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RESEARCH**

APPLICATION NUMBER:

208313Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	208313
Priority or Standard	Standard
Submit Date(s)	February 16, 2018
Received Date(s)	February 16, 2018
PDUFA Goal Date	August 16, 2018
Division/Office	DOP2 / OHOP
Reviewer Name	Naomi Horiba
Team Leader	Martha Donoghue
Established Name	Gemcitabine hydrochloride in sodium chloride injection
Trade Name	Infugem
Applicant	Sun Pharmaceutical Industries, Ltd.
Formulation(s)	solution for injection in single-dose premixed infusion containing 10 mg/mL of gemcitabine in 0.9% sodium chloride
Dosing Regimen	Varies by indication
Applicant Proposed Indication(s)/Population(s)	<ol style="list-style-type: none"> 1. In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy 2. 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 3. In combination with cisplatin for the treatment of non-small cell lung cancer 4. As a single agent for the treatment of pancreatic cancer
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Same as for applicant proposed indications, with instructions in Section 2 for use of another gemcitabine formulation for patients who require a dose less than 1150 mg

Executive Summary

NDA 208313 is a 505(b)(2) submission for Infugem (gemcitabine in sodium chloride injection available in 10 sizes of single-dose pre-filled bags at a concentration of 10 mg/mL). This submission references NDA 020509 for Gemzar (gemcitabine for injection) originally approved on May 15, 1996 and also relies on published literature to support Sun Pharmaceutical Industries' (Sun's) dose-banding approach in which doses are rounded to within 5% of the calculated dose based on body surface area in order to accommodate the finite number of doses that are achievable with the pre-filled bags. The primary review issue in this NDA was whether a 5% absolute difference between the gemcitabine dose calculated based upon body surface area and the dose administered using Infugem prefilled bags using the dose-banding approach would result in a clinically relevant change in the clinical efficacy and safety of gemcitabine for

Infugem. Based on review of published literature provided by Sun, the clinical pharmacology review team determined that the dose-banding approach would not result in clinically relevant changes in gemcitabine exposure and thus would not impact the clinical efficacy and safety of Infugem in the indicated populations, and the clinical review team agrees with this assessment. See the clinical pharmacology review for additional details.

The Package Insert and Instructions for Use include recommendations for bag size selection based on the body surface area (BSA) calculated dose. The clinical review team recommends approval of NDA 208313 for Infugem.

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1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 208313 for Infugem was submitted in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and relies on FDA's findings of safety and efficacy for the listed drug, Gemzar (gemcitabine for injection; NDA 020509, held by Eli Lilly and Company) and published literature to support a dose-banding approach for Infugem. The proposed indications for Infugem, listed below, are identical to the approved indications for Gemzar:

1. In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy
2. 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
3. In combination with cisplatin for the treatment of non-small cell lung cancer
4. As a single agent for the treatment of pancreatic cancer

Aside from the published literature provided to support the dose-banding approach, which was reviewed by the clinical pharmacology review team, no new clinical data was submitted to NDA 020509. The clinical review team recommends approval of this application.

1.2 Risk Benefit Assessment

Please refer to the clinical review of NDA 020509 and the approved package insert for Gemzar.

2. Product Information and Regulatory Background

2.1 Product Information

Trade Name: Infugem

Established Name: Gemcitabine in sodium chloride injection

Applicant: Sun Pharmaceutical Industries Ltd.
Sun House, Plot No. 201 B/1, Sun Pharmaceutical Industries Ltd.
Mumbai, Maharashtra
INDIA 400063

Salamandra, LLC
One Bethesda Center
4800 Hampden Lane, Suite 900
Bethesda, Maryland 20814-2998

Drug Class: Nucleoside antimetabolite

Proposed Indications:

1. In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy
2. 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
3. In combination with cisplatin for the treatment of non-small cell lung cancer
4. As a single agent for the treatment of pancreatic cancer

Proposed Dosage and Administration:

The proposed indication, dose, route, and duration of administration of Infugem will be the same as those of the reference product, Gemzar. As with Gemzar, the product is intended solely for administration by intravenous injection over 30 minutes. At the fixed concentration of 10 mg/mL, the product requires no dilution and is ready to use. The recommended dosages are listed below by indication:

1. Ovarian Cancer: 1000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle
2. Breast Cancer: 1250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle
3. Non-Small Cell Lung Cancer: 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
4. Pancreatic Cancer: 1000 mg/m² over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle

Dosage Forms and Strengths:

Sun proposes 10 presentations of the product at a concentration of 10 mg/mL: 1200 mg (120 mL), 1300 mg (130 mL), 1400mg (140 mL), 1500 mg (150 mL), 1600 mg (160mL), 1700 mg (170 mL), 1800 mg (180 mL), 1900 mg (190 mL), 2000 mg (200 mL), and 2200 mg (220 mL).

Contraindications:

As for Gemzar, gemcitabine in sodium chloride injection is contraindicated in patients with a known hypersensitivity to gemcitabine.

Warnings and Precautions:

As for Gemzar, warnings and precautions are: schedule-dependent toxicity (infusion time beyond 60 minutes), myelosuppression (neutropenia, anemia, thrombocytopenia), pulmonary toxicity and respiratory failure, hemolytic uremic syndrome, hepatic toxicity, embryofetal toxicity, exacerbation of radiation therapy toxicity, capillary leak syndrome, posterior reversible encephalopathy syndrome.

Adverse Reactions:

As for Gemzar, the most common ($\geq 20\%$) adverse reactions of single-agent gemcitabine hydrochloride are: nausea/vomiting, anemia, increased ALT, increased AST, neutropenia,

increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema.

Postmarketing Experience:

For consistency with other gemcitabine labels and based on postmarketing experience, pseudocellulitis was added to the Infugem label.

Reviewer Comment:

The Applicant's product, Infugem, differs from Gemzar in that the Applicant's product requires no prior dilution and is ready to use in pre-filled bags. Because the dose increments of the presentation differ by 100 mg from 1200 mg to 2000 mg, and by 200 mg from 2000 mg to 2200 mg, dose-banding will be necessary. With the available presentations, rounding will not result in a change of more than 5% of the total calculated dose for any patient whose BSA-calculated dose is greater than or equal to 1150 mg.

