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RESEARCH**

*APPLICATION NUMBER:*  
**200795Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION**

Application number: 200795  
Supporting document/s: SD 16  
Applicant's letter date: June 10, 2011  
CDER stamp date: June 10, 2011  
Product: Gemcitabine Injection  
Indication: Patients with ovarian cancer, breast cancer, non-small cell lung cancer (NSCLC), or pancreatic cancer  
Applicant: Hospira, Inc.  
Review Division: Division of Oncology Drug Products (HFD-150)  
Reviewer: Brenda J. Gehrke, Ph.D.  
Acting Supervisor/Team Leader: Whitney S. Helms, Ph.D.  
Division Director: Robert Justice, M.D., M.S.  
Project Manager: Amy Tilley

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Except as specifically identified, all data and information discussed below and necessary for approval of NDA 200795 are owned by Hospira, Inc. or are data for which Hospira, Inc. has obtained a written right of reference.

Any information or data necessary for approval of NDA 200795 that Hospira, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 200795.

**MEMORANDUM**

**MEMO DATE: 07/15/2011**

**TO:** To the file for NDA 200795

**FROM:** Brenda J. Gehrke, Ph.D., Pharmacologist; Division of Drug Oncology Products, OODP

**THROUGH:** Whitney S. Helms, Ph.D., Acting Supervisory Pharmacologist; Division of Drug Oncology Products, OODP

NDA 200795 was submitted on June 10, 2011 as a Class 1 resubmission of a 505(b)(2) NDA for Gemcitabine Injection (200 mg/5.3 mL, 1g/ 26.3 mL, and 2 g/52.6 mL) by Hospira, Inc. This submission is a complete response addressing the deficiencies communicated in the Complete Response letter issued by the FDA on January 11, 2011.

The Hospira, Inc. drug product is an aqueous solution containing the active ingredient (gemcitabine hydrochloride) and water for injection, while the RLD (Gemzar®) is a lyophilized powder containing the active ingredient and the excipients mannitol and sodium acetate. Therefore, the proposed Hospira, Inc. formulation differs from the RLD product in the addition of water for injection and the removal of mannitol and sodium acetate. The Hospira, Inc. formulation of gemcitabine injection contains impurity specification limits that exceed the ICHQ3A qualification threshold of 0.15% and ICHQ3B qualification threshold of 0.2%. In order to qualify these impurities, Hospira, Inc, performed a bridging toxicology study in mice (Study 1632-08670), which tested both Gemzar® and a lot (U022750RA) of the current formulation that contained elevated levels of the impurities (b)(4). The proposed specifications of the impurities and the levels present in the lot used in the toxicology study are listed in the table below.

Intermediate	Name	Proposed drug substance specification	Toxicologic lot (U022750RA)
(b) (4)			

The review of this study was completed on December 8, 2010 by Dr. Robert T. Dorsam at the time of the previous submission. He concluded that in the absence of unique toxicities that can be attributed to (b)(4) this bridging study provides qualification of these impurities in Hospira's gemcitabine injection; however, the chemistry, manufacturing, and controls (CMC) reviewer determined that the analytical

method for impurity identification was not adequately validated for linearity, accuracy, and precision. Based on this quality deficiency, it was not possible to precisely determine the impurity levels that were achieved with the lot used in the non-clinical study, and the impurities could not be qualified.

In the current submission, additional data were submitted to validate the method for linearity, accuracy, and precision at the proposed limits and extending to the higher concentrations of impurities found in lot U022750RA, the lot used in the nonclinical toxicology study conducted for impurity qualification. The CMC reviewer reviewed this data and determined that the analytical method is validated for linearity, accuracy, and precision both at the proposed specifications and at the concentrations present in lot U022750RA used in the toxicology study. Based on this validation of the method, the impurity levels reported in the toxicology study appear to be accurate, and therefore, the impurities are qualified at the proposed specifications. There were no other issues requiring pharmacology/toxicology input that developed during the course of the review process for this or the previous submission. The Hospira formulation for Gemcitabine Injection is, therefore, recommended for approval.

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/s/  
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BRENDA J GEHRKE  
07/15/2011

WHITNEY S HELMS  
07/18/2011

I agree with the findings of Dr. Gehrke and Dorsam that based on the CMC determination that the sponsor has developed a valid assay for quantifying the impurity levels in this gemcitabine formulation, the impurities are qualified based on animal findings. As no further issues requiring pharmacology/toxicology input came to light during the course of this review, I agree that the application is approvable from a pharmacology/toxicology perspective.

## MEMORANDUM

**Date:** December 8, 2010  
**From:** S. Leigh Verbois, Ph.D.  
Supervisory Pharmacologist  
Division of Drug Oncology Products  
**To:** File for NDA #200795  
Gemcitabine Injection  
**Re:** Approvability of Pharmacology and Toxicology

Hospira, Inc submitted a 505(b)2 NDA application for the treatment of patients with ovarian cancer, breast cancer, non-small cell lung cancer or pancreatic cancer. The sponsor submitted data to qualify impurities in order to support specifications for [REDACTED] (b) (4). Although the GLP non-clinical study (Study 1632-08668) was well conducted and did not detect difference between the lots of RLD and the lot with purported elevated impurity levels, the Chemistry, Manufacturing and Controls review was unable to provide assurance that the levels were impurities were accurate or precise based on the analytical method which was used. Therefore it is not possible to qualify impurities or set specifications above qualification thresholds described in ICH Q3A or Q3B at this time.

**Recommendations:** I concur with Dr. Robert Dorsam's conclusion that the sponsor should provide justification for the impurity levels within lot U022750RA the lot used in the Study 1632-08668. This justification should adequately address accuracy and precision of previous reported measures to allow for setting of specifications for [REDACTED] (b) (4).

