHS advised that DDOP can decide to omit the protected pediatric information and approve this 505(b)(2) gemcitabine application.

10. Other Relevant Regulatory Issues

- DSI Audits: Not applicable
- Financial Disclosure: Not applicable
- Other consults: According to DMEPA review by Yelena Maslov dated September 21, 2010, most of previous concerns and recommendations regarding the proposed labels and labeling of Gemcitabine, were addressed by the Applicant. However, evaluation of the revised proposed container labels and carton labeling dated June 23, 2010 and August 20, 2010 noted additional areas of needed improvement in order to minimize the potential of medication errors that were not addressed by the Applicant in the revisions. For details, please see Ms Maslov's review.

11. Labeling

Labeling will need to be revisited at the time of resubmission of the NDA.
Proprietary name: none.

12. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Based on the CMC and pharmacology/toxicology reviewers' findings and recommendations as well as the recommendations from Office of Compliance, I do not recommend approval of this NDA.

- Risk Benefit Assessment

I agree with the risk-benefit assessment by Dr Miksinski. She states in her review that "the review of this NDA is based primarily on chemistry, manufacturing and controls data. The Applicant has not satisfactorily responded to the identified CMC and Pharmacology/Toxicology deficiencies, and the application has received an overall withhold recommendation from the Office of Compliance. Therefore, there are outstanding regulatory issues for this NDA, the cGMP status for all manufacturing sites is unacceptable, and the proposed manufacturing sites are not confirmed as suitable for producing drug product for the commercial market."

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Not applicable.

- Recommendation for other Postmarketing Requirements and Commitments

None.

Amna Ibrahim MD
Deputy Division Director
Division of Drug Oncology Products

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/s/

AMNA IBRAHIM
01/11/2011
For Dr Robert Justice