Dose banding of cytotoxic agents within 10% of the prescribed dose is a strategy endorsed by the Hematology/ Oncology Pharmacy Association and the National Comprehensive Cancer Network.^{1,2} It is a practice that the National Institute for Health and Care Excellence (NICE) in collaboration with the National Health Service (NHS) in the United Kingdom (UK) supports, and for which dose banding tables have been published for 19 commonly used drugs, including gemcitabine. Of note, variance between the prescribed and banded doses of drugs with a concentration of 100 mg/mL, such as gemcitabine, is no more than 6%.³ NHS has also published product specifications to support the production and supply of ready-made chemotherapy medications including gemcitabine, and it should be noted that gemcitabine pre-filled bags are marketed in the UK by Ranbaxy (UK) Limited, a Sun Pharmaceutical Company in Europe.⁴ While a similar document has not been published in the US, it is generally accepted that a difference within 5% will not affect safety or efficacy.

Dose banding of chemotherapy is increasingly being used in oncology practices and infusion centers to improve the efficiency of outpatient clinics. Various institutions have implemented dose-rounding policies, which generally allow dose rounding within 5%–10% of the ordered dose for biologic and cytotoxic anticancer treatments.^{1,5,6,7} The dose-banding approach for Infugem was discussed with a council of medical advisors, and was unanimously endorsed by the council members.

2.2 Availability of Proposed Active Ingredient in the United States

Gemcitabine for injection is marketed in the U.S. as Gemzar and under multiple ANDA's.

2.3 Summary of Pre-submission Regulatory Activity Related to Submission

Date	Event
December 16, 2011	Pre-submission NDA meeting
October 31, 2014	Pre-submission NDA meeting
March 30, 2015	Sun Pharmaceutical Industries, Ltd. submitted NDA 208313

Date	Event
November 24, 2015	Complete Response due to manufacturing facilities deficiencies
November 23, 2016	Class 2 resubmission
May 23, 2017	Complete Response due to manufacturing facilities deficiencies
September 27, 2017	Pre-submission NDA meeting
February 16, 2018	Class 2 resubmission

2.4 Pediatric Waiver

The original NDA submission (submitted on March 30, 2015) included a request for a full waiver of the requirement for conducting pediatric studies under the Pediatric Research Equity Act. On September 9, 2015, the Pediatric Review Committee (PeRC) granted this waiver because pediatric studies would be impossible or highly impractical for the indications being sought.

2.5 Other Relevant Background Information

Refer to NDA 020509.

3. Significant Efficacy/Safety Issues Related to Other Review Disciplines

The presentation of pre-filled bags necessitates the use of a dose-banding approach with rounding to within 5% of the calculated dose based on body surface area. The primary review issue was to determine whether a 5% absolute difference in dose due to dose-banding would result in a clinically relevant change in the clinical efficacy and safety of gemcitabine for Infugem. Based on review of published literature, it was determined that the dose-banding approach would not result in clinically relevant changes in gemcitabine exposure and thus would not impact the clinical efficacy and safety of Infugem in the indicated populations. Please see the clinical pharmacology review for additional details.

There were no other significant clinical efficacy or safety issues identified during review of this application. Please refer to the FDA reviews for NDA 020509 and other disciplines' reviews for this application.

4. Sources of Clinical Data

Refer to NDA 020509.

5. Review of Efficacy

Refer to NDA 020509.

6. Review of Safety

Refer to NDA 020509.

7. Labeling Recommendations

Section 2.6 (“Infusion Bag Selection and Administration”) was added to explain the selection process for Infugem bags according to BSA range, including suggested combinations if more than one bag is needed. Table 5 describes selection of bags for a gemcitabine dose of 1000 mg/m² and Table 6 for a gemcitabine dose of 1250 mg/m². For each indication in Section 2, a reference to the appropriate table was included in the labeling (e.g., “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)*]”).

“Pseudocellulitis” was added to Section 6.2 of the Infugem label based on post-marketing experience with other formulations of gemcitabine.

Instructions for Use were edited for clarity and readability.

8. Appendices

8.1 Literature Review/References

Refer to NDA 020509 and the footnotes listed at the end of this review.

8.2 Advisory Committee Meeting

Not applicable. There were no review issues identified during review of this application that required advice from external stakeholders or subject matter experts.

¹ Fahrenbruch R, Kintzel P, Bott AM, et al: Dose Rounding of Biologic and Cytotoxic Anticancer Agents A Position Statement of the Hematology/Oncology Pharmacy Association. *J Oncol Pract.*;14(3):e130-e136, 2018

² “Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association”. ©2017 [accessed 2018 Apr 03]
<https://www.nccn.org/professionals/OrderTemplates/PDF/HOPA.pdf>.

³ “National dose banding tables” and “National dose banding table – single container 100 mg/mL” [accessed 2018 Apr 03]. <https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/> and <https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2017/01/national-tables-100-mgml-v3.pdf>.

⁴ “Gemcitabine 10 mg/mL, solution for infusion” label on the electronic Medicines Compendium, UK. 27 Jun 2017. [accessed 2018 Apr 03]. https://www.medicines.org.uk/emc/product/7298#PHARMACEUTICAL_PARTS.

⁵ Patel S, Le A: Rounding rituximab dose to nearest vial size. *J Oncol Pharm Pract* 19(3):218-222, 2013

⁶ Francis SM, Heyliger A, Miyares MA, et al: Potential cost savings associated with dose rounding antineoplastic monoclonal agents. *J Oncol Pharm Pract* 21(4):280-284, 2015.

⁷ Dooley MJ, Singh S, Michael M: Implications of dose rounding of chemotherapy to the nearest vial size. *Support Care Cancer* 12(9): 653-6, 2004.

