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RESEARCH**

APPLICATION NUMBER:
200795Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA	200795
Submission Date:	10th June 2011
Brand Name:	Gemcitabine Hydrochloride Injection
Generic Name:	Gemcitabine Hydrochloride
Formulation:	38 mg/mL concentrate for injection
OCP Reviewer:	Elimika Pfuma, Pharm.D. / Ph.D.
OCP Team Leader:	Qi Liu, Ph.D.
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Hospira, Inc.
Submission Type	NDA 200795; Serial # 14; SDN # 16
Indication & Dosing Regimen:	For intravenous use as a 30 minute infusion in: <ul style="list-style-type: none">▪ Ovarian Cancer at 1000 mg/m² on Days 1 and 8 of each 21 day cycle▪ Breast Cancer at 1250 mg/m² on Days 1 and 8 of each 21 day cycle▪ Non-Small Cell Lung Cancer at 1000 mg/m² on Days 1, 8 and 15 of each 28 day cycle or 1250 mg/m² on Days 1 and 8 of each 21 day cycle▪ Pancreatic Cancer at 1000 mg/m² once weekly for up to 7 weeks, followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.
Dosage Form	Sterile solution for injection <ul style="list-style-type: none">▪ 200 mg/5.3 mL, 1000 mg/26.3 mL and 2000 mg/52.6 mL

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1 Executive Summary

The original submission (NDA 200,795/000; letter date: 12/11/09) for the current 505(b)(2) application of Gemcitabine Injection® 38 mg/mL was reviewed previously by the Office of Clinical Pharmacology. The original submission was found to be acceptable from a clinical pharmacology perspective. However, a complete response letter was issued on 11th January, 2011 with the deficiencies related to product quality, microbiology, nonclinical and facility inspection. This is a re-submission in response to the complete response letter. It has no new clinical pharmacology information. The purpose of the current review is to summarize the relevant clinical pharmacology labeling recommendations for this 505(b)(2) application.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 200-795/S-000. This application is acceptable from a clinical pharmacology perspective.

Phase IV commitments

None.

Labeling Recommendations

The only changes to the sections of the proposed Hospira label that contain relevant clinical pharmacology information are the change of the name Gemzar to Gemcitabine Injection. Only sections of the proposed drug product label for Gemcitabine Injection (Hospira, Inc) relevant to Clinical Pharmacology are listed below.

Signatures

Elimika Pfuma, Pharm.D./ Ph.D.

Reviewer

Division of Clinical Pharmacology 5

CC: DDOP: CSO – A Tilley; MTL – J Johnson; MO - M Cohen

DCP- Reviewer - E Pfuma

5: TL - Q Liu

DDD - B Booth

DD - A Rahman

Qi Liu, Ph.D.

Team Leader

Division of Clinical Pharmacology 5

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

ELIMIKA PFUMA
07/20/2011

QI LIU
07/21/2011

Clinical Pharmacology Review

NDA	200,795/000
Submission Date:	11 December 2009
Brand Name:	Gemcitabine injection
Generic Name:	Gemcitabine hydrochloride
Formulation:	38 mg/mL concentrate for injection
OCP Reviewer:	Stacy S. Shord, Pharm.D.
OCP Team Leader:	Qi Liu, Ph.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Drug Oncology Products
Applicant:	Hospira, Inc. (Mayne Pharma Limited)
Submission Type; Code:	NDA Original NDA; S-000
Dosing regimen:	1000 to 1250 mg/m ² IV infusion over 30 min weekly
Indications:	Advanced ovarian cancer in combination with carboplatin; Metastatic breast cancer; Locally advanced or metastatic non-small cell lung cancer in combination with cisplatin; and Locally advanced or metastatic pancreatic cancer

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1 EXECUTIVE SUMMARY

In accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Hospira, Inc. submitted an original New Drug Application (NDA 200-795/S-000) for Gemcitabine Injection® 38 mg/mL.

