CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209604Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 209604
Review #1

Drug Name/Dosage Form	Gemcitabine Injection
Strength	100 mg/mL – 2 mL, 10 mL, 15 mL, and 20 mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare Inc.
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000	*October 13, 2016*	*CMC*
0002	*November 23, 2016*	*Biopharm*
0005	*March 21, 2017*	*Microbiology*
0006	*March 29, 2017*	*Drug Substance, Facility*
0007	*March 29, 2017*	*Labeling*
0008	*April 12, 2017*	*Drug Product, Process*
0009	*April 18, 2017*	*Drug Product*
0010	*April 25, 2017*	*Drug Product, Microbiology*
0011	*April 26, 2017*	*Labeling*
0012	*May 18, 2017*	*Microbiology*
0013	*May 30, 2017*	*Drug Product*
0016	*June 19, 2017*	*Drug Substance, Facility*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Haripada Sarker	Ben Stevens
Drug Product	Paresma Patel	Anamitro Banerjee
Process	Huiquan Wu	Rakhi Shah
Microbiology	Yarery C Smith	Jesse Wells
Facility	Wenzheng Zhang	Derek Smith
Biopharmaceutics	Parnali Chatterjee	Okponanabofa Eradiri
Regulatory Business Process	Steven Kinsley	NA

Manager		
Application Technical Lead	Anamitro Banerjee	NA
Laboratory (OTR)	NA	
ORA Lead	NA	
Environmental	NA	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate, see comments		Adequate
	Type III	(b) (4)				Sufficient information provided
	Type III					Sufficient information provided
	Type III					Sufficient information provided
	Type III					Sufficient information provided
	Type III					Sufficient information provided

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107393	Gemcitabine Injection 100 mg/mL
NDA	020509	Listed Drug (GEMZAR)

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA209604 is recommended for APPROVAL from the CMC point of view. The quality information provided in this NDA is acceptable

Action letter language (to be communicated to the applicant):
An expiry dating period of 24 months is granted for this product when stored at 20 ℃ to 25 ℃ (68 ℉ to 77 ℉).

II. Summary of Quality Assessments

A. Product Overview

This submission (NDA 209604) is a 505(b)(2) application, referencing the lyophilized powder formulation, GEMZAR® (NDA 020509). The listed drug (LD) GEMZAR® is available in 200 mg and 1 g (b) (4) dose vials.
The proposed Gemcitabine Injection is a clear, colorless to yellow, sterile solution filled in a clear glass vial available in 100 mg/mL concentration presented in 2 mL, 10 mL, 15 mL, and 20 mL fill volumes. The drug product is intended for dilution (with 0.9% sodium chloride) into infusion solution and intravenous administration.
The applicant is relying on FDA's finding on safety and efficacy for the listed drug GEMZAR®.

Proposed Indication(s) including Intended Patient Population	Gemcitabine Injection is a nucleoside metabolic inhibitor indicated: • 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.
Duration of Treatment	Gemcitabine Injection is for intravenous infusion use only. • Ovarian cancer: 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. • Breast cancer: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. • Non-small cell lung cancer: 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Pancreatic cancer: 1000 mg/m^2 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.
Maximum Daily Dose	*NA*
Alternative Methods of Administration	*NA*

B. Quality Assessment Overview

Drug substance:
The gemcitabine drug substance is white to off white crystalline powder that is soluble in aqueous and slightly soluble in methanol, but practically insoluble in alcohol (ethanol) and other polar organic solvents.
The (b) (4) is manufactured by (b) (4) (DMF (b) (4), LOA dated July 12, 2016 provided). The applicant refers to the DMF for the drug substance manufacturing process. The DMF was reviewed and was found adequate to support this NDA. The drug substance specifications proposed by the applicant is consistent with the USP monograph. The applicant provided batch analysis data (by the applicant) and the COA from the DS supplier for the several batches of the API.
The drug substance is packaged in (b) (4) (b) (4) he applicant referred to the DMF for further information.
The proposed retest period of (b) (4) months for the API is acceptable. The applicant referred to the DMF for stability data and storage conditions.
The applicant included (b) (4)
The drug substance reviewer recommended approval for this NDA.

