

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200795Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

| Application Information | | |
|--|----------------------|----------------------------------|
| NDA # 200795 | NDA Supplement #: S- | Efficacy Supplement Type SE- |
| Proprietary Name: Established/Proper Name: Gemcitabine Dosage Form: Injectable Strengths: 200 mg/5.3 mL, 1g/26.3 mL, 2g/52.6 mL | | |
| Applicant: Hospira, Inc. | | |
| Date of Receipt: June 10, 2011 | | |
| PDUFA Goal Date: August 10, 2011 | | Action Goal Date (if different): |
| Proposed Indication(s): First line treatment of metastatic breast cancer, inoperable, locally advanced or metastatic NSCLC, and locally advanced or metastatic adenocarcinoma of the pancreas. | | |

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

| Source of information* (e.g., published literature, name of referenced product) | Information provided (e.g., pharmacokinetic data, or specific sections of labeling) |
|---|---|
| Gemzar® (Gemcitabine Hydrochloride Injection) | Clinical |
| Gemzar® (Gemcitabine Hydrochloride Injection) | Clinical Pharmacology |
| | |

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

No clinical or bioequivalence studies were conducted by the Applicant to bridge their product with the reference listed product. However, the conditions of use (indication) and route of administration for the subject drug, Gemcitabine Injection, are the same as prescribed and recommended for the use of the drug. The proposed drug product contains the same active ingredient and inactive ingredient as the RLD. The proposed drug product is in the same dosage form containing the same active ingredient at the same concentration as the RLD, Gemzar®, after reconstitution. Excipients are the same as those used in the RLD except for mannitol and sodium acetate. Exclusion of the (b) (4) mannitol and the (b) (4) sodium acetate, will not have impact on bioavailability of gemcitabine from the sponsor’s proposed solution as compared to the reference formulation. Therefore, the sponsor’s request for a waiver for the CFR’s requirement to provide in vivo bioavailability/bioequivalence (BA/BE) data was granted for the proposed Gemcitabine Injection 38 mg/ml product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

| Name of Drug | NDA/ANDA # | Did applicant specify reliance on the product? (Y/N) |
|---|------------|--|
| Gemzar® (Gemcitabine Hydrochloride Injection) | NDA 020509 | Yes |

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

- Hospira, Inc.'s Gemcitabine Injection is a ready-to-use aqueous solution, where as, the RLD is lyophilized.
- The qualitative/quantitative composition of Hospira, Inc.'s Gemcitabine Injection is different from the innovator. Hospira removed inactive ingredients mannitol and sodium acetate from the RLD.
- Hospira, Inc. is registering an additional presentation (2 g/52.6 mL) that the innovator does not have.
- The labeling for Hospira, Inc.'s Gemcitabine Injection differs from that of Gemzar®, as a result of the items listed above.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary,

that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

| Application # | Product # | Patent # | Patent Expiration |
|---------------|-----------|-------------|-------------------|
| N 020509 | 001 | 4808614*PED | November 15, 2010 |
| N 020509 | 001 | 5464826 | November 7, 2012 |
| N 020509 | 001 | 5464826*PED | May 7, 2013 |

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): 4808614*PED Nov 15, 2010

(On 12/6/10 Hospira amended their application to reflect the above information)

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 4808614*PED, 5464826, 5464826*PED

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): February 16 & 18, 2010

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

Comment: The patent infringement suit regarding the 5464826 patent was terminated by the US District Court for the Southern District of Indiana effective 12/3/10.

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

/s/

AMY R TILLEY
08/04/2011

Internal Consult

****Pre-decisional Agency Information****

To: Amy Tilley, RPM, Division of Drug Oncology Products, (DDOP)

From: Marybeth Toscano, Regulatory Reviewer Officer
Richard Lyght, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Karen Rulli, Professional Review Group II Leader, DDMAC
Amy Toscano, DTC Review Group IV Leader, DDMAC

Date: July 22, 2011

Re: Comments on draft labeling (Package Insert) for
Gemcitabine Injection, NDA 200795

In response to your consult request dated June 29, 2011, we have reviewed the draft version of the Package Insert for Gemcitabine Injection. DDMAC has no comments on the draft version of 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/

MARYBETH TOSCANO
07/22/2011

RICHARD A LYGHT
07/22/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Date: July 13, 2011
Application Type/Number: NDA 200795
To: Robert Justice, MD, Director
Division of Drug Oncology Products
Through: Zachary Oleszczuk, Pharm.D., Team Leader
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis
From: Yelena Maslov, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name(s): Gemcitabine Injection (38 mg/mL)
200 mg/5.26 mL; 1 g/26.3 mL; and 2 g/52.6 mL
Applicant/sponsor: Hospira
OSE RCM #: 2011-2248

1 INTRODUCTION

This review evaluates the container labels, carton and prescribing information labeling for Gemcitabine Injection submitted in response to the Agency's Complete Response, dated January 11, 2011, issued for product quality issues, microbiology issues, and facility inspections issues.

1.1 REGULATORY HISTORY

Gemcitabine Injection (NDA 200795) is the subject of a 505(b)(2) application that references Gemzar for Injection. The original Application was submitted by Hospira on December 11, 2009. At that time, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database and evaluated the container labels, carton and prescribing information labeling in OSE Review #2010-479, dated September 24, 2010. We determined the cases were not relevant to the proposed labels and labeling (See OSE Review #2010-479 for full description). At that time, we provided recommendations to improve the container labels and carton labeling.

The labeling comments for the proposed labels and labeling were deferred until the next review cycle. The Application was re-submitted to the FDA on June 10, 2011.

2 MATERIALS REVIEWED

The container labels, carton, and prescribing information labeling submitted to the FDA on June 10, 2011 (See Appendix A) were evaluated and the recommendations were compared to our recommendations made in and OSE Review #2010-479, dated September 24, 2010.