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/s/

MARGIT N HORIBA
07/12/2018

MARTHA B DONOGHUE
07/12/2018

Division Director Summary Review for Regulatory Action

Date	May 22, 2017
From	Joseph E. Gootenberg, MD
Subject	Deputy Division Director Summary Review
NDA/BLA #	208313
Type of Application	505(b)(2) – Complete Response resubmission
Applicant	Sun Pharmaceuticals Ltd. (SPIL)
Date of Submission	23 November-2016
PDUFA Goal Date	23 May 2017
Proprietary Name / Non-Proprietary Name	INFUGEM, gemcitabine injection (approved by DMEPA 14-Feb-17)
Dosage Form(s) / Strength(s)	Injection 10 mg/mL, fill volumes of 120, 130, 140, 150,160, 170, 180, 190, 200, (b)(4) 220 mL
Route of Administration	Injection
Proposed Indications	<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
Action	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
CDTL Review	Olen Stephens, PhD, dated May 16, 2017
Medical Officer Review	Margit Horiba, MD, MPH; dated May 19, 2017
Pharmacology Toxicology Review	Alexander Putnam, PhD; dated Oct 14, 2015
Drug Product	Nina Ni, PhD; dated Oct 13, 2015
Manufacturing Process	Dhanalakshmi Kasi, PhD; dated Mar 30, 2017
Manufacturing Facilities	Thuy Nguyen, PhD; dated May 10, 2017
Clinical Pharmacology Review	Jun Yang, PhD; dated Oct 21, 2015
OPDP	Nazia Fatima, PharmD; dated Sept 6, 2017
OSE/DMEPA	Otto Townsend, PharmD; dated Apr 17, 2017

1. Introduction

This New Drug Application, NDA 208313, for INFUGEM (Gemcitabine Hydrochloride Injection) was submitted by Sun Pharmaceutical Industries Ltd under the provisions of section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (gemcitabine for injection) manufactured by Eli Lilly and Company. The listed drug, Gemzar, was approved on May 15, 1996 under NDA 20509 and is marketed as a lyophilized powder available in sterile single-use vials containing 200 mg or 1000 mg gemcitabine. Gemzar is administered by reconstituting and diluting the lyophilized powder with 0.9% NaCl. Sun Pharmaceutical Industries Ltd's proposed presentation is a 10 mg/mL solution, available in 100 mL increments to deliver 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, (b) (4) and 2200 mg gemcitabine in infusion bags. The formulation contains only the active ingredient gemcitabine hydrochloride, sodium chloride (0.9%), water for injection, sodium hydroxide and hydrochloric acid for pH adjustment, (b) (4) such that the administered solution is nearly identical to that associated with the listed drug. In addition to the NDA for Gemzar, this active ingredient (gemcitabine) is approved for marketing under a 505(b)(2) NDA (Hospira) and under several ANDAs.

This application is limited to chemistry, manufacturing, and controls information, and proposed product labeling as the application relies on FDA's findings of safety and effectiveness with the listed drug, Gemzar, for non-clinical, clinical pharmacology, and clinical safety and efficacy data. The proposed indication, recommended dose, and route and duration of administration of Sun Pharmaceutical Industries Ltd's INFUGEM are the same as the listed drug, Gemzar. A waiver of bioequivalence studies is granted and this decision will be transmitted to Sun Pharmaceutical Industries Ltd when approval is possible.

However, an inspection in September 2014 of one of the manufacturing facilities, Sun Pharmaceutical Industries Ltd Halol site (FEI 3002809586), conducted to ensure compliance with GMPs and implementation of actions to address items on previous FDA-483s, identified significant deviations from GMPs. An FDA-483 with 23 observations was issued at the end of the inspection and a February 24, 2015 "Official Action Indicated" classification ensued with the Office of Compliance issuing a Warning Letter for this site. The site was re-inspected from November 17, 2016 to December 1, 2016 and the initial classification was OAI. A regulatory meeting was held between OC/OMQ and the firm on May 9, 2017 to discuss the outstanding cGMP compliance issues. The facility's compliance status remained OAI after the regulatory meeting.

This has resulted in an OPQ overall recommendation to withhold approval

2. Background

Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated (1) in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy; (2) 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; (3) in

combination with cisplatin for the treatment of non-small cell lung cancer; and (4) as a single agent for the treatment of pancreatic cancer

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is a nucleoside analog of deoxycytidine in which the hydrogen atoms on the 2' carbon of deoxycytidine are replaced by fluorine atoms. It is a “pro-drug” metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potential). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

The current application relies on the Agency’s determination of safety and efficacy for the gemcitabine lyophilized powder for injection (Gemzar), which was approved for marketing under NDA 20509 on May 15, 1996.

Sun Pharmaceutical Industries Ltd, its research arm Sun Pharma Advanced Research Company Ltd. and its US Agent Salamandra, LLC held two pre-NDA meetings with FDA before the submission of NDA 208313. In December 2011, a Type B Pre-NDA meeting under Pre-NDA 203652 was held between Sun Pharma Advanced Research Company Ltd and FDA to discuss CMC, Non-clinical Pharmacology and Toxicology, Biopharmaceutics and Clinical Pharmacology, and Clinical issues regarding a proposed 505(b)(2) submission for a “ready-to-infuse” formulation of Gemcitabine Hydrochloride Injection. At that meeting FDA pointed out a number of deficiencies that might hinder approval of the proposed product and discussion was held regarding mitigating impediments to the proposed path to approval. In October 2014, a Type C Pre-NDA meeting was held under Pre-NDA 203652 between Sun Pharma Advanced Research Company Ltd and FDA to clarify remaining CMC, Non-clinical Pharmacology and Toxicology, Biopharmaceutics and Clinical Pharmacology, and Clinical issues and to discuss approaches to mitigate potential medication errors that could arise from the use of “ready-to-infuse” fixed dose bags. At this meeting Sun Pharma Advanced Research Company Ltd proposed to undertake a risk assessment for such errors, and to include a full report of the evaluation in the NDA. As a result of this assessment, and with FDA advice, Sun Pharma Advanced Research Company Ltd has completed a Human Factors Study, the results of which are discussed in section 10, “Other Relevant Regulatory Issues” below.

3. Product Quality

I concur with the conclusions reached by the CDTL and Product Quality Lead Olen Stevens that a Complete Response action is recommended due to a “withhold” recommendation from the Office of Process and Facilities reviewer, Thuy Nguyen. The drug product manufacturing, packaging, release, and stability testing site, Sun Pharmaceuticals Industries, Ltd Halol site (FEI 3002809586) received an OAI after an inspection September 8-16, 2014 resulted in the issuance of a FDA-483 with 23 observations and in a Warning Letter issued to the firm on December 17, 2015. The firm was re-inspected from November 17, 2016 to December 1, 2016

and the initial classification was OAI. A regulatory meeting was held between OC/OMQ and the firm on May 9, 2017 to discuss the outstanding cGMP compliance issue after which the facility's compliance status remained OAI. Satisfactory resolution of the inspectional deficiencies is required before this NDA can be approved.