Based on the comparison to the listed drug (Gemzar® for Injection; Eli Lilly and Company, Inc.), Hospira is requesting a waiver of *in vivo* bioequivalence for Gemcitabine Injection® in accordance with 21 CFR 320.22(b). Clinical studies are not included in the current 505(b)2 application and the application relies on the Agency's finding of safety and effectiveness for the approved drug-Gemzar® for Injection (NDA 20-509), as the active ingredient, route of administration (i.v. infusion) and indications for the Hospira drug product are the same as the listed drug product.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 200-795/S-000. This application is acceptable from a clinical pharmacology perspective.

Phase IV commitments

None.

Labeling Recommendations

Sections 5 (Warnings and Precautions), 7 (Drug Interactions), 8 (Use in Specific Populations) and 12 (Clinical Pharmacology) of the proposed labeling for Gemcitabine Injection® (Hospira, Inc.) that are pertinent to clinical pharmacology have been reproduced within **3.0 Detailed Labeling Recommendations**.

1.2 CLINICAL PHARMACOLOGY SUMMARY

Gemzar® for Injection (gemcitabine hydrochloride), a product of Eli Lilly and Company, US, received approval on 15-May-1996 as a first-line treatment for patients with locally advanced (nonresectable stage 2 or stage 3) or metastatic (stage 4) adenocarcinoma of the pancreas under NDA 20-509. Additional approved indications, include in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage 3A or 3B) or metastatic (stage 4) non-small cell lung cancer (25-Aug-1998); in combination with paclitaxel for the first-line treatment of patients with metastatic breast cancer after failure or prior anthracycline-containing adjuvant chemotherapy (19-May-2004); and in combination with carboplatin for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy (14-July-06). Gemzar® (Gemcitabine Hydrochloride) for Injection is available in sterile single-dose vials containing white lyophilized powder of 200 mg and 1000 mg. The powder should be dissolved in 5 mL or 25 mL of 0.9% Sodium Chloride Injection, USP, respectively to yield a concentration of 38 mg of gemcitabine per millimeter. The approved dosage is 1000 mg/m² to 1250 mg/m² administered intravenously as a 30 minute infusion once weekly for up to seven weeks alone or in combination. In the current application,

Gemzar® for Injection is designated as the listed drug by the applicant.

Hospira, Inc. plans to market a new drug product, Gemcitabine Injection® as an alternative to the listed drug. The indications that the applicant is seeking are identical to the indications for the listed drug and include the treatment of advanced ovarian cancer, metastatic breast cancer, locally advanced or metastatic non-small cell lung cancer and locally advanced or metastatic pancreatic cancer.

The innovator product is a lyophilized product that is to be reconstituted with 0.9% Sodium Chloride to a concentration of 38 mg or gemcitabine per millimeter. The innovator product is available in 200 mg and 1 g single use vials. The Hospira drug product is a clear, colorless to light straw-colored solution, free from visible particulates at same concentration of the listed drug and available in three single-use vial sizes: 200 mg, 1000 mg and 2000 mg. The active ingredient and route of administration for the proposed drug product Gemcitabine Injection® are the same as the listed drug Gemzar® for Injection. The Hospira drug product was developed for use at the same therapeutic concentration.

The Hospira Gemcitabine Injection® contains the same active ingredients at the same concentration, but differs in the excipients. Specifically, the Hospira formulation does not contain the excipients mannitol and sodium acetate which are the excipients in Gemzar®. The Hospira formulation contains the solvent Water for Injection, whereas the Gemzar® requires the addition 0.9% Sodium Chloride. The composition of the Gemcitabine Injection® (Hospira) and Gemzar® (Eli Lilly) are summarized in Table 1. The proposed formulation for the Hospira drug product is listed in Table 2.

The applicant Hospira Inc requested a waiver of *in vivo* bioequivalence in accordance with 21 CFR 320.22(b).