Drug Product:
The drug product formulation contains the API, PEG 300 (b) (4) Propylene glycol (b) (4), sodium hydroxide ((b) (4) and pH adjusting agent), hydrochloric acid (pH adjusting agent), dehydrated alcohol (b) (4) and (b) (4). All the ingredients are compendial grade. No novel excipients or excipients with human or animal origin are used.

(b) (4) (b) (4) (b) (4)

The proposed drug product specifications include routine testing needed for this type of product. The drug product specifications include testing for description, identification, pH, (b) (4) volume in container, particulate matter, sterility, bacterial endotoxin, chromatographic purity, assay, alcohol content, (b) (4) clarity, color and achromicity, (b) (4), and (b) (4). The applicant provided description of analytical methods and their validation data. Batch data for several exhibit batches of each strength (about (b) (4) the commercial scale) is provided in the submission. No OOS data is reported.

Stability data, inverted as well as upright, for several batches for each strength under 36 M long term (25°C/60% RH), and 6M accelerated (40°C/75%RH) conditions provided in this submission are acceptable. No OOS data reported. Post approval stability protocol and commitment is adequate. The proposed shelf life of 24 months may be granted for the drug product when stored under controlled room temperature: 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F). The applicant provided adequate data to demonstrate that a vial may be stored for 28 days at room temperature after the initial puncture.

The applicant is requesting categorical exclusion from EA under 21 CFR 25.31(a) and 21 CFR 25.15(d).

Facilities:
(b) (4) (FEI # (b) (4)) (b) (4) Following evaluation of the application and inspectional documents, no significant outstanding facility risks were identified that would prevent the approval of this application.

Biopharmaceutics:
The biopharmaceutics review assessed the adequacy of the Applicant's biowaiver request for the proposed drug product, Gemcitabine Injection. Since the concentration of gemcitabine in all fill volumes is the same, the biowaiver request is granted,

provided bioequivalence of the 10 mL fill volume to the listed drug is demonstrated.

C. Special Product Quality Labeling Recommendations (NDA only)

None

D. Final Risk Assessment (see Attachment)

E. List of Deficiencies for Complete Response

None

Application Technical Lead Name and Date: Anamitro Banerjee, Ph.D. July 11, 2017

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LABELING

R Regional Information

The drug product Gemcitabine Injection 100 mg/mL is available in four fill volumes: 2 mL, 10 mL, 15 mL, and 20 mL. The most recent carton and container labels were submitted on 26-Apr-2017 and are copied and reviewed below. The applicant revised the carton and container labels based on recommendations from CMC and DMEPA. Refer to the review by Otto Townsend submitted in DARRTS on 28-Feb-2017 for the DMEPA recommendations.

Information Requests sent to the applicant on 24-Apr-2017 and Responses Received on 26-Apr-2017 (SD12):

1) Provide the amount of gemcitabine hydrochloride in addition to the free base equivalency for all carton labels. For example, the 200 mg/2 mL carton label should read "Each vial contains: 200 mg gemcitabine (equivalent to 227.7 mg gemcitabine hydrochloride USP)." Refer to Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances found at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf.

Applicant Response: The applicant provided updated carton labels including the revised equivalency statement for gemcitabine hydrochloride. The final carton labels are copied and evaluated below.
Evaluation: ***Adequate.***

2) Revise the NDC number found on the bottom panels for the 1 g/10 mL, 1.5 g/15 mL, and 2 g/20 mL carton labels to be consistent with the assigned NDC number on the principal display panel. For example, the bottom panel for the 1 g/10 mL container currently reads "NDC 16729-**391**-03" and the principal display panel reads "NDC 16729-**419**-03."