The following items were reviewed by Product Quality and found to be adequate:

- (b) (4) Gemcitabine hydrochloride, USP
- The formulation of the Drug Product, including a (b) (4) % overfill
- (b) (4)
- Drug Product impurity levels
- Container closure system compatibility with the Drug Product
- The presentation in an aluminum overlapping pouch
- Drug Product stability, including long-term stability, under real-time and accelerated conditions
- The proposed expiratory dating period of 24 months
- Labelling of the product's strength consistent with FDA salt nomenclature policy

In addition, one manufacturing process deficiency (b) (4) was identified during the prior submission OPQ review. This issue was satisfactorily mitigated in the current re-submission.

4. Nonclinical Pharmacology/Toxicology

This application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). No nonclinical pharmacology/toxicology data were submitted in the Application. I concur with the conclusions of the Nonclinical Pharmacology/Toxicology reviewer that a nonclinical pharmacology/toxicology review is not warranted and that there are no nonclinical pharmacology/toxicology issues that would preclude approval of this product

5. Clinical Pharmacology/Biopharmaceutics

This application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). No clinical pharmacology data were submitted in the Application. Sun Pharmaceutical Industries Ltd has requested a biowaiver. The Division of Biopharmaceutics evaluated the overall information supporting the biowaiver request and found it to be acceptable. Therefore, Sun Pharmaceutical Industries Ltd's request for a waiver of the in vivo bioequivalence study for the proposed product is granted and this decision will be transmitted to Sun Pharmaceutical Industries Ltd when approval is possible. I concur with the conclusions of the Clinical Pharmacology reviewer that a clinical pharmacology review is not warranted and that there are no direct clinical pharmacology issues that would preclude approval of this product. However, Clinical Pharmacology will be involved in the additional labeling review that will ensue upon re-submission of this NDA.

6. Clinical/Statistical-Efficacy

The application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). No Clinical/Statistical-Efficacy data were submitted in the Application. I concur with the conclusions of the clinical reviewer that no clinical issues were identified that

would preclude approval, contingent upon agreement upon labeling. In particular, the labeling issue of “dose-banding” that may result in a change of up to 5% from the total dose calculated using the “recommended dose” will be a review issue when the NDA is resubmitted. The Clinical Reviewer notes the manufacturing site deficiencies identified by the Product Quality review staff, and provides a recommendation not to approve based on those deficiencies.

7. Safety

The application relies on FDA’s previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). No safety data were submitted in the Application. I concur with the conclusions of the clinical reviewer that no clinical issues, including safety issues, were identified that would preclude approval, contingent upon agreement upon labeling.

The Division of Medication Errors Prevention and Analysis (DMEPA) reviewed the Human Factors validation Study, as well as container labels, overwrap and carton labeling, and other labeling for areas of vulnerability that could lead to medication errors. The DMEPA review is discussed in Section 10, “Other Relevant Regulatory Issues” below.

8. Advisory Committee Meeting

This 505(b)(2) application was not referred to an advisory committee because it has the same active ingredient, same route of administration, and same proposed indications as the listed drug and relies on FDA’s finding of safety and efficacy for the listed drug, Gemzar (gemcitabine) for Injection.

9. Pediatrics

In the original NDA application, Sun Pharmaceutical Industries Ltd submitted a request for waiver of pediatric assessment requirements for all pediatric age groups, in accordance with section 505B (a)(4)(A)(iii) of the FD&C Act. No agreed initial Pediatric Study Plan was included in the NDA at that time; however, as all requested indications are on the “automatic” full waiver list no RTF action was taken. This request was reviewed by PeRC on September 9, 2015. Because studies are impossible or highly impracticable for the indications of ovarian cancer, breast cancer, NSCLC and pancreatic cancer because the diseases/conditions do not exist in children, the PeRC agreed with the clinical review team’s recommendation to grant a full waiver for this product. As a CR is recommended, no action will be taken regarding this request at this time. However, if a resubmission of this NDA is recommended for approval, the request for waiver pediatric assessment requirements would be granted.

10. Other Relevant Regulatory Issues

Human Factors Review

The DMEPA review includes evaluation of the Human Factors validation study report for selection of dose strengths, proposed container labels, proposed carton labeling, proposed Prescribing Information (PI) and proposed Instructions for Use (IFU). In the Pre-NDA meeting held on October 31, 2014, FDA expressed concerns with the number of bag strengths that would be available for user selection and the use of more than one bag to provide a prescribed dose. To address concerns with appropriate bag selection to prevent over dosage or under dosage, SPIL conducted a risk-assessment of the packaging and labeling, and completed

human factors testing to validate that users can select the appropriate product (i.e., strength) when presented with an order for gemcitabine.

During the first review cycle, SPIL submitted the protocol for the human factors study regarding dose selection. DMEPA sent recommendations regarding the protocol to the Applicant in the complete response letter for the first review cycle. In this resubmission, the Applicant addressed DMEPA's recommendations enumerated in the complete response letter, so there were no concerns regarding the study protocol. The validation study results were reviewed by DMEPA in the current review cycle.

There was one task failure in the study, where one pharmacy participant (pharmacy technician) failed to identify the correct bag. During a feedback session, this participant stated that he did not read the IFU, but rounded the dose up to 1,600 mg based on his own knowledge.

On a second and third trial this participant was able to perform the task correctly. In the study report, the Applicant concluded that no changes to the IFU were required, and that there is no way to control whether users actually read the IFU.

During internal labeling review, DMEPA provided additional recommendations to further mitigate the residual risk of the "dose banding" proposal. These edits have not been sent to the Applicant, and will be retained for future resubmissions.

11. Labeling

FDA performed a substantial but partially incomplete labeling review of the Applicant's proposed prescribing information this cycle due to the "withhold" recommendation from OPQ and subsequent Complete Response.

The sections covered in the labeling review included

HIGHLIGHTS

INDICATIONS AND USAGE

DOSAGE FORMS AND STRENGTHS

CONTRAINDICATIONS

WARNINGS AND PRECAUTIONS

ADVERSE REACTIONS

USE IN SPECIFIC POPULATIONS

OVERDOSAGE

DESCRIPTION

NONCLINICAL TOXICOLOGY

CLINICAL STUDIES

HOW SUPPLIED/STORAGE AND HANDLING

PATIENT COUNSELING INFORMATION

The review of the DOSAGE AND ADMINISTRATION section was incomplete due to issues regarding the "dose banding" strategy proposed to allow the use of container configurations that are only available in 100 mg increments of gemcitabine over a range from 1500 mg gemcitabine to 2200 mg gemcitabine.