Table 1. Comparison of listed drug and Hospira formulation

	Eli Lilly and Company	Hospira, Inc.
Active Ingredient(s)	Gemcitabine Hydrochloride	Gemcitabine Hydrochloride
Inactive Ingredient(s)	Mannitol Sodium Acetate Hydrochloric Acid Sodium Hydroxide	Water for Injection Hydrochloric Acid Sodium Hydroxide
Route of Administration	Injection (Intravenous)	Injection (Intravenous)
Dosage Form	Injectable	Injectable
Strength	Gemzar® Freeze-Dried product: 200 mg/vial & 1 g/vial Concentration after reconstitution: 38 mg/mL	Gemcitabine Injection solution: 200 mg/5.3 mL, 1 g/26.3 mL, 2 g/52.6 mL Concentration: 38 mg/mL <i>NO RECONSTITUTION REQUIRED</i>

Table 2. Proposed formulation for Gemcitabine Injection

Component	Quantity per Milliliter (mL)	Concentration: 38 mg/mL		
		200 mg/5.3 mL	1 g/26.3 mL	2 g/52.6 mL
		Quantity per unit	Quantity per unit	Quantity per unit
Gemcitabine hydrochloride Ph.Eur./USP ¹	38 mg	200 mg	1 g	2 g
Water for Injection Ph.Eur./USP	q.s. to 1.00 mL	q.s. to 5.3 mL	q.s. to 26.3 mL	q.s. to 52.6 mL
Hydrochloric Acid Ph.Eur./NF (1N)	q.s. pH 2.0 – 3.0	q.s. pH 2.0 – 3.0	q.s. pH 2.0 – 3.0	q.s. pH 2.0 – 3.0
Sodium Hydroxide Ph.Eur./NF (1N)	q.s. pH 2.0 – 3.0	q.s. pH 2.0 – 3.0	q.s. pH 2.0 – 3.0	q.s. pH 2.0 – 3.0
Total Volume	1.00 mL	5.3 mL	26.3 mL	52.6 mL

q.s. = Quantity sufficient; A.R. = As required

1 Used in the formulation as gemcitabine hydrochloride. Actual quantity is equivalent to gemcitabine.
(b) (4)

2. QUESTION BASED REVIEW

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology studies and the clinical studies with PK and/or PD information submitted in the NDA.

The current 505(b)2 application does not include clinical studies and relies on the Agency’s findings of safety and effectiveness of the innovator drug product Gemzar® for Injection (NDA 20-509).

2.2 GENERAL ATTRIBUTES

Refer to the Sections 2.2 to 2.6 of the review of the original NDA 20-509 (Approval date 15-May-1996) of the innovator drug product Gemzar® for Injection.