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

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/s/  
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SANDI L VERBOIS  
12/08/2010

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 200795  
Supporting document/s: 1  
Applicant's letter date: December 11, 2009  
CDER stamp date: December 11, 2009  
Product: Gemcitabine Injection  
Indication: Patients with ovarian cancer, breast cancer,  
non-small cell lung cancer (NSCLC), or  
pancreatic cancer  
Applicant: Hospira, Inc.  
Review Division: Division of Drug Oncology Products  
Reviewer: Robert T. Dorsam, Ph.D.  
Supervisor/Team Leader: S. Leigh Verbois, Ph.D.  
Division Director: Robert Justice, M.D., M.S.  
Project Manager: Amy Tilley

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Any information or data necessary for approval of NDA 200795 that Hospira, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Hospira, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 200795.

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# 1 Executive Summary

## 1.1 RECOMMENDATIONS

### 1.1.1 Approvability

Hospira, Inc. has developed a preparation of Gemcitabine Injection which contains impurities specification limits that exceed the ICHQ3A qualification threshold of 0.15% and ICHQ3B qualification threshold of 0.2%. In order to qualify these impurities, Hospira, Inc. has performed a bridging toxicology study which includes both the Reference Listed Drug (RLD) and a preparation of gemcitabine that contains elevated levels of impurities. During the review of the chemistry, manufacturing, and controls module of the submission, the reviewer identified issues with the analytical methods for impurity identification. Due to this it is not possible to PRECISELY determine the impurity levels that were achieved with the lot used in the non-clinical study. Given this it is not possible to qualify impurities to allow for setting of specification as this time.

### 1.1.2 Additional Non Clinical Recommendations

The sponsor should provide adequate justification that the impurity levels within lot U022750RA, the lot used in Study 1632-08668, have been precisely and accurately reported. This will allow setting of specifications for (b) (4)

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

### 1.1.3 Labeling

The Pharm/Tox studies that were submitted by Hospira, Inc. do not present any findings that require revisions from that submitted.

## 1.2 BRIEF DISCUSSION OF NONCLINICAL FINDINGS

The sponsor conducted a bridging toxicology study in mice to compare the toxicities of the Reference Listed Drug (RLD) and a preparation of gemcitabine that had elevated levels of (b) (4) for qualification purposes. For clarity, the gemcitabine preparation that contains elevated levels of impurities will be referred to as "Hospira's gemcitabine injection" throughout this review. Four dose groups received RLD at 0, 100, 500, or 600 mg/kg on Days 1 and 8 followed by necropsy 7 days later. Another four dose groups received Hospira's gemcitabine injection under the same dose and schedule. Two deaths of mice receiving 600 mg/kg Hospira's gemcitabine injection demonstrated that the drug

targets the lymphoid tissue as is expected with gemcitabine exposure. One male receiving 500 mg/kg of the RLD died without clinical observations or microscopic findings. Treatment with either the RLD or Hospira's gemcitabine injection reduced WBC, RBC, Hb, and lymphocyte counts. Changes in spleen, thymus and testes weight were also similar between drug preparations. Histopathological findings further demonstrate that lymphoid tissues and testes were the major target organs for both the RLD and Hospira's gemcitabine injection. In the absence of unique toxicities that can be attributed to (b) (4) this bridging study provides qualification of these impurities in Hospira's gemcitabine injection.

## 2 DRUG INFORMATION

<b>2.1 Drug</b>	Gemcitabine Hydrochloride
<b>2.1.2 Generic Name</b>	Gemcitabine
<b>2.1.1 CAS Registry Number</b>	122111-03-9
<b>2.1.3 Code Name</b>	N/A
<b>2.1.4 Chemical Name</b>	2'-Deoxy-2',2'-difluorocytidine monohydrochloride ( $\beta$ -isomer) Cytidine: 2'-deoxy-2',2'-difluoro-, monohydrochloride
<b>2.1.5 Molecular Formula/Molecular Weight</b>	$C_9H_{11}F_2N_3O_4 \cdot HCl$
<b>2.1.6 Structure</b>	299.7 (hydrochloride) (b) (4)
<b>2.1.7 Pharmacologic class</b>	Nucleoside metabolic inhibitor
<b>2.2 Relevant IND/s, NDA/s, and DMF/s</b>	IND 106215, (b) (4)

### 2.3 Clinical Formulation

**2.3.1 Drug Formulation**

The active ingredient gemcitabine is suspended in water for injection and the pH is adjusted (b) (4) using hydrochloric acid or sodium hydroxide. Gemcitabine injection is a sterile aqueous solution which is a clear, colorless to straw-colored solution in a clear USP Type I single-use glass vial. A (b) (4) vial will contain 200 mg of drug in 5.3 mL of solution and a (b) (4) vial will contain 1 gram of gemcitabine in 26.3 mL of solution. The sponsor has produced an additional formulation consisting of a (b) (4) vial containing 2 grams of drug in 52.6 mL of solution. All containers will be closed with (b) (4) grey (b) (4) closures and aluminum seal with plastic flip-off tops.

**2.3.2 Comments on Novel Excipients**

There are no novel excipients in this formulation. The sponsor has excluded two excipients, sodium acetate and mannitol, that are present in the RLD. Sodium acetate (b) (4) and mannitol (b) (4). As these excipients are utilized in lyophilized preparations, their exclusion from Gemcitabine Injection appears to be appropriate.

**2.3.3 Comments on Impurities/Degradants of Concern**

Hospira's gemcitabine injection contains the following degradants which have been previously identified<sup>1</sup>:

(b) (4)

(b) (4) is a major metabolite of gemcitabine and does not require qualification (per ICHQ3A). The proposed specifications for (b) (4) exceed 0.15%, as noted in Table 1, and therefore require qualification. The sponsor has evaluated the toxicological properties of (b) (4) in a bridging toxicology study and a DEREK database query.