The planned use of “dose-banding” involves rounding the prescribed dose calculated using the “recommended dosing to a dose that can be administered using one or a combination of the 10 available bag strengths. This dose banding strategy departs from the dose calculation used in the listed product, GEMZAR, which prescribes a defined the recommended dose of gemcitabine based on the patient’s BSA. The issue of dose banding was referred to CDER’s Labeling Coordinating Committee via Ann Marie Trentacosti to set high level expectations and to avoid setting an incorrect precedent for an anticipated entire class of products that are presented as pre-filled infusion bags that may need a dose banding approach. The Coordinating Committee deferred to the clinical division to determine if there is sufficient clinical data to support dose ranges and concluded this is not a labeling issue.

The division initiated a preliminary consult the Office of Regulatory Policy to identify any potential legal implications of introducing a “dose banding” approach for a 505(b)(2) application that relies on the clinical data from an innovator product with defined dosing levels. A finalized response is not available at the time of the complete response action date.

Upon resubmission, this dose banding issue will be revisited. In the complete response letter, the Applicant will be asked to provide justification that the dose banding instructions in Section 2 of the prescribing instructions, which would result in an inherent approximation of the recommended dose, do not affect the safety and efficacy of the drug in its labeled conditions of use.

12. Recommendations

- **Recommended Regulatory Action**

This product is nearly identical to the listed product, Gemzar, when the listed product is reconstituted and diluted for administration. No new clinical or nonclinical data were provided with this submission, as no clinical or nonclinical studies were conducted for this 505(b)(2) application. However, a complete response to the application is recommended based on deficiencies related to inadequate facilities inspections identified by Quality review staff, When the NDA is resubmitted, the applicant’s dose banding strategy will need to be revisited during review and discussed with ORP to confirm there are no legal impediments to relying on data for the listed drug, which prescribes a precise dose.

- **Risk Benefit Assessment**

The application relies on FDA’s previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). There are no new efficacy or safety concerns that would preclude approval of this product. However, a complete response will be issued based on OPQ’s overall recommendation to withhold approval due to facility issues. In addition, during the next review cycle, the Applicant’s dose banding proposal will be evaluated as a labeling issue.

Joseph E.

Gootenberg -S

Joseph E. Gootenberg, MD

Deputy Director, Division of Oncology Products 2

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JOSEPH E GOOTENBERG
05/23/2017

CLINICAL REVIEW OF COMPLETE RESPONSE

Application Type	NDA 505(b)(2)
Application Number(s)	208313
Priority or Standard	Standard
Received Date(s)	11/23/16
PDUFA Goal Date	5/23/17
Division/Office	DOP2 / OHOP
Reviewer Name(s)	M. Naomi Horiba
Team Leader	Steven Lemery
Established Name	Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection
Trade Name	Infugem
Applicant	Sun Pharmaceutical Industries, Ltd.
Formulation(s)	Injectable solution in pre-filled bags 10mg/mL
Dosing Regimen	varies by indication
Applicant Proposed Indication(s)/Population(s)	<ol style="list-style-type: none"> 1. In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy. 2. 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. 3. In combination with cisplatin for the treatment of non-small cell lung cancer. 4. As a single agent for the treatment of pancreatic cancer.
Recommendation on Regulatory Action	Non-approval
Recommended Indication(s)/Population(s)	Same as for Applicant Proposed Indication(s) and only in a population whose dose rounded to the nearest 100 mg falls between 1200 mg and 2200 mg).

REVIEW

NDA 208313 is a 505(b)(2) referencing Gemzar NDA 020509 lyophilized powder for injection solution originally approved on 05/15/1996. The original NDA was originally submitted on 3/29/15. The NDA was not approved due to facility deficiencies identified by quality review staff. No new clinical data were provided with this complete response, as no clinical studies were done. Please see the review from Division of Medication Error Prevention and Analysis (DMEPA) regarding the human factor study submitted with the complete response. The clinical review recommendation is again not to approve the application based on deficiencies identified by quality review staff (i.e., related to facilities). No new clinical issues were identified in the complete response; however, that would preclude approval, contingent upon agreement upon labeling.

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/s/

MARGIT N HORIBA
05/19/2017

STEVEN J LEMERY
05/19/2017

Division Director Summary Review for Regulatory Action

Date	November 24, 2015
From	Joseph E. Gootenberg, MD
Subject	Division Director Summary Review
NDA/BLA #	208313/0
Type of Application	505(b)(2)
Applicant	Sun Pharmaceutical Industries Ltd.
Date of Submission	March 30, 2015
PDUFA Goal Date	January 30, 2016
Proposed Proprietary Name	Gemcitabine Hydrochloride in sodium chloride Injection/
Dosage Form(s) / Strength(s)	Injection, 10 mg/mL, fill volumes of 120, 130, 140, 150,160, 170, 180, 190, 200, (b)(4) 220 mL
Applicant Proposed Indication(s)/Population(s)	Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated: <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 • in combination with cisplatin for the treatment of non-small cell lung cancer. • as a single agent for the treatment of pancreatic cancer.
Recommended Action:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	M. Naomi Horiba
Pharmacology Toxicology Review	Alexander Putnam
OPQ Reviews	Nina Ni, Sharon Kelly, Dhanalakshmi Kasi
Microbiology Review	Helen Ngai
Clinical Pharmacology Review	JunYang
CDTL Review	Olen Stephans
Biopharmaceutics	Om Anand
OSE/DMEPA	Otto Townsend
Manufacturing Facilities	Thuy Nguyen

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis

1. Introduction

This New Drug Application, NDA 208-313, for Gemcitabine Hydrochloride in sodium chloride Injection was submitted by Sun Pharmaceutical Industries Ltd under the provisions of section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (gemcitabine for injection) manufactured by Eli Lilly and Company. The listed drug, Gemzar, was approved on May 15, 1996 under NDA 20509 and is marketed as a lyophilized powder available in sterile single-use vials containing 200 mg or 1000 mg gemcitabine. Gemzar is administered by reconstituting and diluting the lyophilized powder with 0.9% NaCl. Sun Pharmaceutical Industries Ltd's proposed presentation is a 10 mg/mL solution, available in 100 mL increments to deliver 1200 mg, 1300 mg, 1400 mg, 1500 mg, 1600 mg, 1700 mg, 1800 mg, 1900 mg, 2000 mg, (b) (4) and 2200 mg gemcitabine in infusion bags. The formulation contains only the active ingredient gemcitabine hydrochloride, sodium chloride (0.9%), water for injection, sodium hydroxide and hydrochloric acid for pH adjustment, (b) (4) such that the administered solution is nearly identical to that associated with the listed drug. In addition to the NDA for Gemzar, this active ingredient (gemcitabine) is approved for marketing under a 505(b)(2) NDA (Hospira) and under several ANDAs.