2.7 GENERAL BIOPHARMACEUTICS

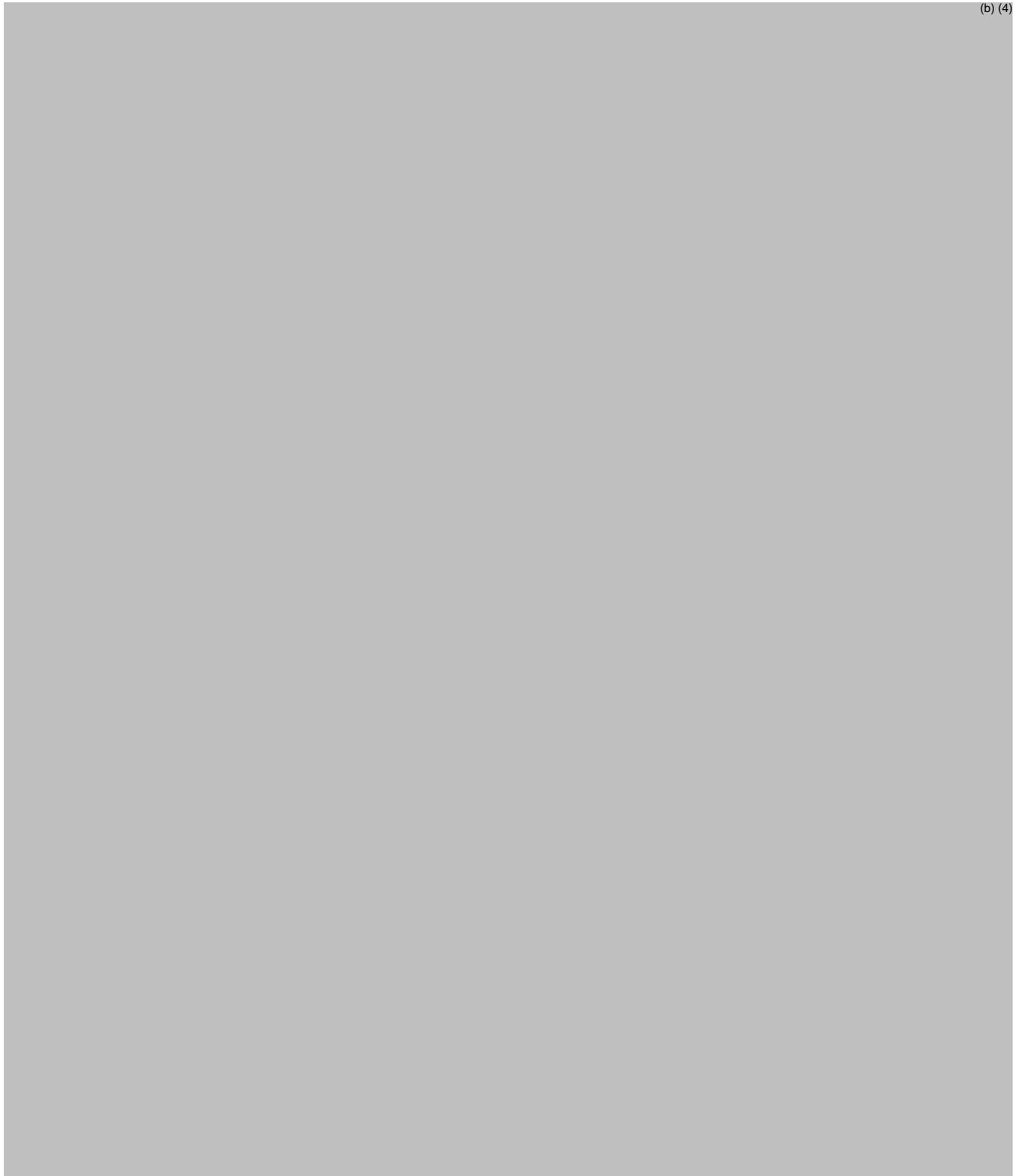
2.7.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

Refer to **Section 1.2, General Clinical Pharmacology**, to examine Tables 1 and 2 for the comparisons of the Hospira proposed formulation and the listed drug.

Hospira requested a waiver of *in vivo* bioequivalence in accordance with 21 CFR 320.22 (b)1.

3 DETAILED LABELING RECOMMENDATIONS

Only sections of the proposed drug product label for Gemcitabine Injection (Hospira, Inc) relevant to Clinical Pharmacology are listed below.



(b) (4)

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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/

STACY S SHORD
04/29/2010

QI LIU
05/03/2010

ONDQA (Biopharmaceutics) Review

NDA: 200-795
Submission Date: 12/11/09
Product: Gemcitabine Injection, 38 mg/ml
Type of Submission: Original Submission
Sponsor: Hospira
Reviewer: Tapash K. Ghosh, Ph.D.

Background: Hospira, Inc. submitted a New Drug Application (NDA) for Gemcitabine Injection for various cancers. 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.

The conditions of use (indication) and route of administration for the subject drug, Gemcitabine Injection, are the same as prescribed and recommended by the Reference Listed Drug (RLD). The proposed drug is formulated as an aqueous solution in three different strengths, 200 mg, 1 gm and 2 gm with concentration upon reconstitution of 38 mg/mL. The 2 gm/52.6 ml configuration is a new configuration not currently marketed by the innovator.

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 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.

Gemcitabine Injection is available as a sterile aqueous solution, which is intended for intravenous use. The drug product is comprised of a clear, colorless to light straw-colored solution, free from visible particles, presented in clear USP Type I glass vials. The single dose vials are (b) (4) with 5.3 mL fill, (b) (4) with 26.3 mL fill, and (b) (4) with 52.6 mL fill, closed with (b) (4) grey (b) (4) closures and aluminum seals with plastic flip-off tops.

The composition of the drug product consists of the active ingredient, gemcitabine hydrochloride, in water for injection prepared with the aid of hydrochloric acid and/or sodium hydroxide for pH adjustment. (b) (4) This product is sterilized (b) (4) and contains no antimicrobial preservatives. Gemcitabine Injection is stored at 2°C to 8°C (36 to 46 °F). A summary of the pharmaceutical information is provided in the Table below.