**Table 1. Proposed Specifications of Intermediates in Hospira's Gemcitabine Injection**

Intermediate	Name	Proposed Drug Substance Specification	Toxicologic batch (U022750RA)
(b) (4)			

Intermediate	Name	Proposed Drug Substance Specification	Toxicologic batch (U022750RA)
(b) (4)			

## 2.4 Proposed Clinical Population and Dosing Regimen

Gemcitabine injection will be administered at varying doses to patients with ovarian cancer, breast cancer, non-small cell lung cancer, and pancreatic cancer. Ovarian cancer patients should have relapsed after completion of platinum-based therapy, and gemcitabine injection will be administered in combination with carboplatin. The dose and schedule for treatment of ovarian cancer is 1000 mg/m<sup>2</sup> gemcitabine injection over 30 minutes on Days 1, 8 of each 21-day cycle. Patients with metastatic breast cancer will receive gemcitabine injection after failure of prior-anthracycline-containing adjuvant chemotherapy. A dose of 1250 mg/m<sup>2</sup> gemcitabine injection will be delivered over 30 minutes on Days 1 and 8 of each 21-day cycle. Patients with inoperable, locally advanced (Stage IIIA or IIIB) metastatic (Stage IV) will receive gemcitabine injection (1000 mg/m<sup>2</sup>) over 30 minutes on Days 1, 8, 15 of each 28 day cycle. Patients with pancreatic cancer that is locally advanced (non-resectable Stage II or Stage III) or metastatic (Stage IV) which has been previously treated with 5-FU can receive 1000 mg/m<sup>2</sup> gemcitabine injection (1000 mg/m<sup>2</sup>) over 30 minutes once weekly for up to 7 weeks, followed by one week rest from treatment. Thereafter, patients will receive 3 weekly administrations of gemcitabine followed by one week rest from treatment.

## 3 Studies Submitted

### 3.1 Studies Reviewed

Study number	Study Title
1632-08668	Gemzar <sup>®</sup> and Hospira's Gemcitabine Injection: A Repeat Intravenous Dose Range-Finding Toxicity Study in Male and Female CD-1 Mice
1632-08670	Gemzar <sup>®</sup> and Hospira's Gemcitabine Injection: A Two-Week Repeat Intravenous Dose Toxicology Study in Male and Female CD-1 Mice

### 3.2 Studies Not Reviewed

None

**3.3 Previous Reviews Referenced**

None

**4 Pharmacology**

**4.1 PRIMARY PHARMACOLOGY**

No pharmacology studies have been submitted.

**4.2 SECONDARY PHARMACOLOGY**

No secondary pharmacology studies have been submitted.

**4.3 SAFETY PHARMACOLOGY**

No safety pharmacology studies have been submitted.

**5 Pharmacokinetics/ADME/Toxicokinetics**

**5.1 PK/ADME**

No PK/ADME studies have been submitted.

**6 General Toxicology**

**6.1 SINGLE-DOSE TOXICITY**

None submitted

## 6.2 REPEAT-DOSE TOXICITY

### 1) Study title: Gemzar<sup>®</sup> and Hospira's Gemcitabine Injection: A Repeat Intravenous Dose Range-Finding Toxicity Study in Male and Female CD-1 Mice

#### Key Study Findings

- No mortality occurred in any dose group. Clinical observations and body weights were similar among all groups in the study.
- Hospira's gemcitabine was similar to the RLD under the conditions of this study.

Study no.: 1632-08668  
 Study report location: Electronic submission, entitled: 4237-other-tox-stud.pdf  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: November 24, 2008  
 GLP compliance: No  
 QA statement: None provided  
 Drug #1, lot #, and % purity: Gemcitabine, U022750RA, 88.8% pure  
 Drug #2, lot #, and % purity: Gemzar<sup>®</sup> (RLD), Lot A468315A, estimated 100% pure

#### Methods

Doses: Hospira's Gemcitabine Injection and Gemzar<sup>®</sup> were administered at similar doses

Gemcitabine dose (mg/kg)	Gemcitabine dose (mg/m <sup>2</sup> )
0	0
100	300
350	1050
500	1500

Frequency of dosing: Days 1 and 8  
 Route of administration: Intravenous, slow bolus infusion into tail vein  
 Dose volume: 16.9 mL/kg for Hospira's gemcitabine injection and control group, 15 mL/kg for Gemzar<sup>®</sup> and the relevant control group. A higher volume was given for Hospira's degraded gemcitabine (88% pure) to deliver the same amount of parent compound. This was an appropriate element of the study.  
 Formulation/Vehicle: Hospira's gemcitabine injection was formulated in sodium chloride for injection adjusted to pH 2 to 3. The RLD was formulated in a solution containing 0.237% sodium acetate and 3.8% mannitol in sodium chloride for injection (pH 2.5 to 3.5).

Species/Strain: CD-1 mice  
Number/Sex/Group: 3 animals/sex/group  
Age: Approximately 9 weeks  
Weight: Males: 31.43 – 35.53 g  
Females: 21.43 – 27.06 g  
Satellite groups: None  
Unique study design: Eight dosing groups in this study.  
Groups 1 to 4 received Hospira's gemcitabine injection  
Groups 5 to 8 received Gemzar<sup>®</sup>  
Deviation from study protocol: There were no deviations that appear to impact the outcome of the study.

## Observations and Results

### Mortality

There were no unscheduled deaths during this study.

### Clinical Signs

Clinical observations were made prior to dosing and then 1 to 2 hours and 4 to 6 hours after dosing on Days 1 and 8. Observations were made once daily on other days. No findings were in greater incidence for any drug-treated group. Blue and white discolorations at the injection site were of equal incidence among all groups in the study.

### Body Weights

Mice treated with Hospira's gemcitabine at doses of 0, 100, 350, or 500 mg/kg (Groups 1 to 4) or the RLD (Groups 5 to 8) showed similar body weights among all groups. There were no differences among dose groups or between the groups treated with RLD and Hospira's gemcitabine injection. Data below are for males, though females also showed no differences among doses or between drug preparations.

