CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200795Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Memorandum

To: NDA 200-795
From: Haripada Sarker, Ph.D. Date: 08/03/2011
Re: CDTL Memo Update - Addendum

Reference is made to the 28-Dec-2010 original CDTL memo by Dr. Sarah Pope Miksinski also updated CDTL memo dated 27-July-20011 by Dr. Haripada Sarker. The purpose of this addendum is to include the drug product expiration dating, and to provide an updated recommendation of approval from a CMC perspective

The application was found to be inadequate because of the insufficient analytical method validation (see first CMC review by Dr. Joyce Crich dated 12/15/2010). Subsequently, the CMC reviewer, Dr. Akm Khairuzzaman has made "Approvable" recommendation dated 07/15/2011 based on the analytical method validation update. However, the decision on the product's shelf life of 18 months was not included in CMC review # 2 dated 07/15/2011. Since the updated analytical method validation is adequate, the proposed drug product shelf life of 18 months at 3 to 8 ºC (refrigerated storage conditions) is found acceptable.

There were no other deficiencies identified for this NDA (see CDTL memo dated 28-Dec-2010 and updated CDTL memo dated 27-July-20011). 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
08/03/2011

SARAH P MIKSINSKI
08/03/2011

Cross-Discipline Team Leader Review

Date	28-DEC-2010
From	Sarah Pope Miksinski, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	200795
Applicant	Hospira, Inc.
Date of Submission	11-DEC-2009 03-AUG-2010 (major amendment – clock extended) 05-AUG-2010 (major amendment – clock extended)
PDUFA Goal Date	11-JAN-2011 (based on extension)
Proprietary Name / Established (USAN) names	Gemcitabine Injection
Dosage forms / Strength	38 mg/mL
Proposed Indication(s)	Proposed indications of ovarian cancer (in combination with carboplatin), breast cancer (in combination with paclitaxel), non-small cell lung cancer (in combination with cisplatin), and pancreatic cancer (single agent)
Recommended:	**Complete Response**

1. Introduction

NDA 200795 was filed by the Agency on 17-FEB-2010. The Agency granted a standard review with an initial PDUFA goal date of 11-OCT-2010. There were no comments conveyed in the 74-day letter. Based on two major Chemistry, Manufacturing and Controls (CMC) amendments received on 04-AUG-2010 and 06-AUG-2010, the review clock was extended three months to 11-JAN-2011.

This CDTL memo serves to highlight the critical approvability issues discussed in all review disciplines and recommends a "Complete Response" action for this application. All individual discipline reviews may be found in DARRTS. Final container/carton and Package Insert (PI) labeling is still pending due to the recommended "Complete Response" action. Any updated container/carton and/or PI labeling will need to be reviewed by all disciplines during subsequent review cycles.

2. Background

The Reference Listed Drug for this submission is Gemzar® (gemcitabine hydrochloride) for Injection (NDA 20-509), which is currently marketed by Lilly. The proposed drug product is a ready to use, sterile and concentrated aqueous injectable solution intended for dilution and subsequent intravenous injection. It is supplied at a concentration of 38

mg/mL gemcitabine (free base), and each of the proposed dosage units contains a total drug content of 200 mg, 1 g, and 2 g contained in sterile, single-use glass vials.

The inactive ingredients in the proposed product are qualitatively and quantitatively the same as the inactive ingredients contained in the RLD, with the exception of the removal of mannitol, sodium acetate, and sodium chloride relative to the RLD. Mannitol functions (b) (4) in the lyophilized RLD; therefore, it is not required for the proposed drug product in the solution form. Sodium acetate (b) (4) was not included in this proposed formulation. Similarly, the Applicant determined that sodium chloride was not required for this proposed formulation. These formulation details are further discussed in the 15-DEC-2010 Chemistry Review.

Dosing Regimen and Administration
The recommended dose of Gemcitabine Injection is as follows:

- Ovarian Cancer: 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle
- Breast Cancer: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle
- Pancreatic Cancer: 1000 mg/m^2 over 30 minutes once weekly for up to 7 weeks
- Non-Small Cell Lung Cancer: 4-week schedule - 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle; 3-week schedule - 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle

3. CMC

NDA 200795 was initially submitted on 11-DEC-2009 as a 505(b)(2) application. The NDA included a full dossier of CMC information, along with proposed container/carton and PI labeling. Chemistry Review #1 (15-DEC-2010) identifies one major unresolved CMC deficiency.

- General product quality considerations
  The major product quality issue is related to the inadequacy of the Applicant's proposed chromatographic methodology. As described in the 15-DEC-2010 Chemistry Review, the proposed method for the detection and monitoring of related substances (Method Number 6.320) was not appropriately validated during the Applicant's development program. This lack of adequate validation was identified early in the review cycle and was communicated and discussed with the Applicant on numerous occasions. Ultimately, the Applicant was unable to provide sufficient and acceptable supporting evidence for the method validation, which calls into question all submitted batch data generated using Method Number 6.320.

  The inadequacy of the proposed analytical method renders it impossible to determine acceptability of several key components in the CMC dossier including: drug product specifications, expiration dating period, and overall method validation. Additionally, the inadequate validation of Method Number 6.320 calls all data generated using that method into question (e.g. preclinical data, batch data in Module 3). The CMC team

cannot recommend approval due to the impact of this outstanding deficiency on several key quality areas of the NDA.