Pharmaceutical Information

Reference Listed Drug Name:	Gemzar®
Innovator Company Name:	Eli Lilly and Company
Established Product Name:	Gemcitabine Injection 38 mg/mL
Applicant Name:	Hospira, Inc.
Drug Substance:	Gemcitabine hydrochloride
Strength:	38 mg/mL
Presentations:	200 mg/5.3 mL, 1 g/26.3 mL, 2 g/52.6 mL
Route of Administration:	Injection (Intravenous)
Dosage Form:	Injectable
Proposed Indication(s):	Ovarian cancer, breast cancer, non-small cell lung cancer and pancreatic cancer

The composition of the finished drug product is presented in the Table below.

Composition

Component	Quantity per Milliliter (mL)	Function	Reference to Standards
Gemcitabine hydrochloride ¹	38 mg	Active ingredient	Ph.Eur./USP
Hydrochloric Acid (1 N)	(b) (4)	pH adjustment	Ph.Eur./NF
Sodium Hydroxide (1 N)	(b) (4)	pH adjustment	Ph.Eur./NF
Water for Injection	(b) (4)	(b) (4)	Ph.Eur./USP
			(b) (4) Ph.Eur./NF
Total Volume	1.00 mL		

q.s. = Quantity sufficient; A.R. = As required

1 Used in the formulation as gemcitabine hydrochloride. Actual quantity is equivalent to gemcitabine.

(b) (4)

Comparison Between Proposed Drug Product and Reference Listed Drug Product:

Vials of Gemzar® (Reference Listed Drug) contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3.

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. In addition, Hospira's proposed drug product is also available in 2 gram strength. The proposed product is formulated in Water for Injection and pH adjusted, if necessary, with hydrochloric acid and/or sodium hydroxide.

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Hospira, Inc. hereby requests a waiver of the *in vivo* study requirements for their product.

Table 1. Comparison Between Generic Drug and Reference Listed Drug

	Reference Listed Drug	Generic Equivalent
	Eli Lilly and Company Gemzar®	Hospira, Inc. Gemcitabine Injection
Conditions of Use	<p><i>Ovarian Cancer:</i> In combination with carboplatin is indicated for treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum based therapy.</p> <p><i>Breast Cancer:</i> In combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.</p> <p><i>Non-small Lung Cancer:</i> Is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIA or IIB), or metastatic (Stage IV) non-small cell lung cancer.</p> <p><i>Pancreatic Cancer:</i> Is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Is indicated for patients previously treated with 5-FU.</p>	<p><i>Ovarian Cancer:</i> In combination with carboplatin is indicated for treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum based therapy.</p> <p><i>Breast Cancer:</i> In combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.</p> <p><i>Non-small Lung Cancer:</i> Is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIA or IIB), or metastatic (Stage IV) non-small cell lung cancer.</p> <p><i>Pancreatic Cancer:</i> Is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Is indicated for patients previously treated with 5-FU.</p>
Active Ingredient(s)	Gemcitabine Hydrochloride	Gemcitabine Hydrochloride
Inactive Ingredient(s)	Mannitol Sodium Acetate Hydrochloric Acid Sodium Hydroxide	Water for Injection Hydrochloric Acid Sodium Hydroxide
Route of Administration	Injection (Intravenous)	Injection (Intravenous)
Dosage Form	Injectable	Injectable
Strength	Gemzar® Freeze-Dried product: 200 mg/vial & 1 g/vial Concentration after reconstitution: 38 mg/mL	Gemcitabine Injection solution: 200 mg/5.3 mL, 1 g/26.3 mL, 2 g/52.6 mL Concentration: 38 mg/mL <i>NO RECONSTITUTION REQUIRED</i>

Recommendation: Exclusion of (b) (4) mannitol and (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 of the *in vivo* study can be granted for their proposed product.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT by Patrick Marroum, Ph. D. _____

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/

TAPASH K GHOSH
02/02/2010

PATRICK J MARROUM
02/02/2010