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APPLICATION NUMBER:

208313Orig1s000

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

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA208313/SDN23
Link to EDR	\\CDSESUB1\evsprod\NDA208313\208313.enx
Submission Date	NDA
Submission Type	<i>Resubmission</i>
Brand Name	Infugem
Generic Name	Gemcitabine Hydrochloride
Dosage Form and Strength	Sterile solution for injection with 10 mg/mL strength, fill volumes of 120, 130, 140, 150, 160, 170, 180, 190, 200, (b) (4) 220 mL
Route of Administration	Intravenous infusion
Proposed Indication	<p>Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated:</p> <ul style="list-style-type: none"> • in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy • in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated • in combination with cisplatin for the treatment of non-small cell lung cancer • as a single agent for the treatment of pancreatic cancer
Applicant	Sun Pharmaceuticals Ltd. (SPIL)
Associated IND	
OCP Review Team	<i>Edwin Chiu Yuen Chow, Ph.D.</i> <i>Jiang Liu, Ph.D.</i> <i>Jeanne Fourie Zirkelbach, Ph.D.</i>

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1. EXECUTIVE SUMMARY

Sun Pharmaceutical Industries Ltd. submitted a complete response amendment to NDA208313 for Infugem (Gemcitabine Hydrochloride for Injection). The applicant originally submitted a 505(b)(2) application (NDA 208313) for gemcitabine hydrochloride in sodium chloride injection (proposed proprietary name: Infugem), 10 mg/mL prefilled bags, on March 30, 2015, but FDA issued a complete response (CR) on November 24, 2015 (Reference ID: 3851154). The CR letter listed deficiencies related to facilities inspections and manufacturing, and contained several recommendations regarding the proposed human factor study to support product labelling and safety. FDA issued another CR on May 23, 2017 (in response to a class 2 resubmission submitted on November 23, 2016; Reference ID: 4101806) related to manufacturing facility deficiencies. Sun submitted a class 2 resubmission amendment to their application on February 16, 2018.

Sun Pharmaceuticals Ltd. proposes that Infugem has the same active ingredient, route of administration (intravenous infusion), and indications as the listed drug product, Gemcitabine for injection (Gemzar®). Unlike, Gemzar®, Infugem is developed as an intravenous infusion package with 10 available volume presentations (fill volumes of 120, 130, 140, 150, 160, 170, 180, 190, 200, (b) (4) and 220 mL) that are dissolved in 0.9% saline solution. According to Gemzar's current FDA-approved prescribing information, the recommended dosing for each Gemzar indication is based on body surface area (BSA) (e.g., the recommended dose for pancreatic cancer is 1,000 mg/m² and the recommended dose for breast cancer is 1,250 mg/m²). However, for the Infugem drug product, patients within specific BSA ranges are dosed based on Table 1 and 2, which may result in a maximum of up to 5% difference in the absolute dose when compared to the intended dose. Sun is seeking approval for ovarian (1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle), breast (1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle), non-small cell lung (1000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle), and pancreatic (1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle) cancer indications, which are the same as that approved for Gemzar.

(b) (4)



Sun did not conduct clinical studies, including bioequivalence studies to support approval of the application. For approval, Sun relies on FDA's finding of safety and effectiveness for the listed drug, Gemzar® (gemcitabine for injection), (NDA 20509) as well as supportive literature data. In addition, Sun submitted simulated pharmacokinetic data (SDN 1 and SDN 20) using a population pharmacokinetic modeling approach. Specifically, a virtual 2-way crossover trial was submitted to provide additional supportive evidence of bioequivalence between the listed product, Gemzar®, and Infugem. Based on several prior clinical pharmacology reviews (Reference ID: 3836375, 4148463, and 4177469 that did not rely on the PK simulation data found in SDN 1, 20 and 25), the recommendation for this application was approval. The purpose of the current clinical pharmacology review is to review the submitted PK simulation data (SDN 1 and SDN 20 and SDN 25), and literature data which serve an additional supportive role for the approval of the Sun product.