(the following male body weight data was excerpted from the sponsor's study report)

**Table 2. Male Body Weights - Hospira's Gemcitabine injection**

			Day Numbers Relative to Start Date						
Group	Sex	Animal	1	3	5	8	10	11	
1	m	20554	32.41	30.57	31.14	31.67	31.03	30.94	
		20555	32.35	32.25	32.67	32.93	33.00	32.74	
		20556	33.38	34.03	34.35	35.38	35.27	35.03	
		Mean	32.713	32.283	32.720	33.327	33.100	32.903	
		S.D.	0.578	1.730	1.606	1.887	2.122	2.050	
		N	3	3	3	3	3	3	
2	m	20560	33.33	31.30	31.13	31.26	.	.	
		20561	32.19	29.26	28.21	29.87	.	.	
		20562	33.02	30.32	30.30	31.19	.	.	
		Mean	32.847	30.293	29.880	30.773	.	.	
		S.D.	0.589	1.020	1.505	0.783	.	.	
		N	3	3	3	3	.	.	
3	m	20566	31.76	30.63	30.05	31.41	.	.	
		20567	32.69	31.95	31.67	32.95	.	.	
		20568	32.30	31.74	31.25	33.30	.	.	
		Mean	32.250	31.440	30.990	32.553	.	.	
		S.D.	0.467	0.709	0.841	1.006	.	.	
		N	3	3	3	3	.	.	
4	m	20572	32.29	31.06	32.11	33.10	33.38	33.48	
		20573	34.54	34.09	33.53	34.69	35.46	35.12	
		20574	32.04	32.09	32.49	33.40	27.53	26.06	
		Mean	32.957	32.413	32.710	33.730	32.123	31.553	
		S.D.	1.377	1.541	0.735	0.845	4.112	4.828	
		N	3	3	3	3	3	3	

- Not applicable

Group 1 - 0 mg/kg  
Group 2 - 100 mg/kg Test article  
Group 3 - 350 mg/kg Test article  
Group 4 - 500 mg/kg Test article

**Table 3. Male Body Weights - Gemzar®**

			Day Numbers Relative to Start Date						
Group	Sex	Animal	1	3	5	8	10	11	
5	m	20578	32.74	32.08	31.93	33.91	33.27	32.49	
		20579	32.77	31.80	31.68	33.52	32.71	32.65	
		20580	31.98	31.84	31.56	33.86	33.34	33.44	
		Mean	32.497	31.907	31.723	33.763	33.107	32.860	
		S.D.	0.448	0.151	0.189	0.212	0.345	0.509	
		N	3	3	3	3	3	3	
6	m	20584	35.53	34.69	35.03	36.06	.	.	
		20585	31.73	32.45	34.22	36.89	.	.	
		20586	32.05	32.98	31.79	33.17	.	.	
		Mean	33.103	33.373	33.680	35.373	.	.	
		S.D.	2.108	1.171	1.686	1.953	.	.	
		N	3	3	3	3	.	.	
7	m	20590	32.14	32.92	32.38	33.73	.	.	
		20591	32.14	32.46	32.26	32.88	.	.	
		20592	33.79	33.12	33.79	35.17	.	.	
		Mean	32.690	32.833	32.810	33.927	.	.	
		S.D.	0.953	0.338	0.851	1.158	.	.	
		N	3	3	3	3	.	.	
8	m	20596	33.90	33.08	33.90	35.74	35.16	34.75	
		20597	31.43	31.64	31.08	32.27	33.08	33.49	
		20598	32.62	32.08	32.12	33.56	33.65	33.84	
		Mean	32.650	32.267	32.367	33.857	33.963	34.027	
		S.D.	1.235	0.738	1.426	1.754	1.075	0.650	
		N	3	3	3	3	3	3	

- Not applicable

Group 1 - 0 mg/kg  
Group 2 - 100 mg/kg Test article  
Group 3 - 350 mg/kg Test article  
Group 4 - 500 mg/kg Test article  
Group 5 - 0 mg/kg  
Group 6 - 100 mg/kg Reference article  
Group 7 - 350 mg/kg Reference article  
Group 8 - 500 mg/kg Reference article

**2) Study title:** Gemzar<sup>®</sup> and Hospira's Gemcitabine Injection: A Two-Week Repeat Intravenous Dose Toxicology Study in Male and Female CD-1 Mice

**Key Study Findings**

- Gemzar<sup>®</sup> and Hospira's gemcitabine targeted lymphoid tissues, bone marrow, testes. Minimal to mild inflammation was present in the heart, liver and kidneys.
- This study contains degraded gemcitabine for the purposes of impurity qualification. During this study, mice were exposed to 16.56 mg/m<sup>2</sup> (b) (4) 27.36 mg/m (b) (4) and 46.8 mg/m of (b) (4)

Study no.: 1632-08670  
 Study report location: Electronic submission, entitled: 4237-other-tox-stud.pdf  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: January 16, 2009  
 GLP compliance: Yes, signed on 8/6/09  
 QA statement: Yes, signed on 8/6/09  
 Drug #1, lot #, and % purity: Gemcitabine Injection, U022750RA, 88.8% pure  
 Drug #2, lot #, and % purity: Gemzar<sup>®</sup> (RLD), Lot A468315A, estimated 100% pure

**Reported Impurity Levels in Hospira's Gemcitabine Injection\***

Intermediates	U022750RA Tox Batch (b) (4)
(b) (4)	
Purity	88.80%

\*based on current analytical capabilities.

**Methods**

Doses:

Gemcitabine dose (mg/kg)	Gemcitabine dose (mg/m <sup>2</sup> )
0	0
100	300
500	1500
600	1800

Frequency of dosing: Dosing on Days 1 and 8  
 Route of administration: Intravenous  
 Dose volume: Gemzar<sup>®</sup> – 17.1 mL/kg, slow bolus  
 Hospira's gemcitabine injection– 19.3 mL/kg, slow bolus  
 Formulation/Vehicle: Hospira's gemcitabine injection was formulated in sodium chloride for injection adjusted to pH 2 to 3. The RLD was formulated in a solution containing 0.237% sodium acetate and 3.8%

mannitol in sodium chloride for injection (pH 2.5 to 3.5).

Species/Strain: CD-1 mice  
 Number/Sex/Group: 10 animals/sex/group  
 Age: 8 to 9 weeks  
 Weight: Males – 28.18 to 35.93 grams  
 Females – 22.7 to 29.58 grams

Satellite groups: None  
 Unique study design: Hospira's Gemcitabine Injection (Groups 1 to 4) and Gemzar® (Groups 5 to 8) are administered at four doses each for side-by-side comparison. There are a total of eight groups in this study.

Deviation from study protocol: No deviations have affected the outcome of this study.