This application is limited to chemistry, manufacturing, and controls information, and proposed product labeling. A waiver of bioequivalence studies is requested and the application relies on FDA's findings of safety and effectiveness with the listed drug, Gemzar, for non-clinical, clinical pharmacology, and clinical safety and efficacy data. The proposed indication, dose, and route and duration of administration of Sun Pharmaceutical Industries Ltd's Gemcitabine Hydrochloride in sodium chloride Injection are the same as the listed drug, Gemzar.

However, an inspection in September 2014 of one of the manufacturing facilities, Sun Pharmaceutical Industries Ltd Halol site (FEI 3002809586), conducted to ensure compliance with GMPs and implementation of actions to address items on previous FDA-483s, identified significant deviations from GMPs. An FDA-483 with 23 observations was issued at the end of the inspection and a February 24, 2015 "Official Action Indicated" classification ensued. , The Office of Compliance is currently working on issuing a Warning Letter for this site. This has resulted in an OPQ overall recommendation to withhold approval. In addition, one manufacturing process deficiency (b) (4) was identified during OPQ review. A Complete Response letter will be issued requesting resolution of the GMP issues which preclude approval at that facility and mitigation of the manufacturing issues (b) (4).

2. Background

Gemcitabine hydrochloride is a nucleoside metabolic inhibitor indicated (1) in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6

months after completion of platinum-based therapy; (2) 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; (3) in combination with cisplatin for the treatment of non-small cell lung cancer; and (4) as a single agent for the treatment of pancreatic cancer

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is a nucleoside analog of deoxycytidine in which the hydrogen atoms on the 2' carbon of deoxycytidine are replaced by fluorine atoms. It is a “pro-drug” metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potential). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

The current application relies on the Agency’s determination of safety and efficacy for the gemcitabine lyophilized powder for injection (Gemzar), which has been previously approved for marketing under NDA 20509 on May 15, 1996.

Sun Pharmaceutical Industries Ltd, its research arm Sun Pharma Advanced Research Company Ltd. And its US Agent Salamandra, LLC held two pre-NDA meetings with FDA before the submission of NDA 208313. In December 2011, a Type B Pre-NDA meeting under Pre-NDA 203652 was held between Sun Pharma Advanced Research Company Ltd and FDA to discuss CMC, Non-clinical Pharmacology and Toxicology, Biopharmaceutics and Clinical Pharmacology, and Clinical issues regarding a proposed 505(b)(2) submission for a “ready-to-infuse” formulation of Gemcitabine Hydrochloride Injection. At that meeting FDA pointed out a number of deficiencies that might hinder approval of the proposed product and discussion was held regarding mitigating impediments to the proposed path to approval. In October 2011, a Type C Pre-NDA meeting was held under Pre-NDA 203652 between Sun Pharma Advanced Research Company Ltd and FDA to clarify remaining CMC, Non-clinical Pharmacology and Toxicology, Biopharmaceutics and Clinical Pharmacology, and Clinical issues and to discuss approaches to mitigate potential medication errors that could arise from the use of “ready-to-infuse” fixed dose bags. At this meeting Sun Pharma Advanced Research Company Ltd proposed to undertake a risk assessment for such errors, and to include a full report of the evaluation in the NDA. As a result of this assessment, Sun Pharma Advanced Research Company Ltd has proposed to undertake a Human Factors Study.

3. Product Quality

I concur with the conclusions reached by the CDTL and Product Quality Lead Olen Stevens that a Complete Response action is recommended due to a withhold recommendation from the Office of Process and Facilities reviewer, Thuy Nguyen and to a manufacturing deficiency noted by the Manufacturing Process reviewer Dhanalakshmi Kasi. The drug product manufacturing, packaging, release, and stability testing site, Sun Pharmaceuticals Industries, Ltd Halol site (FEI 3002809586) received an initial OAI status and a compliance action is pending. This site was last inspected 8-16-Sep-14, which resulted in an OAI classification based on the issuance of a FDA-483 with 23 observations. The Office of Compliance is currently working on issuing a warning letter for this site. A manufacturing process deficiency (b)(4) will also be sent with the complete response letter. Satisfactory resolution of the inspectional and manufacturing process deficiencies is required before this NDA can be approved.

The following items were reviewed by Product Quality and found to be adequate:

- (b)(4) Gemcitabine hydrochloride, USP
- The formulation of the Drug Product, including a (b)(4) % overfill
- (b)(4)
- Drug Product impurity levels
- Container closure system compatibility with the Drug Product
- The presentation in an aluminum overlapping pouch
- Drug Product stability, including long-term stability, under real-time and accelerated conditions
- The proposed expiratory dating period of 24 months
- Labelling of the product's strength consistent with FDA salt nomenclature policy

4. Nonclinical Pharmacology/Toxicology

This application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). No nonclinical pharmacology/toxicology data were submitted in the Application. I concur with the conclusions of the Nonclinical Pharmacology/Toxicology reviewer that a nonclinical pharmacology/toxicology review is not warranted and that there are no nonclinical pharmacology/toxicology issues that would preclude approval of this product.

5. Clinical Pharmacology

This application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). No clinical pharmacology data were submitted in the Application. Sun Pharmaceutical Industries Ltd has requested a biowaiver. The Division of Biopharmaceutics evaluated the overall information supporting the biowaiver request and found it to be

acceptable. Therefore, Sun Pharmaceutical Industries Ltd's request for a waiver of the in vivo bioequivalence study for the proposed product is granted and this decision will be transmitted to Sun Pharmaceutical Industries Ltd when approval is possible. I concur with the conclusions of the Clinical Pharmacology reviewer that a clinical pharmacology review is not warranted and that there are no clinical pharmacology issues that would preclude approval of this product.