In the current submission (SDN 23 and SDN 25), the pharmacokinetics of gemcitabine as reported in the literature (refs) and population pharmacokinetic data submitted by Sun (SDN 1, 20 and 25) are reviewed to further provide supportive evidence that a difference in the absolute dose between Gemzar® and Infugem of up to 5% would not lead to clinical meaningful differences in efficacy and safety. After thorough review of the pharmacokinetic (PK) data from the listed product and published literature, FDA determined that the proposed formulation, that requires the dose to be rounded to the nearest intended dose, results in a maximum difference in dose of 5% compared to Gemzar®. This difference in absolute dose is determined not to result in clinically relevant differences in gemcitabine exposure when comparing Gemzar® and Infugem. This conclusion is based the following:

1. Gemcitabine is a cytotoxic anticancer agent, which is dosed at or near the maximum tolerated dose (MTD) to maximize efficacy. Studies have shown that the MTD¹ is defined at 1800 mg/m² and the efficacious dose range is between 800 to 1250 mg/m²,^{2,3} which is within the recommended approved dose range. Therefore, if the difference in the absolute dose is 5% higher for Infugem vs Gemzar®, there is not expected to be a clinically relevant safety concern.

¹ Mavroudis D, Pappas P, Kouroussis C, Kakolyris S, Agelaki S, Kalbakis K, Androulakis N, Souglakos J, Vardakis N, Nikolaidou M, Samonis G, Marselos M, Georgoulas V (2003) A dose-escalation and pharmacokinetic study of gemcitabine and oxaliplatin in patients with advanced solid tumors. *Ann Oncol*. **14**(2):304-12.

² Carmichael J, Fink U, Russell RC, Spittle MF, Harris AL, Spiessi G, Blatter J (1996) Phase II study of gemcitabine in patients with advanced pancreatic cancer. *Br J Cancer*. **73**(1):101-5.

³ FDA drug product label, Gemzar®, Revised: 9/2017, https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020509s0791bl.pdf

Gemcitabine is administered intravenously and has linear pharmacokinetic characteristics,³ which mean that a change in dose (e.g., 5% change as proposed) is proportional to the change in drug exposure.

2. In addition, gemcitabine has moderate to high variability in clearance,^{4,5,6,7,8} which results in higher variability than the proposed maximum difference in dose between Gemzar® and Infugem of 5%. Therefore, based on the inter-occasion variability in clearance, the proposed 5% difference in absolute dose will not result in a clinically meaningful change in gemcitabine exposure.

Sun has conducted additional supportive PK simulations using a gemcitabine population pharmacokinetic (PopPK) model from the literature^{5,7} to provide additional support for the intended dosage form that results in a maximum 5% difference in the absolute gemcitabine dose compared to Gemzar®. The objective of the simulation was to demonstrate that a maximum difference in dose of 5% compared to Gemzar would not result in clinically meaningful differences in exposure. The pharmacokinetic simulations were performed using a two-compartment model with linear distribution and elimination, both for gemcitabine and for its metabolite, dFdU. The model code can be found in the submission under Module 5.3.1.2 bioequivalence simulation study report. The model parameter estimates (Table 3) were selected for the simulations. A gender effect was included in the PopPK model for the simulations. In order to properly simulate a crossover trial, an intra-occasion variability (IOV) was added to clearance parameter to be consistent with the literature. One thousand virtual simulation trials for a two-period crossover study design with 120 subjects were performed under the worst-case scenarios as follows:

1. Group 1: Male, BSA: 2.1 m²: IOV of 30% in clearance
2. Group 2: Female, BSA: 1.7 m²: IOV of 30% in clearance
3. Group 3: Female, BSA: 1.4 m²: IOV of 30% in clearance

⁴ Jiang X, Galettis P, Links M, Mitchell PL, and McLachlan AJ (2008) Population pharmacokinetics of gemcitabine and its metabolite in patients with cancer: effect of oxaliplatin and infusion rate. *Br J Clin Pharmacol* **65**:326-333.

⁵ Joerger M, Huitema AD, Koeberle D, Rosing H, Beijnen JH, Hitz F, Cerny T, Schellens JH, and Gillessen S (2014) Safety and pharmacology of gemcitabine and capecitabine in patients with advanced pancreatico-biliary cancer and hepatic dysfunction. *Cancer Chemother Pharmacol* **73**:113-124.

⁶ Nieto Y, Aldaz A, Rifon J, Perez-Calvo J, Zafra A, Zufia L, Viudez A, Viteri S, Aramendia JM, Aristu J, Centeno C, Moreno M, Sayar O, and Hernandez M (2007) Phase I and pharmacokinetic study of gemcitabine administered at fixed-dose rate, combined with docetaxel/melphalan/carboplatin, with autologous hematopoietic progenitor-cell support, in patients with advanced refractory tumors. *Biol Blood Marrow Transplant* **13**:1324-1337.