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the container label, carton and prescribing information labeling identified several deficiencies that can be improved upon to minimize the potential for medication errors. Additionally, we note that all three strengths of the Gemcitabine Injection (i.e., 200 mg/5.26 mL, 1g/26.3 mL, and 2 g/52.6 mL) employ (b) (4) which increases the similarity among different strengths and may lead to selection errors.

Since the Applicant did not receive DMEPA's comments regarding the container labels and labeling outlined in OSE Review #2010-479 during the previous review cycle, our recommendations relating to container label and carton labeling remain the same and are repeated in Section 3.2. However, because the package insert labeling was revised by the Applicant, we provide additional labeling comments related to the prescribing information. Section 3.1, *Comments to the Division*, contain our recommendations for the prescribing information labeling. We request the recommendations in Section 3.1 and 3.2 be communicated to the Applicant prior to approval.

3.1 COMMENTS TO THE DIVISION

Package Insert Labeling

1. Section 2, *Dosage and Administration*

As a part of the campaign to reduce medication errors related to error-prone medical abbreviations, symbols, and dose designations, the FDA agreed not to approve labels and labeling that includes the use of error-prone abbreviations, symbols, and dose designations. Thus, we recommend the following revisions be implemented in support of that campaign.

- Revise all instances of the symbols ‘<’, ‘≤’, and ‘≥’ to read “less than”, “less than or equal to”, “greater than or equal to” respectively. The symbols ‘<’, ‘≤’, and ‘≥’ are dangerous symbols that appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations¹ because these symbols are often mistaken and used as opposite of intended.
- Revise the abbreviation AGC to read absolute granulocyte count because the abbreviation ‘AGC’ can also mean advanced gastric cancer, atypical glandular cells, acute gallstone cholecystitis, etc.

2. Section 2.1, *Ovarian Cancer*

The phrase “AUC 4” in the sentence “Carboplatin AUC 4 should be administered intravenously on Day 1 after Gemcitabine Injection administration” is unclear and confusing. It is unclear if this is an unintentional error or if this statement is intended to be there. We recommend deleting this phrase from the sentence or revising this phrase to be more clear.

3. *Highlights of Prescribing Information* and Section 2.3, *Non-Small Cell Lung Cancer*

Separate the 28 day schedule and 21 day schedule by using bullet points for each type of schedule. The information appears cluttered together which reduces the clarity and readability of the information; and thus, can be misinterpreted or overlooked.

4. Section 2.5, *Preparation and Administration Precautions*

Revise the sentence “The use of gloves is recommended” to read “Use gloves when handling Gemcitabine Injection”. The word “recommend” implies a suggestion rather than a necessity. Animal studies showed that rabbits developed drug-related systemic toxicities (death, hypoactivity, nasal discharge, shallow breathing) as a result of dermal absorption of the drug. Thus, it is important to emphasize that gloves should be worn while handling of Gemcitabine Injection.

¹ Institute for Safe Medication Practices, “List of Error-Prone Abbreviations, Symbols, and Dose Designations. www.ismp.org.

3.2 COMMENTS TO THE APPLICANT

A. Container Label and Carton Labeling (All Strengths)

1. All three strengths of the Gemcitabine Injection (200 mg/5.26 mL, 1 g/26.3 mL, and 2 g/52.6 mL) employ (b) (4) which increases their similarity to one another. This similarity can lead to product selection errors resulting in wrong strength or wrong dose errors. Although you revised the labeling to employ (b) (4) for the 200 mg/5.26 mL strength of Gemcitabine Injection and (b) (4) for the 2 g/52.6 mL strength of Gemcitabine Injection, this subtle difference (b) (4) is not sufficient to minimize the potential for selection errors. Use of a totally different color (b) (4) is recommended. Revise the labels and labeling to utilize different contrasting colors, boxing, or some other means to minimize the potential for selection errors among the three different product strengths (i.e., only one strength should (b) (4)).
2. Ensure the expiration date and the lot number are included on the labels and labeling in accordance with 21 CFR 201.17 and 21 CFR 201.100 (b)(6).

B. Container Labels (All strengths)

1. We note that the container labels (b) (4). Typically, container labels use one bar code. (b) (4)
2. Increase the prominence of the statements “Single Use Vial. Discard Unused Portion” by relocating this statement from the side panel to the principle display panel. In their current locations, these statements are not prominent on the container labels; and thus, may be overlooked and may lead to the reuse of the single use vial. Increased prominence may be achieved by decreasing the prominence of the storage statement by debolding and printing the information in a smaller font. Although it is important to differentiate the storage conditions from the reference listed drug product Gemzar, it is also important to emphasize the product is packaged in to a single use vial and that the unused portion needs to be discarded in order to prevent reuse of the same vials of Gemcitabine.

4 REFERENCES

1. Maslov, Yelena, OSE Review #2010-479, Gemcitabine Injection Label and Labeling Review; September 24, 2010.

4 Pages of Draft Labeling have 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/

YELENA L MASLOV
07/13/2011

ZACHARY A OLESZCZUK
07/13/2011

CAROL A HOLQUIST
07/14/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
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Food and Drug Administration
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Pediatric and Maternal Health Staff Review – Pediatric Team Review

Date: November 16, 2010 **Date Consulted:** October 8, 2010

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff

Through: Hari Cheryl Sachs, MD
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, M.D.
OND Associate Director, Pediatric and Maternal Health Staff

To: Division of Drug Oncology Products (DDOP)

Drug: Gemcitabine Injection, NDA 200-795

Subject: Pediatric Use Labeling

Materials Reviewed:

- Draft Gemcitabine Injection labeling, NDA 200-795
- Orange Book Patent and Exclusivity Information for Gemzar, NDA 20-509

Consult Question:

The purpose of this consult request is to ask for PMHS to assist with review of the pediatric language regarding negative studies in the proposed gemcitabine 505(b)(2) labeling for NDA 200795. DDOP proposes removal of information protected by pediatric exclusivity in the Gemzar label, which is not expected to affect safe use of the drug. DDOP recommends that for 505b2 drugs for Gemzar, only the sentence “The safety and effectiveness of Gemzar in pediatric patients has not been established” remain in the label at this time.