Applicant Response: The applicant revised NDC number on the bottom panels of the carton labels to be consistent with the principal display panel. The final carton labels are copied and evaluated below.
Evaluation: ***Adequate.***

Information Requests sent to the applicant on 27-Mar-2017 and Responses Received on 29-Mar-2017 (SD8):

1) Indicate sterility of your drug product on the container label and carton labeling if space allows.

Applicant Response: The applicant provides revised container and carton labels that indicate the drug product is sterile.
Evaluation: ***Adequate.***

2) The proposed carton and immediate container label indicate that the drug product should be (b) (4). (b) (4) Provide a justification for the statement (b) (4) on the container and carton labeling.

Applicant Response: The applicant removes the (b) (4) statement from the drug product.
Evaluation: ***Adequate.***

1.14 Labeling

Immediate Container Label

(b) (4)

[redacted]

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Table 1. *Immediate Container Label Review of Regulatory Requirements*

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Route of administration 21.CFR 201.100(b)(3))		Adequate
Net contents* (21 CFR 201.51(a))		Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Provided on carton labeling due to space limitations.	Adequate
Lot number per 21 CFR 201.18	Space provided	Adequate
Expiration date per 21 CFR 201.17	Space provided	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)***		Adequate
Name of manufacturer/distributor (21 CFR 201.1)		Adequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Reviewer's Assessment: ***Adequate.***

During the review cycle the sponsor was asked to include sterility information on the immediate container labeling. The (b) (4) statement was removed (b) (4)

The final immediate container labeling was submitted on 26-Apr-2017 (SD12) and meets all regulatory requirements.

Carton Labels

(b) (4)

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Table 2. *Carton Label Review of Regulatory Requirements*

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]		Adequate
Sterility Information (if applicable)	Resolved by IR.	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)		Adequate
Storage Conditions		Adequate
NDC number (per 21 CFR 201.2)(requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
"See package insert for dosage information" (21 CFR 201.55)		Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Not provided; not required	Not Required
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))		Adequate

Reviewer's Assessment: *Adequate.*

During the review cycle the sponsor was asked to make the following edits to the carton labels:

-include sterility information

-remove the [redacted] (b) (4) statement based on [redacted] (b) (4) submitted in the NDA submission

- revise the equivalency statement for gemcitabine hydrochloride to be consistent with the salt nomenclature guidance

-revise the NDC number on the bottom panels to be consistent with the principal display panel

The final carton labels were submitted on 26-Apr-2017 (SD12) and meet all regulatory requirements.

Package Insert

Highlights

----------**DOSAGE FORMS AND STRENGTHS**----------

- 200 mg/2 mL multiple-dose vial (100 mg/mL) (3)
- 1 g/10 mL multiple-dose vial (100 mg/mL) (3)
- 1.5 g/15 mL multiple-dose vial (100 mg/mL) (3)
- 2 g/20 mL multiple-dose vial (100 mg/mL) (3)

Reviewer's Assessment: *Adequate.*

The following minor editorial edits are suggested:

Gemcitabine Injection in multiple dose vials containing:
•200 mg/2 mL (100 mg/mL) ~~multiple dose vial (100 mg/mL)~~(3)
•1 g/10 mL (100 mg/mL) ~~multiple dose vial (100 mg/mL)~~ (3)
•1.5 g/15 mL (100 mg/mL) ~~multiple dose vial (100 mg/mL)~~ (3)
•2 g/20 mL (100 mg/mL) ~~multiple dose vial (100 mg/mL)~~ (3)

The applicant made the suggested edits to the Highlights section of the PI, and the revised PI was submitted on 15-June-2017 (SD 16).

2 DOSAGE AND ADMINISTRATION

2.6 Preparation and Administration

Gemcitabine is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1] Exercise caution and wear gloves when preparing Gemcitabine Injection solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if Gemcitabine Injection contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption.
OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

Preparation

- Discard vial if particulate matter or discoloration is observed.

- Dilute Gemcitabine Injection with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

- Mix diluted solution by gentle inversion. Do not shake.