⁷ Ramon-Lopez A, Escudero-Ortiz V, Duart-Duart MJ, Perez-Ruixo JJ, and Valenzuela B (2012) [Population pharmacokinetics of gemcitabine applied to personalize the dosage used in cancer patients]. *Farm Hosp* **36**:194-206.

⁸ Sugiyama E, Kaniwa N, Kim SR, Hasegawa R, Saito Y, Ueno H, Okusaka T, Ikeda M, Morizane C, Kondo S, Yamamoto N, Tamura T, Furuse J, Ishii H, Yoshida T, Saijo N, and Sawada J (2010) Population pharmacokinetics of gemcitabine and its metabolite in Japanese cancer patients: impact of genetic polymorphisms. *Clin Pharmacokinet* **49**:549-558.

Table 3: summary of compartmental PK parameters used for simulations

Parameters	Method B Average (RSE)
Cl _{GEM} (l/min)	2.70 (1)
V1 (l)	15
Q2 (l/min)	0.727
V2 (l)	15
Cl _{DFDU} (l/min)	0.0599
V3 (l)	46
Q4 (l/min)	0.204
V4 (l)	192
interindividual variability (%)	
W _{ClGEM}	28.4
W _{v1}	41.8
W _{Q2}	42.1
W _{v2}	63.9
W _{ClDFDU}	35.6
W _{v3}	28.2
W _{Q4}	29.1
W _{v4}	37.8
Residual variability (%)	
σ _{GEM}	46.8

Data adapted from Method B of Lopez, R, et al (2012).

Source: Module 5.3.1.2 Bioequivalence simulation study report, Table 3, page 15

The simulation results demonstrated that the 90% confidence interval (CI) of the geometric mean ratios (GMR) of AUC and C_{max} remained within the confidence limits of 80% to 125% under the worst-case scenarios. Sun's simulation and bioequivalence analyses appear acceptable.

Table 4: Bioequivalence Passing rate under worst-case scenarios in 1000 virtual trials

Scenarios	Conditions	Percent dose difference between Gemzar and Infugem	Trials that passed bioequivalence for C _{max} and AUC (80-125%)
Group 1	120 subjects, Male, BSA: 2.1 m ² : IOV of 30% in clearance	-4.8%	97%
Group 2	120 subjects, Female, BSA: 1.7 m ² : IOV of 30% in clearance	+3.5%	98%
Group 3	120 subjects, BSA: 1.4 m ² : IOV of 30% in clearance	+2.9%	98%

Source: Module 5.3.1.2 Addendum to Bioequivalence simulation study report, pages 11-13

A minor limitation of the simulation and bioequivalence analyses was that the model did not include evaluation of a ±5% dose difference scenario. However, even if under this condition, the virtual trial simulations will still be able to demonstrate bioequivalence by using the same number of subjects, or by increasing the number of subjects in the virtual trial. Given the fact that both gemcitabine drug products are given as a solution intravenously to patients and that gemcitabine PK is linear, the bioequivalence criteria are deemed to be met for a maximum difference in dose of 5% with a sufficient sample size. From a clinical pharmacology perspective, the maximum difference in gemcitabine dose of 5% will not lead to clinically meaningful changes in gemcitabine exposure based on the PK characteristics of gemcitabine and the rationale summarized above. The additional simulated data provided with the submitted PK

simulations, in this case, are supportive for the proposed dose banding. The effect of dose differences >5% on the efficacy and safety of gemcitabine is unknown, may require additional clinical data.

1.1 Recommendations

The recommendation for the current resubmission is approval. For labeling recommendations for Infugem (Gemcitabine hydrochloride), please refer to Section 2.4.

1.2 Post-Marketing Requirements and Commitments

There is no clinical pharmacology requested postmarketing requirements (PMRs) or postmarketing commitments (PMCs).

Signatures:

Edwin Chiu Yuen Chow, PhD
Reviewer
Division of Clinical Pharmacology V

Jeanne Fourie Zirkelbach, PhD
Team Leader
Division of Clinical Pharmacology V

Jiang Liu, PhD
Team Leader
Division of Pharmacometrics
Cc: OHOP: RPM - **N Fesenko**; MTL - **M Donoghue**; MO - **M Horiba**
DCP-V Deputy DD - **B Booth**; DD - **A Rahman**

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Refer to package insert of GEMZAR®.