6. Product Quality Microbiology

I concur with the Microbiology reviewer's conclusion that the validation of the (b)(4) process has been deemed adequate and no pending microbiological concerns remain that would preclude approval of this product.

7. Clinical/Statistical-Efficacy

The application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). No Clinical/Statistical-Efficacy data were submitted in the Application. I concur with the conclusions of the clinical reviewer that no clinical issues were identified that would preclude approval, contingent upon agreement upon labeling. In particular, the issue of "dose-rounding" that may result in a change of up to 5% from the total calculated dose has been determined by the Clinical reviewer to be acceptable. The Clinical Reviewer notes the deficiencies identified by the Product Quality review staff, and provides a recommendation not to approve based on those deficiencies.

8. Safety

The application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). No safety data were submitted in the Application. I concur with the conclusions of the clinical reviewer that no clinical issues, including safety issues, were identified that would preclude approval, contingent upon agreement upon labeling.

The Division of Medication Errors Prevention and Analysis (DMEPA) reviewed the proposed Human Factors Study protocol, as well as container labels, overwrap and carton labeling, and other labeling for areas of vulnerability that could lead to medication errors. The following sections paraphrase the DMEPA Reviews.

In the Pre-NDA meeting held on October 31, 2014, FDA expressed concerns with the number of bag strengths that would be available for user selection and the use of more than one bag to provide a prescribed dose. To address concerns with appropriate bag selection to prevent

overdose or underdose, Sun Pharmaceutical Industries Ltd commissioned (b) (4) to conduct a risk-assessment of the packaging and labeling. As a result of that report, Sun Pharmaceutical Industries Ltd plans to complete human factors testing to validate that users can select the appropriate product when presented with an order for gemcitabine. In addition, an “Information for Users” (IFU) document has been developed with the goal of providing detailed instructions for administration of the product. However, the proposed IFU lacks sufficient details and instructions for the user, and FDA will provide recommendations for revisions in a communication to Sun Pharmaceutical Industries Ltd.

FDA evaluation of the summative human factors protocol identified areas that require revision to ensure that the study adequately assesses the safe and effective use of the proposed product by the intended population. Detailed recommendations for revisions of the protocol will be conveyed to Sun Pharmaceutical Industries Ltd before they begin their summative human factor study: Based on the results of the Human Factors Study; FDA may have additional recommendations for revisions to the IFU. In addition, FDA will provide recommendations to improve container labels and overwrap and carton labeling to promote safe use of the product.

9. Advisory Committee Meeting

This 505(b)(2) application was not referred to an advisory committee because it has the same active ingredient, same route of administration, and same proposed indications as the listed drug and relies on FDA’s finding of safety and efficacy for the listed drug, Gemzar (gemcitabine) for Injection.

10. Pediatrics

Sun Pharmaceutical Industries Ltd submitted a request for waiver of pediatric assessment requirements for all pediatric age groups, in accordance with section 505B (a)(4)(A)(iii) of the FD&C Act, in the NDA application. No agreed initial Pediatric Study Plan was included in the NDA; however, as all requested indications are on the “automatic” full waiver list no RTF action was taken. This request was reviewed by PeRC on September 9, 2015. Because studies are impossible or highly impracticable for the indications of ovarian cancer, breast cancer, NSCLC and pancreatic cancer because the diseases/conditions do not exist in children, the PeRC agreed with the clinical review team’s recommendation to grant a full waiver for this product. As a CR is recommended, no action will be taken regarding this request at this time. However, were a resubmission of this NDA recommended for approval, the request for waiver pediatric assessment requirements would be granted.

11. Other Relevant Regulatory Issues

As discussed in the Introduction and in Section 3 of this review, the Office of Compliance has recommended that approval be withheld until the applicant has satisfactorily addressed the deficiencies identified at Sun Pharmaceutical Industries Ltd Halol site (FEI 3002809586), one of the manufacturing facilities identified in the NDA

12. Labeling

FDA performed no formal labeling review of the applicant's proposed prescribing information this cycle due to the "withhold" recommendation from OPQ and Complete Response.

DMEPA reviewed the prescribing information and carton/container labeling and made suggestions to be considered in the next review cycle.

13. Decision/Action/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product is nearly identical to the listed product, Gemzar, when the listed product is reconstituted and diluted for administration. No new clinical or nonclinical data were provided with this submission, as no studies were conducted for this 505(b)(2) application. However, a **complete response** to the application is recommended based on deficiencies identified by Quality review staff, related to inadequate facilities inspections and a manufacturing process deficiency.

- **Risk Benefit Assessment**

The application relies on FDA's previous findings of safety and efficacy for the listed drug, Gemzar (Eli Lilly). There are no new efficacy or safety concerns that would preclude approval of this product.

- **Postmarketing Risk Evaluation and Mitigation Strategies**

N/A

- **Other Postmarketing Requirements and Commitments**

N/A

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**Joseph E.
Gootenberg -S**
Joseph E. Gootenberg, MD
Deputy Director, Division of Oncology Products 2

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JOSEPH E GOOTENBERG
11/24/2015

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	208313
Priority or Standard	standard
Submit Date(s)	03-29-2015
Received Date(s)	03-30-2015
PDUFA Goal Date	01-30-2016
Division/Office	DOP2 / OHOP
Reviewer Name(s)	M. Naomi Horiba
Team Leader	Steven Lemery
Established Name	Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection
(Proposed) Trade Name	n/a
Applicant	Sun Pharmaceutical Industries, Ltd.
Formulation(s)	Injectable solution in pre-filled bags 10mg/mL
Dosing Regimen	varies by indication
Applicant Proposed Indication(s)/Population(s)	<ol style="list-style-type: none"> 1. In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy. 2. 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. 3. In combination with cisplatin for the treatment of non-small cell lung cancer. 4. As a single agent for the treatment of pancreatic cancer.
Recommendation on Regulatory Action	Non-approval
Recommended Indication(s)/Population(s)	Same as for Applicant Proposed Indication(s) and only in a population whose dose rounded to the nearest 100 mg falls between 1200 mg and 2200 mg).