### Observations

Clinical signs: 1 to 2 hour post dose, 4 to 6 hours post-dose, then twice weekly  
Body weights: Days 1, 4, 8, 11, 14, and 15 (prior to necropsy)  
Food consumption: Twice weekly  
Ophthalmoscopy: Pre-dose, Day 14 (males), Day 13 (females)  
Hematology: Day 15 prior to necropsy (5/sex/group)  
Clinical chemistry: Day 15 prior to necropsy (5/sex/group)  
Urinalysis: Day 15 (prior to necropsy)  
Gross pathology: Day 15  
Organ weights: Full battery, including organs in histopath table  
Histopathology: Groups 1 and 4 (Control and 600 mg/kg Hospira's Gemcitabine)  
 Groups 5 and 8 (Control and 600 mg/kg RLD)  
 Also: Groups 2 and 3 had spleen, thymus, mandibular and mesenteric lymph nodes, testes and injection site preserved.  
 Adequate Battery: Yes Peer review: No

### Results

#### Mortality

Table 4. Mortality

Drug	Dose	Gender	Animal No.	Study Day	Observation
Hospira's gemcitabine injection	600 mg/kg	Male	21088	5	Languid, pale appearance. Lymphoid depletion, lymphocytolysis of the thymus, spleen and mesenteric lymph node. Bone marrow hypocellularity. Degeneration/regeneration of jejunum and colon glandular endothelium
Hospira's gemcitabine injection	600 mg/kg	Female	21095	13	No clinical signs. Lymphocytolysis and increased hematopoiesis in the spleen.
Gemzar®	500 mg/kg	Male	21144	15	No clinical observations. No microscopic findings.

### Clinical Signs

Total number of mice per group (20) is from the combination of males and females. The noted observations occurred only in the males.

**Table 5. Clinical Signs**

Clinical Sign	Incidence and Duration	Hospira's Gemcitabine (mg/kg)		Gemzar <sup>®</sup> (mg/kg)	
		0	600	0	600
	Total animals	20	20	20	20
Hunched	Incidence Duration (Day)		1 15		
Languid	Incidence Duration (Day)		1 5		1 1
Pale	Incidence Duration (Day)		1 5		

### Body Weights

There were no differences in body weights among dose groups in this study.

Body weight gain data, however, demonstrates that both 500 and 600 mg/kg of the RLD and Hospira's gemcitabine caused less body weight gain or body weight loss in the male and females during the intervals Day 1 to 4 followed by an increase during Day 4 to 8. This trend was statistically significant for Hospira's gemcitabine but was less robust with RLD-treated animals and was not statistically significant. There were no differences after the second dosage and body weight gain was similar among all groups after the 14 day study.

**Table 6. Male Body Weight Gain**

Males	Dose (mg/kg)	Body weight gain (grams)	
		Days 1 to 4	Days 4 to 8
Hospira's Gemcitabine	0	0.711	0.617
	100	0.813	1.007
	500	-1.798*	2.301*
	600	-1.537*	1.807*
Gemzar <sup>®</sup>	0	0.798	0.932
	100	0.304	1.392
	500	-0.21	1.376
	600	-0.502	1.973

\*p < 0.05

**Table 7. Female Body Weight Gain**

Females	Dose (mg/kg)	Body weight gain (grams)	
		Days 1 to 4	Days 4 to 8
Hospira's Gemcitabine	0	0.318	1.128
	100	0.156	1.383
	500	0.226	1.167
	600	-1.022*	2.647*
Gemzar <sup>®</sup>	0	0.521	1.11
	100	0.320	0.806
	500	0.258	0.965
	600	0.198	0.734

\*p &lt; 0.05

**Food Consumption**

Decreases in food consumption in the 500 and 600 mg/kg groups dosed with Hospira's gemcitabine correlates with their decreased body weight gain. Similar decreases were observed in the animals dosed with the RLD. Females treated with 600 mg/kg Hospira's gemcitabine also had a reduction in food consumption compared to control on Days 1 to 4 (not shown), but there were no other differences on other days or among other groups. The decrease during Day 1 to 4 is followed by a rebound increase in food consumption during Days 4 to 8, similar to body weight.

**Table 8. Food Consumption**

Males	Dose (mg/kg)	Food consumption (grams)	
		Days 1 to 4	Days 4 to 8
Hospira's Gemcitabine	0	4.65	5.48
	100	4.15	6.17
	500	2.94*	5.26
	600	3.4*	5.38
Gemzar <sup>®</sup>	0	4.23	5
	100	3.92	5.44
	500	3.24*	5.14
	600	3.13*	5.88*

\*p &lt; 0.05

**Ophthalmoscopy** No lesions were observed in any mice in this study.

**Hematology**

Decreases in WBCs, RBCs, and lymphocytes in groups treated with Hospira's gemcitabine and the RLD indicate that these compounds are targeting the bone marrow and lymphoid tissues. Greater suppression of lymphocytes and WBCs in the groups

treated with Hospira's gemcitabine are based on two males in the control group with high lymphocyte and WBC counts that raised the average of the control group.

## Males

**Table 9. Hematology - Males**

Hematology	Hospira's Gemcitabine (mg/kg)				Gemzar <sup>®</sup> (mg/kg)			
	0	100	500	600	0	100	500	600
	Raw	%	%	%	Raw	%	%	%
WBC (k/ $\mu$ L)	10.846			-49	7.756		-21	-8
RBC (M/ $\mu$ L)	9.288		-3	-9	9.408			-10*
HGB (g/dL)	14.9			-12	14.84			-10*
Neutrophil (K/ $\mu$ L)	1.864			-47				
Lymph (K/ $\mu$ L)	8.478	-19	-30	-51*	5.908		-36	-14
Reticulocytes ( $10^9$ /L)	248.1		50*	75*	253.66		96*	78*
RDW (%)	11.7		23*	24*	11.78		21*	27*