INTRODUCTION

Hospira, Inc. submitted a 505(b)(2) NDA (200-795) for Gemcitabine Injection on December 11, 2009. The Reference Listed Drug (RLD) is Gemzar (gemcitabine hydrochloride) Injection, Powder, Lyophilized, For Solution For Intravenous Use, (NDA 20-509, Eli Lilly & Company). The Division of Oncology Drug Products (DDOP) extended the review clock and the current PDUFA date is January 11, 2011. The proposed changes in the labeling for this 505(b)(2) product are limited to a change in the dosage form (a ready to use aqueous solution), removal of mannitol and sodium acetate as inactive ingredients, and the addition of a 2 g strength.

This new gemcitabine dosage form (a ready to use aqueous solution) triggered the Pediatric Research Equity Act (PREA). Hospira, Inc. submitted a full waiver for pediatric studies at the time of NDA submission and was subsequently granted the waiver by the Pediatric Review Committee (PeRC) on September 1, 2010, because the proposed indications do not exist in children. A description of pediatric studies conducted under a Pediatric Written Request (PWR) appear in the Pediatric Use subsection of RLD (Gemzar) labeling. The Gemzar pediatric use information is protected by Pediatric Exclusivity under the Best Pharmaceuticals for Children Act (BPCA) until May 17, 2013.

The Division of Drug Oncology Products (DDOP) consulted the Pediatric Team of the Pediatric and Maternal Health Staff (PMHS) on October 8, 2010, to determine whether protected pediatric use information that appears in Gemzar labeling can be carved-out of this 505(b)(2) gemcitabine labeling. DDOP believes a carve out of this information would not affect safe use of this product.

BACKGROUND

Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis.

Gemzar (gemcitabine) is currently approved in adult patients for use in the treatment 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 as a single-agent

Gemzar is not approved for use in pediatric cancer patients; however, pediatric studies were conducted and Gemzar labeling contains information regarding safety, dosing (including dose-limiting toxicity), and lack of effectiveness in pediatric patients with refractory leukemia. The pediatric use information was added to labeling as a result of studies performed under the Best Pharmaceuticals for Children Act (BPCA).

FDA issued a Pediatric Written Request for gemcitabine on October 5, 2001, reissued July 3, 2002, and amended November 13, 2003, and July 9, 2004, for the following studies in children with cancer:

- Phase 1: A dose-finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25.
- Phase 2 or pilot studies: Enrollment of at least 14 pediatric patients with refractory ALL or AML or relapsed tumor(s). Studies should be performed at facilities that have the experience, support, and expertise to care for children with cancer.

Eli Lilly & Company submitted a supplemental application (NDA 20-509/S-033) on October 26, 2004 (received October 27, 2004), containing the pediatric study data conducted in response to the PWR. Efficacy was not demonstrated for the pediatric cancers studied. The pediatric maximum tolerated dose was determined and the toxicities observed were similar to those observed in adult patients. No unexpected safety concerns were observed.

Gemzar, NDA 20-509/S-033, was approved on April 26, 2005, and the labeling was revised to include the pediatric study data conducted in response to the PWR. Six months of Pediatric Exclusivity under BPCA (expires November 17, 2013) were granted to Eli Lilly & Company for Gemzar for fairly meeting the terms of the PWR.

Best Pharmaceuticals for Children Act of 2007

The goal of both the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) is to provide pediatric information in drug labeling to encourage the appropriate use of drugs in treating pediatric patients. BPCA [section 505A(o)(2)(A) and 505A(o)(2)(B) the Act] addresses the approval of generic drugs when pediatric information protected by exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] has been added to the innovator labeling so that when possible, innovator pediatric labeling will not block generics from entering the market. In summary, 1) when new pediatric information in labeling is protected by patent or exclusivity [either six-month pediatric exclusivity (BPCA) or three-year new clinical studies exclusivity (Waxman-Hatch)] and “carved out,” a disclaimer is necessary; and, 2) important pediatric safety information, particularly if related to Contraindications, Warnings and Precautions, or Use in Specific Populations (Pediatric Use) may be retained.

BPCA does not address the carve-out of protected pediatric information from 505(b)(2) product labeling; however, approval of a 505(b)(2) application may be delayed because of patent and exclusivity rights that apply to the listed drug (see 21 CFR 314.50(i), 314.107, 314.108, and section 505(A)(b)(B)(ii) of the Act.¹

¹ See Draft Guidance for Industry – Applications Covered by Section 505(b)(2), October 1999

PEDIATRIC USE LABELING

Sponsor's Proposed Pediatric Use 505(b)(2) Gemcitabine Injection labeling (April, 2010)

(b) (4)

Current Approved Pediatric Use Gemzar labeling (March 19, 2010)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Gemzar in pediatric patients has not been established. Gemzar was evaluated in a Phase 1 trial in pediatric patients with refractory leukemia and determined that the maximum tolerated dose was 10 mg/m²/min for 360 minutes three times weekly followed by a one-week rest period. Gemzar was also evaluated in a Phase 2 trial in patients with relapsed acute lymphoblastic leukemia (22 patients) and acute myelogenous leukemia (10 patients) using 10 mg/m²/min for 360 minutes three times weekly followed by a one-week rest period. Toxicities observed included bone marrow suppression, febrile neutropenia, elevation of serum transaminases, nausea, and rash/desquamation, which were similar to those reported in adults. No meaningful clinical activity was observed in this Phase 2 trial.