2.2 Dosing and Therapeutic Individualization

The applicant did not propose an indication or a new dosing regimen for pediatrics.

2.2.1 General dosing

This section is not applicable for this NDA.

2.2.2 Therapeutic individualization

This section is not applicable for this NDA.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

Only relevant clinical pharmacology sections are included. The Applicant's proposed labeling change are in **BLUE** and modifications are made by the Agency in **RED**.

2 DOSAGE AND ADMINISTRATION

2.1 Ovarian Cancer

Recommended Dose and Schedule

The recommended dose of INFUGEM is 1000 mg/m² as an intravenous infusion over 30 minutes on Days 1 and 8 of each 21-day cycle, in combination with carboplatin AUC 4 intravenously after INFUGEM administration on Day 1 of each 21-day cycle. Select the INFUGEM premixed bag(s) that allow for a variance of up to 5% of the BSA-calculated dose as described in Table 5 [see *Dosage and Administration (2.6)*].

2.2 Breast Cancer

Recommended Dose and Schedule

The recommended dose of INFUGEM is 1250 mg/m² intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle that includes paclitaxel. Paclitaxel should be administered at 175 mg/m² on Day 1 as a 3 hour intravenous infusion before INFUGEM administration. Select the INFUGEM premixed bag(s) that allow for a variance of up to 5% of the BSA-calculated dose as described in Table 5 [see *Dosage and Administration (2.6)*].

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/s/

EDWIN C CHOW
06/20/2018

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JEANNE FOURIE ZIRKELBACH
06/21/2018

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA208313/SDN22
Link to EDR	\\CDSESUB1\evsprod\NDA208313\208313.enx
Submission Date	NDA, 505(b)(2)
Submission Type	<i>Response to Complete Response letter</i>
Brand Name	Infugem
Generic Name	Gemcitabine Hydrochloride
Dosage Form and Strength	Sterile solution for injection with 10 mg/mL strength, fill volumes of 120, 130, 140, 150, 160, 170, 180, 190, 200, (b)(4) 220 mL
Route of Administration	Intravenous infusion
Proposed Indication	<p>Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated:</p> <ul style="list-style-type: none"> • in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy • in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated • in combination with cisplatin for the treatment of non-small cell lung cancer • as a single agent for the treatment of pancreatic cancer
Applicant	Sun Pharmaceuticals Ltd. (SPIL)
Associated IND	
OCP Review Team	<i>Edwin Chiu Yuen Chow, Ph.D. Jeanne Fourie Zirkelbach, Ph.D.</i>

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1. EXECUTIVE SUMMARY

Sun Pharmaceutical Industries Ltd. submitted a response to the FDA Complete Response letter (DARRT on 05/23/2017; ID: 4101806) for Gemcitabine in Sodium Chloride Injection. Specifically, Sun clarified that the introduction of up to 5% deviation from the calculated dose with the Sun formulation would result in gemcitabine exposure changes that are within the bioequivalence margins.

Sun developed new ready-to-use gemcitabine solution packages intended for the same indications as the listed product, Gemzar. The dosing instructions for the Sun drug product requires a combination of different filled volume packages, and the dose may be rounded to the nearest intended dose (“dose banding”) within specified BSA ranges. Thus, this may result in a maximum 5% absolute dose difference as compared to the intended dose.

During the second Pre-NDA meeting for Gemcitabine in Sodium Chloride Injection held on October 31, 2014 (final minutes dated November 5, 2014), FDA recommended that Sun submits a pharmacokinetic model for review to support that dose banding of the Sun drug product would not result in either increased toxicity or compromised efficacy as compared to the listed drug.

On November 24, 2015, the FDA issued a Complete Response letter to Sun with major inspection site and CMC deficiencies. On November 23, 2016, Sun submitted a response to the Complete Response letter with additional population pharmacokinetic model results to support that the 5% deviation in dose would be within the bioequivalence margins for exposure. However, the FDA reissued a Complete Response letter on May 23, 2017, identifying major inspection site deficiencies. In addition, justification was needed to address the potential effects of the inherent approximation of the recommended dose with the Sun drug production the safety and efficacy of gemcitabine.