\*p < 0.05

## Females

**Table 10. Hematology - Females**

Hematology	Hospira's Gemcitabine (mg/kg)				Gemzar <sup>®</sup> (mg/kg)			
	0	100	500	600	0	100	500	600
	Raw	%	%	%	Raw	%	%	%
WBC (k/ $\mu$ L)	10.168	-16	-24	-32	8.928		-22	-19
RBC (M/ $\mu$ L)	10.04	-6*	-7*	-9*	9.668	-4	-3	-6
HGB (g/dL)	16.12		-6*	-8*	16.1	-4	-4	-8
Lymph (K/ $\mu$ L)	8.484	-23	-32	-36	7.115		-26	-24
Reticulocytes ( $10^9$ /L)	242.88	45	67*	70*	260.38	30	53	51
RDW (%)	12.56		12*	13*	1.75			9

\*p < 0.05

## Clinical Chemistry

**Table 11. Clinical Chemistry**

Clinical Chemistry	Hospira's Gemcitabine (mg/kg)				Gemzar® (mg/kg)			
	0	100	500	600	0	100	500	600
	Raw	%	%	%	Raw	%	%	%
Cholesterol (mg/dL)	154.2			18	157.6		13	11

A single female dosed with 500 mg/kg of the RLD had AST and ALT that were 5-10 fold higher than all other mice in the study but had no histopathological findings in the liver.

## Gross Pathology

No toxicologically relevant lesions were observed in animals throughout the study.

One male in the 100 mg/kg RLD group had a small right seminal vesicle. Gemcitabine targets the male reproductive organs however the finding did not correlate with dose.

One female receiving 500 mg/kg Hospira's gemcitabine and a female dosed with 600 mg/kg of the RLD had fluid-filled and distended uterus.

## Organ Weights

A trend toward increased heart weight was observed in the mice treated with Hospira's gemcitabine that was not statistically significant and did not show dose correlation. Though this trend was not present in mice treated with the RLD, increased heart weight in mice treated with Hospira's gemcitabine injection was not evident in data that are normalized to brain weight.

**Table 12. Organ Weights - Males**

Male	Hospira's Gemcitabine (mg/kg)				Gemzar® (mg/kg)			
	0	100	500	600	0	100	500	600
	Raw	%	%	%	Raw	%	%	%
Heart (g)	0.1635	10	5	8	0.1702	2	-1	-1
Spleen (g)	0.0985	11	71*	46*	0.107	9	21	28*
Testes (g)	0.2969	-6	-22*	-22*	0.3085	-14*	-18*	-18*
Thymus (g)	0.0419	-12	-35*	-32*	0.0371	-5	-15	-13

\*p < 0.05

**Table 13. Organ Weights - Females**

Female	Hospira's Gemcitabine (mg/kg)				Gemzar® (mg/kg)			
	0	100	500	600	0	100	500	600
	Raw	%	%	%	Raw	%	%	%
Heart (g)	0.1341	9	11	6	0.1441	-3	-2	2
Spleen (g)	0.0951	48	55	36	0.1009	5	36*	36*
Ovary (g)	0.01114	30	32	18	0.01369	11	0	1
Thymus (g)	0.0481	33	-6	23	0.0499	-10	2	11

\*p &lt; 0.05

**Histopathology**

Adequate Battery: Yes  
Peer Review: No

Several histopathological findings were similar between the RLD and Hospira's gemcitabine, including: osteoarthritis of the femur, minimal to mild inflammation in the heart, hematopoiesis of the spleen, and germ cell depletion of the testes.

Some findings were in slightly higher incidence in Hospira's gemcitabine treated groups. Two males treated with high dose gemcitabine (Hospira) had mild inflammation in the kidney, an effect also found in one vehicle-treated male (Group 5). Inflammation was also found in the mesenteric and mandibular lymph nodes of mice treated with Hospira's gemcitabine (high dose). Histopathological evidence of thymic atrophy (1 of 9) in the high dose males occurred in mice treated with Hospira's gemcitabine though alterations in thymus weight and reductions in lymphocytes occurred with both the RLD and Hospira's gemcitabine. Effects on the thymus therefore appear to be similar between these drug preparations. Degeneration of myofibers at the site of injection occurred in all mice in the study, with mild or minimal inflammation occurring in those animals treated with Hospira's gemcitabine.

Male

**Table 14. Histopathology - Males**

Tissue	Finding	Severity	Hospira's Gemcitabine (mg/kg)				Gemzar® (mg/kg)			
			0	100	500	600	0	100	500	600
		Total Examined	10			9	10			10
Bone marrow - femur	Osteoarthritis	Total Findings	3	-	-	4	3			3

Tissue	Finding	Severity	Hospira's Gemcitabine (mg/kg)				Gemzar® (mg/kg)			
			0	100	500	600	0	100	500	600
		Minimal	1							
		Mild	1			1				1
		Moderate	1			1	3			2
		Marked				2				
Heart	Fibrosis, myocardial, multifocal	Minimal		-	-	1		-	-	
	Inflammation, acute, myocardial, focal	Minimal		-	-	1		-	-	
	Inflammation, acute, vascular, focal	Mild						-	-	1
Kidney	Inflammation, chronic, interstitial, focal	Total Findings		-	-	2	1	-	-	
		Minimal				1	1			
		Mild				1				
	cyst, cortical, focal	Mild		-	-	1		-	-	
Lymph node - mandibular		Total examined	9	10	10	9	10	-	-	10
	Erythrophagocytosis, multifocal	Minimal				2				
	Lymphocytolysis, multifocal	Minimal			-	1				
	Inflammation, acute, pericapsular, multifocal	Moderate				1				
	Hyperplasia, lymphoid	Mild				1				
Lymph nodes - mesenteric		Total Examined	9	10	10	9	10	-	-	10
	Depletion, lymphoid	Mild				1				
Mandibular salivary gland	Inflammation, acute, interstitial, pericapsular, multifocal	Moderate				1				
Skin	Granuloma, focal	Minimal		-	-			-	-	1
Spleen		Total examined	10	10	10	9	10	10	9	10
	Hematopoiesis, increased	Total findings	1	7	10	9	3	8	9	10
		Mild	1	2	2	3	2	2	2	2
		Moderate		5	8	6	1	6	7	8
	Lymphocytolysis, multifocal	Mild			1					
Testes		Total	10	10	10	9	10	10	9	10