DDOP Proposal for Pediatric Use 505(b)(2) Gemcitabine Injection Labeling

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of gemcitabine in pediatric patients has not been established.

DISCUSSION AND CONCLUSIONS

BPCA allows for the retention of protected pediatric use information in generic labeling if the information describes important pediatric safety information, particularly if it related to Contraindications, Warnings and Precautions, or Use in Specific Populations (Pediatric Use). In this manner, when possible, pediatric labeling will not block generics from entering the market. However, when protected pediatric use information can be safely carved-out of generic labeling because the carve-out does not impact the safe use of the drug in pediatric

patients, a disclaimer for the carved-out information is required under BPCA. The disclaimer states that due to an innovator's marketing exclusivity, the pediatric use information does not appear in the generic labeling. The Office of Chief Counsel (OCC) must approve the language of disclaimers used when protected pediatric information is carved-out of generic labeling.

BPCA does not address the carve-out or retention of protected pediatric information from 505(b)(2) products, nor does BPCA address the use of disclaimers for protected pediatric use information that is carved-out of 505(b)(2) product labeling. If FDA determines that the protected pediatric information is important safety information; and therefore, must be retained in 505(b)(2) product labeling for reasons of safe use, then a full approval for the affected 505(b)(2) product cannot be issued until Pediatric Exclusivity has expired.

In the case of gemcitabine, pediatric use information was added to Gemzar (NDA 20-509/S-033) labeling on April 26, 2005 and six months of Pediatric Exclusivity was granted to Eli Lilly & Company for Gemzar for fairly meeting the terms of the PWR. Pediatric Exclusivity expires on November 17, 2013; therefore, the pediatric use information in Gemzar labeling is protected until the Pediatric Exclusivity expires. Although efficacy was not demonstrated with gemcitabine in pediatric cancer patients in studies conducted under the PWR; information was added to labeling regarding the maximum tolerated dose as well as lack of meaningful clinical activity. However, no unexpected safety concerns were seen and toxicities observed were similar to those observed in the adult population with this cytotoxic chemotherapeutic drug.

The Division of Drug Oncology Products (DDOP) recommends the carve-out of protected pediatric information from this 505(b)(2) gemcitabine labeling because the DDOP opinion is that the carve-out of this information is not expected to affect the safe use of the product, given that most children in the U.S. with cancer are treated on Children's Oncology Group (COG) treatment protocols. While this assumption is likely, the Sponsor has not submitted data to support the opinion that pediatric patients are treated outside of COG protocols. Gemcitabine has toxicities that were seen in pediatric clinical trials that were the same as the toxicities seen in adult clinical trials. Those toxicities are monitored routinely in patients receiving chemotherapy, and are not unique to gemcitabine or use of gemcitabine in the pediatric population. Because gemcitabine is not labeled for use in the pediatric population and there is nothing unique that would create a safety concern for pediatric patients administered this product off label through COG protocols, there does not appear to be potential for harm if the protected pediatric information is omitted from labeling.

Although not the situation with gemcitabine, when there is a pediatric safety concern conveyed in protected labeling, and where omitting the information may lead to harm, PMHS believes that the FDA has the authority to require that the information remain in labeling, and thus approval of a 505(b)(2) product must wait for expiration of the protections to be approved.

The Agency has been implementing pediatric legislation for over 10 years. This legislation was passed because of the lack of pediatric data in labeling. The legislation provides for a carve-out of protected information in generic products' labeling, when removing this

information will not affect the safe use of a product, because generic drugs are generally more affordable, and allowing a carve-out serves a public health need. 505(b)(2) products do not serve a public health need, and are often not any cheaper than the innovator. With the approval of 505(b)(2) gemcitabine products, only the innovator gemcitabine product will include pediatric data in labeling (data which was made available at a cost to the U.S. government and thus taxpayers, based on exclusivity granted). Despite the fact that PMHS believes this approach is not consistent with the intent of BPCA, the legislation does not provide the FDA with the authority to carve-out language and add a disclaimer for applications other than 505(j)s. Therefore, a 505(b)(2) product can simply omit protected pediatric information and not contain a disclaimer.

RECOMMENDATIONS

PMHS would prefer 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, DDOP can decide to omit the protected pediatric information and approve this 505(b)(2) gemcitabine application. The following pediatric use statement proposed by DDOP, while not optimum, is accurate for this 505(b)(2) gemcitabine product labeling:

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of gemcitabine in pediatric patients have not been established.

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/s/

JEANINE A BEST
11/16/2010

HARI C SACHS
11/16/2010

LISA L MATHIS
11/17/2010

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 17, 2010
Application Type/Number: NDA 200795
To: Robert Justice, MD, Director
Division of Drug Oncology Products
Through: Zachary Oleszczuk, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis
From: Yelena Maslov, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name(s): Gemcitabine Injection (38 mg/mL)
200 mg/5.26 mL; 1 g/26.3 mL; and 2 g/52.6 mL
Applicant/sponsor: Hospira
OSE RCM #: 2010-479

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1 BACKGROUND

1.1 INTRODUCTION

This review responds to a request from the Division of Drug Oncology Products dated March 2, 2010 for DMEPA evaluation of the container label, carton and package insert labeling for Hospira Inc.'s Gemcitabine Injection for the potential to contribute to medication errors. There is no proposed proprietary name for this product at this time.

1.2 REGULATORY HISTORY

Gemcitabine Injection is the subject of a 505 (b)(2) application submitted on December 11, 2009 that references Gemzar. Gemzar for Injection was approved on May 15, 1996 under NDA 020509. The Applicant (Hospira) based the filing of this 505 (b)(2) application on the NDA 020509 for Gemzar manufactured by Eli Lilly.