NDA 200795 included a request for a biowaiver. This request was evaluated in a 02-FEB-2010 review (Dr. T. Ghosh) which grants the Applicant's request.

The Applicant's original submission included a full primary stability data package. This data were fully assessed in the 15-DEC-2010 Chemistry Review. However, due to the intended "CR" action, an expiration dating period will not be specified in the action letter, and updated stability data should be reassessed for adequacy, as needed, in future review cycles. This is particularly important for any stability data that are updated due to revised chromatographic methodology (e.g., Method Number 6.320).

- Facilities review/inspection
  An Establishment Evaluation Request (EER) was submitted to the Office of Compliance, and an overall withhold recommendation was issued for the application on 06-DEC-2010.

- Microbiology
  Gemcitabine Injection is an (b) (4) product. The microbiology reviewer (Dr. S. Langille) recommends approval of this NDA in his review dated 14-SEP-2010. In a follow up memorandum dated 02-DEC-2010, the reviewer issued a labeling deficiency related to the proposed post-dilution storage time, which should be included in the action letter.

- Other notable issues (resolved or outstanding)
  None

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical pharmacology/toxicology studies provided in this submission. The final Pharmacology/Toxicology memo was finalized in DARRTS on 08-DEC-2010 and captures one outstanding Pharmacology/Toxicology issue for the NDA. The stated deficiency concerns the inability to link or confirm preclinical batch data generated using Method Number 6.320 (see above Chemistry deficiency above), which creates a gap in the Pharmacology/Toxicology team's confirmation of proposed impurity specifications and qualification. The Pharmacology/Toxicology deficiency should be issued in the action letter. Final language for the deficiency is located in Dr. L. Verbois' memorandum dated 08-DEC-2010.

5. Clinical Pharmacology

There were no clinical pharmacology data submitted to this NDA. The clinical pharmacology reviewer (Dr. S. Shord) recommends approval of this NDA in her review dated 03-MAY-2010. This review also captures recommended revisions to the PI.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

There are no new clinical data provided in the current submission. Accordingly, there was no clinical review of this submission.

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Due to pediatric exclusivity issues, the Agency's Pediatric and Maternal Health Staff (PMHS) was consulted to confirm the acceptability of the pertinent labeling sections. In a 17-NOV-2010 review, Jeanine Best, MSN, RN, PNP, confirms that the team's proposal to remove information protected by pediatric exclusivity in the Gemzar label is acceptable. The review also captures the acceptability of including a single statement regarding pediatric studies (The safety and effectiveness of Gemzar in pediatric patients has not been established.") in this 505b2 label.

The current overall recommendation for this action is a "Complete Response", and final labeling was not negotiated with the Applicant during this review cycle. Therefore, all proposed labeling will need to be re-confirmed for acceptability during subsequent review cycles. This includes the preceding discussion of pediatric exclusivity issues and the resulting impact on this 505b2 labeling.

11. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): This was not raised during the pre-approval inspections for this NDA.

- Exclusivity or patent issues of concern: No issues were noted for this NDA due to the recommended CR action. Note the preceding discussion on pediatric exclusivity issues, outlined in Section 10.
- Financial disclosures: Not applicable
- Other GCP issues: None
- DSI audits: Not applicable
- Other discipline consults: None
- Any other outstanding regulatory issues: None, other than discipline-specific deficiencies as stated above.

12. Labeling

General:
All disciplines participated in internal labeling meetings held throughout the review clock. Specific labeling recommendations are captured in each discipline-specific review.

Proprietary name:
There was no proprietary name proposed for this product.

DMEPA comments:
In an initial review dated 17-SEP-2010, the DMEPA reviewer (Y. Maslov) identified several specific deficiencies in the proposed container/carton labeling. These deficiencies were not conveyed to the firm due to the anticipated CR action. Consequently, proposed container/carton labeling will need to be re-evaluated by DMEPA (and ONDQA) in subsequent review cycles.

Issues not resolved at the time of CDTL memo completion:
There is one CMC deficiency, one Pharmacology/Toxicology deficiency, and an unacceptable recommendation from the Office of Compliance. These aspects are described in detail in the pertinent reviews and are summarized in the appropriate preceding sections of this summary. There is one microbiological labeling deficiency; while final labeling was not negotiated during this review cycle, this deficiency should be inserted into the action letter as a proactive alert to the Applicant, as its resolution may require the initiation and completion of additional microbiology studies.

All container/carton and PI labeling will need to be re-evaluated for acceptability by all disciplines during any subsequent review cycle.

Patient labeling/Medication guide:
This is not required for this product.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  This reviewer does not recommend approval of this NDA. 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.

- Risk Benefit Assessment
  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 Management Activities
  This does not apply to this NDA.

- Recommendation for other Postmarketing Study Commitments
  None

- Recommended Comments to Applicant
  The standard language for conveying an unacceptable Compliance recommendation should be inserted into the action letter. Appropriate language, as located in each discipline's reviews, should be incorporated into the action letter for the respective CMC, Microbiology, and Pharmacology/Toxicology deficiencies.

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/s/

SARAH P MIKSINSKI
12/28/2010