Tissue	Finding	Severity	Hospira's Gemcitabine (mg/kg)				Gemzar® (mg/kg)			
			0	100	500	600	0	100	500	600
		examined								
	Germ cell depletion	Total findings		9	10	9		10	9	10
		Mild		9	9			10	9	9
		Moderate			1	9				1
Thymus		Total examined	10	10	10	9	10	10	9	10
	Lymphocytolysis, diffuse	Moderate				1				
	Atrophy	Moderate				1				
Injection site		Total examined	10	10	10	9	10	10	9	10
	Degeneration, myofiber, multifocal	Total findings	9	6	3	9	10	-	-	10
		Minimal	1	5	3		1			1
		Mild	8	1		9	9			9
	Degeneration, myofiber, focal	Minimal			1					
	Degeneration / necrosis, vascular, focal	Total findings	1	1	1	2				
		Mild	1	1		1				
		Moderate			1	1				
	Inflammation, chronic, vascular, focal	Mild				1				
	Inflammation, subacute, subcutaneous, multifocal	Mild			1					
	Hemorrhage, subcutaneous, focal	Minimal			3					
	Hemorrhage, subcutaneous, multifocal	Mild			1					
	Thrombosis, multifocal	Mild			1					
	Exudate, fibrinous, subcutaneous, focal	Total findings			2					
		Minimal			1					
		Mild			1					
	Exudate, epidermal, focal	Mild			2					

**Table 15. Histopathology - Females**

Tissue	Finding	Severity	Hospira's Gemcitabine (mg/kg)				Gemzar® (mg/kg)			
			0	100	500	600	0	100	500	600
		Total Examined	10			9	10			10
Bone marrow - femur	Osteoarthritis	Total Findings	1			1				
		Mild	1							
		Moderate				1				
Kidney	Basophilia, tubular, focal	Minimal				2				
Liver	Infiltrate, mononuclear cell, focal	Minimal				1				
	Necrosis, hepatocellular, multifocal	Minimal								1
Mandibular - Salivary gland	Inflammation, chronic, interstitial, focal	Minimal				1	1			1
Spleen	Hematopoiesis, increased	Total Findings	1	8	10	9	2	8	10	10
		Mild	1	3	2	5	1	5		2
		Moderate		5	8	4	1	3	10	8
Thymus	Hemorrhage, focal	Minimal	1	2						2
Injection site		Total examined	10	10	10	9	10			10
	Degeneration, myofiber, multifocal	Total findings	9	6	3	9	10	-	-	10
		Minimal	1	5	3		1			1
		Mild	8	1		9	9			9
	Degeneration / necrosis, vascular, focal	Total findings			2	2	1			
		Mild			1	2	1			
		Moderate			1					
		Inflammation, chronic, subcutaneous, multifocal	Minimal		1	4		1		1
		Degeneration / necrosis, vascular, multifocal	Mild			1				
		Inflammation, subacute,	Minimal				1			

Tissue	Finding	Severity	Hospira's Gemcitabine (mg/kg)				Gemzar® (mg/kg)			
			0	100	500	600	0	100	500	600
	subcutaneous, diffuse									
	Inflammation, subacute, cutaneous, multifocal	Mild			1					
	Mineralization, subcutaneous, focal	Total Findings			2					
		Minimal			1					
		Mild			1					
	Acanthosis, focal	Moderate			1					
	Exudate, fibrinous, subcutaneous, focal	Minimal		2	3					
	Exudate, fibrinous, subcutaneous, multifocal	Minimal		1						
	Ulcer, focal	Mild			1					

## 7 Genetic Toxicology

### 7.4 Other Genetic Toxicity Studies

The sponsor performed a quantitative structure activity relationship analysis using the Derek database to assess the potential genotoxicity of (b) (4). The intermediates did not produce alerts for genotoxicity, whereas gemcitabine was positive for genotoxic potential, as expected.

## 11 Integrated Summary and Safety Evaluation

### OVERALL CONCLUSIONS AND RECOMMENDATIONS

The sponsor, Hospira Inc., is developing gemcitabine in solution. The sponsor seeks approval for this change to the gemcitabine formulation through a 505b2 application and has submitted toxicology data to qualify gemcitabine degradants that are above the 0.15% qualification threshold. Previously, the sponsor submitted (b) (4) with gemcitabine in solution; however the package contained 6 months of real-time stability data rather than the required 12 months of real-time data. In addition, accelerated degradation data demonstrated excessive instability of the resuspended gemcitabine such that (b) (4) would require qualification in a repeat dose toxicology study. (b) (4) resulted in a refuse to file (RTF) letter and the sponsor has now submitted NDA 200795 with a repeat dose toxicology bridging study to qualify (b) (4). In this application, the sponsor has also tightened specifications for the intermediates and total impurity (see Table below).

The repeat dose toxicology study incorporates 4 groups of mice treated with Hospira's gemcitabine and 4 groups of mice treated with the RLD at doses up to 1800 mg/m<sup>2</sup> for a comparison of the toxicities. Both the RLD and Hospira's gemcitabine targeted the lymphoid tissues (thymus and spleen) as demonstrated in the altered organ weights and histopathological findings of hematopoiesis, hemorrhage, and atrophy in these organs. Suppression of RBC, WBC and lymphocyte counts indicate that both the RLD and Hospira's gemcitabine target the bone marrow and lymphoid tissue. The testes were also reduced in weight and had germ cell depletion. Effects on the lymphoid organs, bone marrow, and testes are typical of gemcitabine-mediated toxicities.

All mice in the study had signs of degradation of myofibers at the site injection site. In addition to myofiber degradation, mice treated with 500 mg/kg Hospira's gemcitabine had minimal to mild inflammation, mineralization, and exudate of the injection site in 1 or 2 out of 10 mice in the dose group. Inflammation was mainly noted in the 500 mg/kg group for both males and females who received Hospira's gemcitabine and was not present in the higher dose group (600 mg/kg). The absence of inflammation in the high dose group is not due to suppression of immune function; immune cell levels are roughly similar between the 500 and 600 mg/kg groups.