DMEPA evaluated the container labels and carton labeling submitted to the FDA on December 11, 2009, and the package insert labeling submitted on April 19, 2010. We provided comments regarding labels and labeling to Hospira on June 15, 2010 (see Appendix B). Hospira revised Gemcitabine's labels and labeling to incorporate the recommendations provided by DMEPA and submitted the revised labels and labeling for the FDA to review on June 23, 2010. On August 20, 2010, Hospira submitted additional revisions of Gemcitabine's container labels and carton labeling that involved changing of the product's total drug content's presentation. These labels and labeling are the subject of this review.

1.3 PRODUCT INFORMATION

Gemcitabine is an antineoplastic agent used alone or in combination with other antineoplastic agents indicated for treatment of pancreatic cancer, non-small cell lung cancer, breast cancer, and ovarian cancer.

- Single-Agent Use:

First line treatment or treatment of patients previously treated with 5-FU for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) pancreatic cancer at a dose of 1000 mg/m² via intravenous infusion over 30 minutes once weekly for up to 7 weeks.

- Combination Use:

First line treatment in combination with cisplatin of patients with inoperable, locally advanced (b) (4) or metastatic (Stage IV) non-small cell lung cancer at a dose of 1000 mg/m² via intravenous infusion over 30 minutes on days 1,8, 15 of each 28 day cycle or 1250 mg/m² on days 1 and 8 of each 21 day cycle.

First line treatment in combination with paclitaxel of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant therapy at a dose of 1250 mg/m² via intravenous infusion over 30 minutes on days 1 and 8 of each 21-day cycle.

In combination with carboplatin, treatment of patients with advanced ovarian cancer at a dose 1000 mg/m² via intravenous infusion over 30 minutes on days 1 and 8 of each 21 day cycle.

Gemcitabine Injection will be supplied in the standard concentration of 38 mg/mL in bulk 10 mL, 30 mL, and 100 mL sized vials, containing 200 mg/5.26 mL, 1 g/26.3 mL, and 2 g/52.6 mL of product respectively.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Gemzar has been marketed since 1996; thus, DMEPA conducted a search of the FDA AERS database for medication errors involving the reference-listed product Gemzar. Identification of these errors may be indicative of potential issues with the proposed 505 (b)(2) application for Gemcitabine Injection.

A search was conducted on March 18, 2010 using the MedDRA high level group term (HLGT) “Medication Error” and the preferred term (PT) “Product Quality Issues” along with active ingredient names of Gemcitabine, the trade name Gemzar, and the verbatim names “Gemzar%,” and “Gemcitabi%”. Since Gemzar was approved in 1996, we limited the search dates from 1996 to 2010.

2.2 LABELS AND LABELING RISK ASSESSMENT

We use Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling; thereafter, we provide recommendations that aim at reducing the risk of medication errors.

For Gemcitabine Injection, the Applicant submitted the following container labels and carton labeling on December 11, 2009 and insert labeling on April 19, 2010. The Applicant submitted revised container labels as well as carton and package insert labeling on June 23, 2010. On August 20, 2010, the Applicant submitted additional revisions of the container labels and carton labeling (See Appendices A and C for container labels and carton labeling images):

- Container Label and Carton Labeling: 200 mg/5.26 mL Single Use Vial (38 mg/mL)
- Container Label and Carton Labeling: 1 g/26.3 mL Single Use Vial (38 mg/mL)
- Container Label and Carton Labeling: 2 g/ 52.6 mL Single Use Vial (38 mg/mL)

3 RESULTS

3.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

DMEPA’s search of the Adverse Event Reporting System database retrieved two hundred and fifteen (n=215) reports. After eliminating reports not relevant to medication errors (adverse events related to the use of the drug and progression of the disease) and grouping duplicate reports into cases, eight medication error cases (n=8) remained.

Five (n=5) of the eight cases (n=8) were foreign. One case (n=1) from Mexico involved an overdose of Gemzar, three cases (n=3) from Ukraine involved the wrong route of administration of Gemzar by the intra-arterial (n=2) and oral (n=1) routes, and one case (n=1) from Belgium involved the administration of Gemzar to the wrong patient.

Three (n=3) of the eight cases were from the United States. Two (n=2) of the three cases related to the wrong administration technique, in which Gemzar was infused over 90 minutes instead of labeled 30 minutes. Both patients experienced vasculitis. The package insert provides clear instructions for use; thus, from a labeling perspective, there is not much improvement that can be made to the insert.

The third US case (n=1) related to the established name confusion between Mylotarg (Gemtuzumab) and Gemzar (Gemcitabine). The medication order was written for Gemtuzumab, but the wrong drug was selected (Gemcitabine) in a pharmacy computer system. The error was intercepted by the nurse and did not reach the patient.

4 RECOMMENDATIONS

Most of our previous concerns and recommendations regarding the proposed labels and labeling of Gemcitabine, communicated to the Applicant on June 15, 2010 (See Appendix C), were addressed by the Applicant.

However, our 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. Section 4.1 *Comments to the Applicant* contains our recommendations for the carton labeling and container labels. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval (See Appendices A and B for the revised container labels and carton labeling).

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Sarah Simon at 301-796-5205.