In the current submission (letter date August 23, 2017), Sun provided a response indicating that the 5% deviation in dose would still be within the bioequivalence margin. During the previous clinical pharmacology review of the original submission (SDN14), the review team determined that a maximum 5% difference in dose with the Sun formulation may not result in clinically significant differences in exposure (See clinical pharmacology review for detail; ID: 4148463; 10/04/2017).

Sponsor’s Questions and FDA Response Submitted in the Current Submission

- 1. Because the introduction of up to 5% deviation from the calculated dose is expected to result in exposure to gemcitabine that is within the accepted bioequivalence bounds, safety and efficacy would not be affected. Does the Division agree? If not, SPIL wishes to discuss what other information should be included in the forthcoming Complete Response.*

FDA Response: FDA agrees that up to a 5% deviation of the administered dose from the calculated dose appears unlikely to affect the safety and efficacy of gemcitabine.

The FDA response was conveyed to sponsor through preliminary meeting minutes. The sponsor subsequently withdrew the meeting request. No further actions needed from a Clinical Pharmacology perspective. The current submission is approvable from a Clinical Pharmacology perspective.

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/s/

EDWIN C CHOW
11/06/2017

JEANNE FOURIE ZIRKELBACH
11/16/2017

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA208313/SDN1
Link to EDR	\\CDSESUB1\evsprod\NDA208313\208313.enx
Submission Date	NDA
Submission Type	<i>Standard Review</i>
Brand Name	Infugem
Generic Name	Gemcitabine Hydrochloride
Dosage Form and Strength	Sterile solution for injection with 10 mg/mL strength, fill volumes of 120, 130, 140, 150, 160, 170, 180, 190, 200, (b) (4) 220 mL
Route of Administration	Intravenous infusion
Proposed Indication	<p>Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated:</p> <ul style="list-style-type: none">• in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy• in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated• in combination with cisplatin for the treatment of non-small cell lung cancer• as a single agent for the treatment of pancreatic cancer
Applicant	Sun Pharmaceuticals Ltd. (SPIL)
Associated IND	
OCP Review Team	<i>Edwin Chiu Yuen Chow, Ph.D.</i> <i>Jeanne Fourie Zirkelbach, Ph.D.</i>

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1. EXECUTIVE SUMMARY3

1. EXECUTIVE SUMMARY

In accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Sun Pharmaceuticals Ltd. submitted an original New Drug Application (NDA 208313/S-0000) for Infugem (Gemcitabine Hydrochloride for Injection). Sun Pharmaceuticals Ltd. proposed that Infugem has the same active ingredient, route of administration (intravenous infusion), and indications as the listed drug product, Gemcitabine HCl for injection (Gemzar®).

Unlike the listed product, Gemzar®, which is formulated as a lyophilized powder, Sun Pharmaceutical Industries Ltd. developed a ready-to-use formulation drug product package with 10 available volume presentations, (fill volumes of 120, 130, 140, 150, 160, 170, 180, 190, 200, (b) (4) and 220 mL), which are already dissolved in 0.9% saline solution. The intend of this new drug product package presentation is to provide the intended 1000 mg/m² dose for body surface areas (BSAs) of 1.2 to 2.6 m² (or higher if needed) with one or two packages for convenience. For this same range of BSAs, the intended 1250 mg/m² dose can be achieved within ± 5%. Thus, some rounding to the nearest intended dose may occur (“dose banding”) within specified BSA ranges. In order words, patients with certain BSA range may receive Infugem with a maximum of 5% absolute dose difference as compared to the intended dose.

Sun Pharmaceutical Industries Ltd. has submitted population pharmacokinetic analyses, supporting that a 5% difference in dose may not affect the overall exposure and clinical outcome in the general population. However, FDA did not review the data as the pharmacokinetic parameters used in the model were not from data generated by Sun Pharmaceutical Industries Ltd.

After review of PK data from the listed product and published literature, FDA determined that the proposed formulation that requires the dose to be rounded to the nearest intended dose, resulting in a maximum of 5% difference in dose, may not result in clinically significant differences in exposure. This is based on the fact that gemcitabine pharmacokinetics is linear¹, and the variability in clearance is high^{2,3,4,5,6}. Thus, a maximum of 5% difference in gemcitabine dose will not lead to clinically meaningful changes in gemcitabine exposure. gemcitabine.