Inflammation in the heart was noted in a single mouse in the high dose groups that received either the RLD or Hospira's gemcitabine. There was also a 5 to 10% increase in heart weight in those animals treated with Hospira's gemcitabine that was not dose dependent nor statistically significant due to variability in the data. Additionally, the heart weight was not different among treatment groups when normalized according to brain weight therefore this does not appear to be toxicologically relevant. Because inflammation was noted with both preparations of gemcitabine, observations in the heart are not unique to Hospira's gemcitabine. In summary, the toxicities in the groups treated with the RLD and degraded Hospira's gemcitabine appear to be similar.

The structures of gemcitabine and (b) (4) were evaluated for genotoxic and carcinogenic potential based on a quantitative structure activity relationship analysis using the Derek database. As expected, gemcitabine scored positive for both genotoxic and carcinogenic potential. (b) (4) were each negative for genotoxic and carcinogenic potential according to this analysis and therefore possess less genotoxic potential than gemcitabine, the parent compound.

During the CMC review, the CMC reviewer noted issues with analytical validation which called into question the quantification of (b) (4). Due to this, it is not possible to precisely or accurately determine the levels of impurities with the nonclinical studies at this time. However, based on the data that was provided, Hospira's gemcitabine was degraded to 88.8% impurity with elevated levels of (b) (4) (Table below). (b) (4) is a major inactive metabolite of gemcitabine not require qualification. The maximal dose used in the mouse study (600 mg/kg or 1800 mg/m<sup>2</sup>) resulted in exposure of mice to levels of these impurities that are above the proposed specifications for the clinical dose of Hospira's gemcitabine. When

accounting for a patient taking the typical dose of 1000 mg/m<sup>2</sup> which may be degraded to the maximal specification, mouse exposure to the impurities in the general toxicology study was 2.76 to 3.34 fold higher than a single clinical dose (Table 16). Gemcitabine dosage may be escalated up to 1500 mg/m<sup>2</sup>, in which case mice were exposed to 1.38 to 1.95 fold higher impurities than the predicted human exposure during a single administration.

During a therapeutic cycle, the RLD is administered to patients once weekly for 3 weeks followed by a one week break during a 28-day cycle. Alternatively, patients may receive up to 7 weekly doses or until toxicity necessitates holding the dose, followed by once weekly doses over three weeks in a 4 week cycle. The dosing schedule used in this repeat dose toxicology study is once weekly for two consecutive weeks. Though the toxicology study dose schedule is not as intense, the mice gained higher exposure to the intermediates in two doses than to four doses of maximally degraded 1000 mg/m<sup>2</sup> gemcitabine on a 28-day cycle (Table 17). Similarly, animals in the toxicology studies received higher exposure to the impurities than if humans were exposed to three doses of 1500 mg/m<sup>2</sup> maximally degraded gemcitabine. The closest margin between mouse and human exposure is found with (b) (4). Mice received two doses of 8.28 mg/m<sup>2</sup> (b) (4) for a total exposure of 16.6 mg/m<sup>2</sup> in the study whereas patients receiving 3 doses of 1500 mg/m<sup>2</sup> maximally degraded gemcitabine would theoretically receive a dose of 13.5 mg/m<sup>2</sup> of (b) (4). Mice therefore receive higher exposure to (b) (4) under this “worst case scenario” considering maximally degraded gemcitabine at the highest dose (1500 mg/m<sup>2</sup>).

Considering this, should the deviations in the analytical methods indicate that there was a substantial change in impurities in Hospira’s gemcitabine, specifications may need to be lowered or an additional nonclinical study may be required to support the proposed specifications and approval.

**Table 16. Single Dose Impurity Qualification**

Intermediates	Tox Batch U022750RA <sup>(b) (4)</sup>	1800 mg/m <sup>2</sup> dose	Clinical Batch Proposed Spec (%) <sup>(b) (4)</sup>	1000 mg/m <sup>2</sup> RLD		1500 mg/m <sup>2</sup> RLD	
		Mouse exposure  to intermediates		Human exposure from specs (mg/m <sup>2</sup> )	Mouse/ human ratio (fold)	Human exposure from specs (mg/m <sup>2</sup> )	Mouse/ human ratio (fold)
		8.28 mg/m <sup>2</sup>		3	2.76	4.5	1.38
		13.68 mg/m <sup>2</sup>		4	3.42	7.5	1.824
		23.4 mg/m <sup>2</sup>		7	3.34	10.5	1.95
Total Impurity							
Purity	88.80%						

**Table 17. Multiple-dose impurity qualification**

Cancer	Gemcitabine Dose (mg/m <sup>2</sup> )	Administration Days	Cycle Length (Days)	Number of Administrations	Total Exposure Per Cycle (human)	Intermediates	Clin. Batch Proposed Spec. (%) (b) (4)	Maximal Human Exposure (mg/m <sup>2</sup> )	1800 mg/m <sup>2</sup> Dose Mouse Exposure to Intermediates (mg/m <sup>2</sup> )	Mouse/Human Exposure Ratio (fold)
Ovarian	1000	Days 1, 8	21	2	2000			6	16.56	2.8
								8	27.36	3.4
Breast	1250	Days 1, 8	21	2	2500			14	46.8	3.3
								7.5	16.56	2.2
NSCLC	1000	1, 8, 15	28	3	3000			10	27.36	2.7
								17.5	46.8	2.7
Pancreatic	1000	1, 8, 15, 21	28	4	4000			9	16.56	1.8
								12	27.36	2.3
Pancreatic	1000	1, 8, 15	28	3	3000			21	46.8	2.2
								7.5	16.56	2.2
								10	27.36	2.7
								17.5	46.8	2.7
								12	16.56	1.4
								16	27.36	1.7
Pancreatic	1500 (dose escalated)	1, 8, 15	28	3	4500			28	46.8	1.7
								9	16.56	1.8
								12	27.36	2.3
								21	46.8	2.2
								13.5	16.56	1.2
								18	27.36	1.5
										1.5

## References

1. Jansen PJ, Akers MJ, Amos RM, Baertschi SW, Cooke GG, Dorman DE, Kemp CA, Maple SR, McCune KA. (2000) The degradation of the antitumor agent gemcitabine hydrochloride in an acidic aqueous solution at pH 3.2 and identification of degradation products. *J. Pharm. Sci.* 89 (7): 885-91.

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/s/  
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12/08/2010

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