4.1 COMMENTS TO THE APPLICANT

A. All Carton Labeling and Container Labels

1. All three strengths of the Gemcitabine Injection (200 mg/5.26 mL, 1 g/26.3 mL, and 2 g/52.6 mL) employ (b)(4) increasing their similarity, which can lead to selection errors. Although you revised the labeling to employ (b)(4) for Gemcitabine Injection 200 mg/5.26 mL to differentiate from (b)(4) employed for Gemcitabine Injection 2 g/52.6 mL, this differentiation (b)(4) is not sufficient to minimize the potential for selection errors. Use of a totally different color (b)(4) is recommended. Revise the labels and labeling to utilize different contrasting colors to minimize the potential for selection errors among the three different product strengths (b)(4)
2. Add the expiration date and the lot number to the side panel in accordance with 21 CFR 201.17 and 21 CFR 201.100 (b)(6)

B. Container Labels

1. (b)(4)
Typically, container labels use one bar code. (b)(4)
2. Increase the prominence of the statements “Single Use Vial. Discard Unused Portion” by relocating this statement from the side panel to the principle display panel. As currently presented, these statements are not prominent on the container labels; and thus, may be overlooked and may lead to the reuse of the single use vial. Increased prominence may be achieved by decreasing the prominence of the storage statement by debolding and printing the information in a smaller font. Although it is important to differentiate the storage conditions from the reference listed drug product Gemzar, it is also important to emphasize the product is packaged in to a single use vial and that the unused portion needs to be discarded in order to prevent reuse of the same vials of Gemcitabine.

12 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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Appendix C: PREVIOUS RECOMMENDATIONS COMMUNICATED TO THE APPLICANT ON JUNE 15, 2010

Our evaluation of the proposed container labels as well as carton and package insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. Section 4.1 *Comments to the Division* contains our recommendations regarding package insert labeling. Section 4.2 *Comments to the Applicant* contains our recommendations for the container labels and the carton labeling. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval..

COMMENTS TO THE DIVISION COMMUNICATED TO THE APPLICANT ON JUNE 15, 2010

We have evaluated the insert labeling for Gemcitabine Injection. As a result, we have the following recommendations for the revision of the insert labeling. We note that these recommendations were discussed in the May 25, 2010 label and labeling meeting with the ONDQA and OCPB reviewers.

1. Clarify the manufacturing, marketing, and distribution of this product in accordance with 201.1(h)(5). The current statement (b)(4) is confusing and does not clearly identify the manufacturer, etc.
2. In the Highlights of Prescribing Information, Dosage Form and Strength Section, Delete the phrase (b)(4) (b)(4) Replace the phrase (b)(4) with the dosage form 'injection' (e.g., 200 mg/5.26 mL injection vial).
3. In the Full Prescribing Information, Section 2 Dosage and Administration Section
 - a. See comment one above which also applies to Section 2.1 Ovarian Cancer.
 - b. In Section 2.5 Preparation and Administration Precautions revise the sentence (b)(4) (b)(4) to read "Caution should be exercised in handling and preparing Gemcitabine Injection *and its diluted* solution. If Gemcitabine Injection *or its diluted* solution..." Please note changes in italics are for identification only.
 - c. In Section 2.6 Preparation for Intravenous Infusion Administration
 - i. Revise the statement (b)(4) to state "Each vial contains..."
 - ii. revise the last sentence in the first paragraph to read "The appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.
 - iii. Delete the statements, (b)(4) (b)(4)
4. In the Full Prescribing Information, Section 3 Dosage Forms and Strengths

Add the concentration in milligrams per milliliter (38 mg/mL) to the product and its dosage form to state "Gemcitabine Injection 38 mg/mL..." in the first sentence.
5. Full Prescribing Information, Section 8.1 and Section 11

Delete the word (b)(4) from the statement (b)(4) in the first sentence of the first paragraph in Section 8.1 and Section 11. (b)(4)

(b) (4) the drug substance itself-
Gemcitabine can cause adverse events.

6. Full prescribing Information, Section 16.1 How Supplied

Delete the (b) (4)
misleading (b) (4) These statements are confusing and (b) (4)

COMMENTS TO THE APPLICANT COMMUNICATED TO THE APPLICANT ON JUNE 15, 2010

We have evaluated the container labels and carton labeling for Gemcitabine Injection. The evaluation of these container labels and carton labeling resulted in the identification of several areas of needed improvement. Please revise labels and labeling as follows.

A. All Labels and Labeling (200 mg/5.26 mL, 1 g/26.3 mL, 2 g/52.6 mL)

1. All three strengths of the Gemcitabine Injection (200 mg/5.26 mL, 1 g/26.3 mL, and 2 g/52.6 mL) employ (b) (4) increasing their similarity, which can lead to selection errors. Revise the labels and labeling to utilize (b) (4) to minimize the potential for selection errors among the three different product strengths.
2. Present information on the labels and labeling in a manner to foster clarity and comprehension. Furthermore, linking relevant phrases to one another helps to ensure that important steps conveyed on the labels and labeling are not omitted due to fragmentation of those steps. Accordingly, please revise the information on the label and labeling as follows.
 - a. (b) (4) Revise the presentation so that the total drug content statement appears on a solid one color background which clearly displays '200 mg/5.26 mL or xx g/mL.'
 - b. Delete the term (b) (4) from the labels and labeling (e.g., on principal display panel beneath the concentration statement) when used in conjunction with the dosage form. The correct dosage form for this product is injection.
 - a. Place the statement "Discard Unused Portion" immediately after or on the same line as the statement "Single Use Vial."
 - b. Delete the term (b) (4) from the container label and carton labeling. This term is unnecessary and occupies space.
 - c. Decrease the prominence of the "Rx only" statement. As currently presented, it is more prominent than the concentration statement. Additionally relocate the Rx only statement to a less prominent location on the principle display panel such as the upper right corner (b) (4) or lower right or left corner.
 - d. The labels and labeling have references to both Gemcitabine and Gemcitabine Hydrochloride USP. We recommend using consistent terminology when referring to the active ingredient.