¹ FDA drug product label, Gemzar®, Revised: 6/2014,

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020509s0751bl.pdf

² Jiang X, Galettis P, Links M, Mitchell PL, and McLachlan AJ (2008) Population pharmacokinetics of gemcitabine and its metabolite in patients with cancer: effect of oxaliplatin and infusion rate. *Br J Clin Pharmacol* **65**:326-333.

³ Joerger M, Huitema AD, Koeberle D, Rosing H, Beijnen JH, Hitz F, Cerny T, Schellens JH, and Gillissen S (2014) Safety and pharmacology of gemcitabine and capecitabine in patients with advanced pancreatico-biliary cancer and hepatic dysfunction. *Cancer Chemother Pharmacol* **73**:113-124.

⁴ Nieto Y, Aldaz A, Rifon J, Perez-Calvo J, Zafra A, Zufia L, Viudez A, Viteri S, Aramendia JM, Aristu J, Centeno C, Moreno M, Sayar O, and Hernandez M (2007) Phase I and pharmacokinetic study of gemcitabine administered at fixed-dose rate, combined with docetaxel/melphalan/carboplatin, with autologous hematopoietic progenitor-cell support, in patients with advanced refractory tumors. *Biol Blood Marrow Transplant* **13**:1324-1337.

⁵ Ramon-Lopez A, Escudero-Ortiz V, Duart-Duart MJ, Perez-Ruixo JJ, and Valenzuela B (2012) [Population pharmacokinetics of gemcitabine applied to personalize the dosage used in cancer patients]. *Farm Hosp* **36**:194-206.

⁶ Sugiyama E, Kaniwa N, Kim SR, Hasegawa R, Saito Y, Ueno H, Okusaka T, Ikeda M, Morizane C, Kondo S, Yamamoto N, Tamura T, Furuse J, Ishii H, Yoshida T, Saijo N, and Sawada J (2010) Population pharmacokinetics of gemcitabine and its metabolite in Japanese cancer patients: impact of genetic polymorphisms. *Clin Pharmacokinet* **49**:549-558.

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/s/

EDWIN C CHOW
09/05/2017

JEANNE FOURIE ZIRKELBACH
10/04/2017

Clinical Pharmacology NDA Review-Memorandum

NDA	208,313/0
Product Name	Gemcitabine Hydrochloride
Submission Date	3/29/2015
Submission Type; Code	505 (b)(2)
PDUFA Due Date	11/6/2015
Proposed Dosage Form / Strength	Single ^{(b)(4)} infusion bags 1200 mg/120 mL, 1300 mg/130 mL, 1400 mg/140 mL, 1500 mg/150 mL, 1600 mg/160 mL, 1700 mg/170 mL, 1800 mg/180 mL, 1900 mg/190 mL, 2000 mg/200 mL, and 2200 mg/220 mL
Proposed Dosing Regimen	Intravenous Infusion over 30 minutes
Proposed Indication	The same as Gemzar®
Applicant	Sun Pharmaceutical Industries, Ltd.
OCP Reviewer	Jun Yang, Ph.D.
OCP Team Leader	Hong Zhao, Ph.D.
Clinical Division	Division of Oncology Products 2 (DOP2)

Sun Pharmaceutical Industries submitted a NDA for "ready-to-infuse" formulation of Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL under Section 505(b)(2). Gemzar (Gemcitabine Hydrochloride) is the Reference Listed Drug (NDA 20,509; approved in 1996 for 200 mg/vial and 1 g/vial). The proposed indication, dose, route, and duration of administration for Sun Pharmaceutical product are the same as those of Gemzar and the approval will be primarily based on publicly available information for Gemzar.

The primary differences in composition of the solutions to be administered as intravenous infusion between the two products are the presence of mannitol and sodium acetate in the reference listed drug, but not in Sun's product. In the current NDA submission, Sun Pharmaceutical Industries requests a waiver of *in vivo* bioequivalence (BE) studies between the proposed product and Gemzar. Sun Pharmaceutical Industries has not conducted or sponsored any clinical pharmacokinetic or BE study to support this NDA. Thus, a clinical pharmacology review is not warranted and there are no clinical pharmacology issues if the applicant's biowaiver request will be granted (See detail in ONDQA review).

Signatures:

Jun Yang, Ph.D. Clinical Pharmacology Reviewer Division of Clinical Pharmacology V	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V
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/s/

JUN YANG
10/21/2015

HONG ZHAO
10/21/2015
I concur.