Summary

NDA 208313 is a 505(b)(2) referencing Gemzar NDA 020509 lyophilized powder for injection solution originally approved on 05/15/1996. No new clinical data were provided with this submission, as no clinical studies were done for this 505(b)(2) application. The clinical review recommendation is to not approve the application based on deficiencies identified by Quality review staff (i.e., related to facilities). No clinical issues were identified; however, that would preclude approval, contingent upon agreement upon labeling.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA for Gemcitabine Hydrochloride Injection was submitted in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act to request approval of the therapeutic equivalence of the proposed product to Gemzar, as defined in the FDA Orange Book. The sponsor of NDA 020509 for Gemzar is Lilly.

1. In combination with carboplatin, for the treatment of advanced **ovarian cancer** that has relapsed at least 6 months after completion of platinum-based therapy
2. 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
3. In combination with cisplatin for the treatment of **non-small cell lung cancer**
4. As a single agent for the treatment of **pancreatic cancer**

No new clinical data was submitted for this NDA. The Gemzar NDA 020509 has been previously reviewed for efficacy and safety. The clinical review recommendation is to not approve the application based on deficiencies identified by Quality review staff (i.e., related to facilities). No clinical issues were identified; however, that would preclude approval, contingent upon agreement upon labeling.

1.2 Risk Benefit Assessment

Please refer to NDA 020509.

2 Product Information and Regulatory Background

2.1 Product Information

Established Name: gemcitabine hydrochloride

Applicant: Sun Pharmaceutical Industries Ltd.
Acme Plaza, Andheri-Kurla Road, Andheri (East)
Mumbai, Maharashtra
INDIA 400059

Salamandra, LLC
One Bethesda Center
4800 Hampden Lane, Suite 900
Bethesda, Maryland 20814-2998

Drug Class: nucleoside antimetabolite

Proposed Indications:

1. In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy
2. 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
3. In combination with cisplatin for the treatment of non-small cell lung cancer
4. As a single agent for the treatment of pancreatic cancer

Proposed Dosage and Administration:

The proposed indication, dose, route, and duration of administration of Sun Pharmaceutical Industries Limited's Gemcitabine Hydrochloride in 0.9% Sodium Chloride Injection, 10 mg/mL, will be the same as those of the reference product, Gemzar. As with Gemzar, the product is intended solely for administration by intravenous injection over 30 minutes. At the fixed concentration of 10 mg/ mL, the product requires no dilution and is ready to use.

1. Ovarian Cancer: 1,000 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.
2. Breast Cancer: 1,250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.
3. Non-Small Cell Lung Cancer: 1,000 mg/m² over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1,250 mg/m² over 30 minutes on Days 1 and 8 of each 21-day cycle.
4. Pancreatic Cancer: 1,000 mg/m² over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.

Dosage Forms and Strengths:

Sun is proposing 10 presentations of the product at 10 mg/mL: 1200 mg (120 mL), 1300 mg (130 mL), 1400mg (140 mL), 1500 mg (150 mL), 1600 mg (160mL), 1700 mg (170 mL), 1800 mg (180 mL), 1900 mg (190 mL), 2000 mg (200 mL), and 2200 mg (220 mL).

Contraindications:

As for Gemzar, gemcitabine hydrochloride in sodium chloride injection is contraindicated in patients with a known hypersensitivity to gemcitabine.

Warnings and Precautions:

As for Gemzar, warnings and precautions are schedule-dependent toxicity (infusion time beyond 60 minutes), myelosuppression (neutropenia, anemia, thrombocytopenia), pulmonary toxicity and respiratory failure, hemolytic uremic syndrome, hepatic toxicity, embryofetal toxicity, exacerbation of radiation therapy toxicity, capillary leak syndrome, posterior reversible encephalopathy syndrome.

Adverse Reactions:

As for Gemzar, the most common ($\geq 20\%$) adverse reactions of single-agent gemcitabine hydrochloride are nausea/vomiting, anemia, increased ALT, increased AST, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema.

Reviewer:

The applicant's product, gemcitabine hydrochloride, differs from Gemzar in that the applicant's product requires no prior dilution and is ready to use. Because the increments of the presentation differ by 100mg from 1200mg to 2000mg, and by 200mg from 2000mg to 2200mg, dose-rounding will be necessary. With the available presentations, rounding will not result in a change of more than 5% of the total calculated dose.

Because Gemzar is available only in 200 mg and 1000 mg vials, it is a common practice in US infusion center pharmacies to round to the nearest vial size with the goal of cost-containment. In fact, a guideline to facilitate the introduction of dose-banding into hospitals in England and Wales was published by the Cancer Network Pharmacists Forum (CNPF) in August 2008. It is the CNPF's opinion that within 5%, "dose banding does not add significantly to the level of imprecision inherent in BSA-based dose calculations nor significantly alter the dose-density of chemotherapy administered over a treatment course. The quantifiable service and patient benefits achieved by banding outweigh any theoretical disadvantages."¹ While a similar document has not been published in the US, it is generally accepted that a difference within 5% will not affect safety or efficacy.

Other differences between the sponsor's product and Gemzar (listed below) are not expected to result in clinically meaningful differences:

1. Inactive ingredients are present in different concentrations.
2. Gemzar contains mannitol and sodium acetate (b) (4) and neither is present in Sun's formulation.

2.2 Availability of Proposed Active Ingredient in the United States

Gemcitabine hydrochloride is marketed in the US as Gemzar and under multiple ANDA's.

2.3 Summary of Presubmission Regulatory Activity Related to Submission

December 16, 2011: pre-submission NDA meeting

October 31, 2014: pre-submission NDA meeting

(b) (4)

2.4 Pediatric Waiver

Submitted.

2.5 Other Relevant Background Information

Refer to NDA 020509.

3 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to NDA 020509 and other disciplines' reviews.

4 Sources of Clinical Data

Refer to NDA 020509.

5 Review of Efficacy

Refer to NDA 020509.

6 Review of Safety

Refer to NDA 020509.

7 Appendices

7.1 Literature Review/References

Refer to NDA 020509.

7.2 Advisory Committee Meeting

None

¹ http://www.bopaweb.org/contentimages/publications/Toolkit_Ver_3.0_FINAL.pdf

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/s/

MARGIT N HORIBA
10/28/2015

STEVEN J LEMERY
10/28/2015