3. Because the referenced listed drug, Gemzar is a different dosage form with different storage recommendations, ensure that the information on proper storage for this product is prominent. Increase the prominence of the statement “Store at 2⁰ to 8⁰ C (36⁰ to 46⁰ F) by relocating it to the principal display panel below the route of administration statement. Do not use the red font for the storage requirements, since red font should only be used to emphasize critical statements such as “Caution: Cytotoxic Agent.”
4. Delete [REDACTED] (b) (4)
5. Prominence can be achieved by printing the statement in bold letters, and/or using a bigger font if space permits.

B. Container Labels (200 mg/5.26 mL, 1 g/26.3 mL, 2 g/52.6 mL)

1. [REDACTED] (b) (4)
replace with the statement “For Dosing and Administration: See package insert.” [REDACTED] (b) (4)
2. Delete [REDACTED] (b) (4)

C. Carton Labeling (200 mg/5.26 mL, 1 g/26.3 mL, 2 g/52.6 mL)

1. [REDACTED] (b) (4)
2. [REDACTED] (b) (4)
3. Delete the statements from the side panel [REDACTED] (b) (4) and replace with the statement “For Dosing and Administration: See package insert.” [REDACTED] (b) (4)
4. [REDACTED] (b) (4)

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/s/

YELENA L MASLOV
09/21/2010

ZACHARY A OLESZCZUK
09/21/2010

DENISE P TOYER
09/22/2010

CAROL A HOLQUIST
09/24/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 1, 2010

To: Robert Justice, M.D., Division Director
Division of Drug Oncology Products (DDOP)

Through: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: Memo to File re: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Gemcitabine Injection

Application Type/Number: NDA 200-795

Applicant/sponsor: Hospira, Inc

OSE RCM #: 2010-480

The Division of Drug Oncology Products (DDOP) requested that the Division of Risk Management (DRISK) review proposed patient labeling for a 505(b)(2) New Drug Application, NDA#200-795, submitted by Hospira Inc. on December 11, 2009 for Gemcitabine Injection.

DDOP informed DRISK that since the approved labeling for the Reference Listed Drug, NDA# 20-509 Gemzar (gemcitabine hydrochloride) Injection, does not have patient labeling, the 505(b)(2) product will not have patient labeling. As a result, there is no patient labeling for DRISK to review for this consult request. This memo serves to close-out this consult request for Gemcitabine Injection.

Please let us know if you have any questions.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|---------------------------------|
| NDA-200795 | ORIG-1 | HOSPIRA INC | GEMCITABINE INJECTION (38MG/ML) |

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/s/

LATONIA M FORD
06/03/2010

SHARON R MILLS
06/03/2010

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 200795 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Gemcitabine Injection
Established Name:
Strengths: 200 mg/5.3 mL, 1g/26.3 mL, 2g/52.6 mL

Applicant: Hospira, Inc.
Agent for Applicant (if applicable):

Date of Application: December 11, 2009
Date of Receipt: December 11, 2009
Date clock started after UN:
Date of Filing Meeting: February 2, 2010
Filing Date: February 9, 2010
Action Goal Date (optional): October 11, 2010 User Fee Goal Date:

Indication(s) requested: First line treatment of metastatic breast cancer, inoperable, locally advanced or metastatic NSCLC, and locally advanced or metastatic adenocarcinoma of the pancreas.

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, _____ Years NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as “To the best of my knowledge”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B) YES NO

- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

Electronic submissions are not required based on the “Guidance to Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications” June 2008 section II K: “FDA District offices have access to documents submitted in electronic format. Therefore, when sending submissions in electronic format, you need not provide any documentation to the FDA Office of Regulatory Affairs District Office.”

- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in DARRTS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to DARRTS for the supporting IND if it is not already entered.

- List referenced IND numbers: 106215

- Are the trade, established/proper, and applicant names correct in DARRTS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 10-30-09 (Prelim Comments sent) NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO

- If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
 - If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 2, 2010

NDA #: 200795

DRUG NAMES: Gemcitabine Injection

APPLICANT: Hospira, Inc.

BACKGROUND:

The basis for this submission is Eli Lilly and Co., NDA # 20-509 for Gemzar® (Gemcitabine Hydrochloride for Injection) 200 mg/vial and 1 g/vial Lyophilized, approved on May 15, 1996.

Reference is also made to (b) (4) the precursor 505(b)(2) application for the above mentioned drug product filed and withdrawn as a result of a Refuse to File (RTF) determination on May 1st, 2009. Reference is also made to IND 106215 and the Agency preliminary comments correspondence of October 30th, 2009.

Gemcitabine Injection is presented in three fill volumes with different packaging configurations as described below:

| (Total Product Content) | Fill Volume | Container Size | Dosage Form |
|---------------------------|-------------|----------------|-------------|
| 200 mg/5.26 mL (38 mg/mL) | 5.3 | (b) (4) | Injectable |
| 1 g/26.3 mL (38 mg/mL) | 26.3 | | |
| 2 g/mL (38 mg/mL) | 52.6 | | |

The conditions of use (indication) and route of administration for the subject drug, Gemcitabine Injection, are the same as prescribed and recommended the Reference Listed Drug (RLD). The proposed drug product contains the same active ingredient at the same concentration, as the RLD, Gemzar®, after reconstitution. Excipients are the same as those used in the RLD except for mannitol and sodium acetate. A high-level summary of the differences between Hospira, Inc.'s Gemcitabine Injection and the Reference Listed Drug, Gemzar®, is provided below:

- Hospira, Inc.'s Gemcitabine Injection is a ready-to-use aqueous solution, where as, the RLD is lyophilized
- The qualitative/quantitative composition of Hospira, Inc.'s Gemcitabine Injection is different from the innovator.

- Hospira, Inc. is registering an additional presentation (2 g/52.6 mL) that the innovator does not have.
- The labeling for Hospira, Inc.'s Gemcitabine Injection differs from that of Gemzar®, as a result of the items listed above.

Hospira, Inc. requests (b) (4) month expiration dating for all presentations of the subject drug product based on the accelerated and room temperature data.

ATTENDEES: Justice, Robert; Johnson, John R; Cohen, Martin H; Williams, Gene; Ocheltree, Terrance; Crich, Joyce; Verbois, Leigh; Dorsam, Robert; Tilley, Amy

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Reviewer

| | |
|---|----------------------|
| Medical: | Martin Cohen, M.D. |
| Secondary Medical: | John Johnson, M.D. |
| Statistical: | |
| Pharmacology: | Robert Dorsam, Ph.D. |
| Clinical Pharmacology: | Stacy Shord, PharmD. |
| Chemistry: | Joyce Crich, Ph.D. |
| Environmental Assessment (if needed): | |
| Biopharmaceutical: | Tapash Ghosh, Ph.D. |
| Microbiology, sterility: | Stephen Langille |
| Microbiology, clinical (for antimicrobial products only): | |
| DSI: | |
| OPS/OSE: | TBD |
| Regulatory Project Management: | Amy Tilley |
| Other Consults: | |
| DDMAC | TBD |

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO
If no, explain:

• Advisory Committee Meeting needed? YES, date if known _____ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

• Biopharm. study site audits(s) needed? YES NO

| | | | |
|---|------------------------------|--|---|
| PHARMACOLOGY/TOX | N/A <input type="checkbox"/> | FILE <input checked="" type="checkbox"/> | REFUSE TO FILE <input type="checkbox"/> |
| • GLP audit needed? | | YES <input type="checkbox"/> | NO <input checked="" type="checkbox"/> |
| CHEMISTRY | | FILE <input checked="" type="checkbox"/> | REFUSE TO FILE <input type="checkbox"/> |
| • Establishment(s) ready for inspection? | | YES <input checked="" type="checkbox"/> | NO <input type="checkbox"/> |
| • Sterile product? | | YES <input checked="" type="checkbox"/> | NO <input type="checkbox"/> |
| If yes, was microbiology consulted for validation of sterilization? | | YES <input checked="" type="checkbox"/> | NO <input type="checkbox"/> |

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into DARRTS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DARRTS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Amy Tilley
Regulatory Project Manager

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|------------------------------------|
| NDA-200795 | ORIG-1 | HOSPIRA INC | GEMCITABINE INJECTION (38MG/ML) |

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

/s/

AMY R TILLEY
02/02/2010

ALICE KACUBA
02/02/2010

505(b)(2) ASSESSMENT

| Application Information | | |
|--|----------------------|----------------------------------|
| NDA # 200795 | NDA Supplement #: S- | Efficacy Supplement Type SE- |
| Proprietary Name: Gemcitabine Injection Established/Proper Name: Dosage Form: Injectable Strengths: 200 mg/5.3 mL, 1g/26.3 mL, 2g/52.6 mL | | |
| Applicant: Hospira, Inc. | | |
| Date of Receipt: December 11, 2009 | | |
| PDUFA Goal Date: October 11, 2010 | | Action Goal Date (if different): |
| Proposed Indication(s): First line treatment of metastatic breast cancer, inoperable, locally advanced or metastatic NSCLC, and locally advanced or metastatic adenocarcinoma of the pancreas. | | |

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

| Source of information* (e.g., published literature, name of referenced product) | Information provided (e.g., pharmacokinetic data, or specific sections of labeling) |
|---|---|
| Gemzar® (Gemcitabine Hydrochloride Injection) | Clinical |
| Gemzar® (Gemcitabine Hydrochloride Injection) | Clinical Pharmacology |
| | |

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The conditions of use (indication) and route of administration for the subject drug, Gemcitabine Injection, are the same as prescribed and recommended for the use of the. The proposed drug product contains the same active ingredient and inactive ingredient as the RLD. The proposed drug product is in the same dosage form containing the same active ingredient at the same concentration as the RLD, Gemzar®, after reconstitution. Excipients are the same as those used in the RLD except for mannitol and sodium acetate. Mannitol is used in the freeze-dried RLD (b) (4) and therefore is not included in the solution dosage form. Sodium acetate is used in the RLD (b) (4) but was found not to be required in the proposed drug product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

| Name of Drug | NDA/ANDA # | Did applicant specify reliance on the product? (Y/N) |
|---|------------|--|
| Gemzar® (Gemcitabine Hydrochloride Injection) | NDA 020509 | Yes |
| | | |

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

- Hospira, Inc.'s Gemcitabine Injection is a ready-to-use aqueous solution, where as, the RLD is lyophilized.
- The qualitative/quantitative composition of Hospira, Inc.'s Gemcitabine Injection is different from the innovator. Hospira removed inactive ingredients mannitol and sodium acetate from the RLD.
- Hospira, Inc. is registering an additional presentation (2 g/52.6 mL) that the innovator does not have.
- The labeling for Hospira, Inc.'s Gemcitabine Injection differs from that of Gemzar®, as a result of the items listed above.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including*

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

*If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

| Application # | Product # | Patent # | Patent Expiration |
|---------------|-----------|-------------|-------------------|
| N 020509 | 002 | 4808614 | May 15, 2010 |
| N 020509 | 002 | 4808614*PED | November 15, 2010 |
| N 020509 | 002 | 5464826 | November 7, 2012 |
| N 020509 | 002 | 5464826*PED | May 7, 2013 |

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph

III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 4808614, 4808614*PED, 5464826, 5464826*PED

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|------------------------------------|
| NDA-200795 | ORIG-1 | HOSPIRA INC | GEMCITABINE INJECTION (38MG/ML) |

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

/s/

AMY R TILLEY
02/02/2010