Storage

- Store diluted gemcitabine at controlled room temperature 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Discard after 24 hours.

Administration

- Inspect (b) (4) solution (b) (4) for particulate matter and discoloration prior to administration.
- The compatibility of Gemcitabine Injection with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

(b) (4)

After dilution with 0.9% Sodium Chloride Injection the solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permits. If particulate matter or discoloration is found, do not administer.

(b) (4)

Reviewer's Assessment: *Adequate.*
The preparation and administration section was updated to only include the bulleted sections. Statements were included to inspect the solution in the vial and the diluted IV solution prior to preparation and administration. Additionally, a statement was included to dispose of multiple-dose vials within 28 days after initial puncture. The suggested changes are highlighted in red below.

2.6 Preparation and Administration

Gemcitabine is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]
Exercise caution and wear gloves when preparing Gemcitabine Injection solutions. Immediately wash the skin thoroughly or rinse the mucosa with copious amounts of water if Gemcitabine Injection contacts the skin or mucus membranes. Death has occurred in animal studies due to dermal absorption.
~~OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html~~

Preparation

•Inspect solution and discard vial if particulate matter or discoloration is observed.

•Dilute Gemcitabine Injection with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

•Mix diluted solution by gentle inversion. Do not shake.

After dilution with 0.9% Sodium Chloride Injection, inspect the solution visually for particulate matter and discoloration, prior to administration, whenever solution or container permits. If particulate matter or discoloration is found, do not administer.

Storage
•After initial withdrawal with a needle, the remaining portion in the vial should be used or discarded within 28 days.

•Store diluted Ggemcitabine Injection at controlled room temperature 20°C to 25°C (68°F to 77°F) (b) (4) . Discard after 24 hours.

Administration
•Inspect (b) (4) the infusion solution (b) (4) for particulate matter and discoloration prior to administration. If particulate matter or discoloration is found, do not administer.

•The compatibility of Gemcitabine Injection with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

The applicant made the suggested edits to section 2.6 Preparation and Administration of the PI, and the revised PI was submitted on 15-June-2017 (SD 16).

3 DOSAGE FORMS AND STRENGTHS

Gemcitabine Injection is a clear, colorless to pale yellow solution available in sterile multiple-dose vials containing:

- 200 mg/2 mL multiple-dose vial (100 mg/mL)
- 1 g/10 mL multiple-dose vial (100 mg/mL)
- 1.5 g/15 mL multiple-dose vial (100 mg/mL)
- 2 g/ 20 mL multiple-dose vial (100 mg/mL)

Reviewer's Assessment: *Adequate.*
The suggested edits are shown below and are consistent with the Highlights section of the PI.

3 DOSAGE FORMS AND STRENGTHS

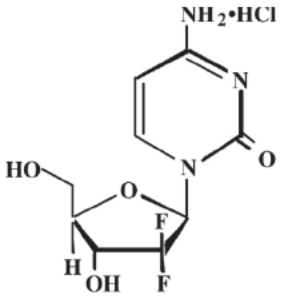
Gemcitabine Injection is a clear, colorless to pale yellow solution available in sterile multiple-dose vials containing:

- 200 mg/2 mL (100 mg/mL) ~~in multiple-dose vial (100 mg/mL)~~
- 1 g/10 mL (100 mg/mL) ~~in multiple-dose vial (100 mg/mL)~~
- 1.5 g/15 mL (100 mg/mL) ~~in multiple-dose vial (100 mg/mL)~~
- 2 g/ 20 mL (100 mg/mL) ~~in multiple-dose vial (100 mg/mL)~~

The applicant made the suggested edits to the Dosage Forms and Strengths section of the PI, and the revised PI was submitted on 15-June-2017 (SD 16).

11 DESCRIPTION

Gemcitabine is a nucleoside metabolic inhibitor [redacted] (b) (4). Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer).
The structural formula is [redacted] (b) (4):



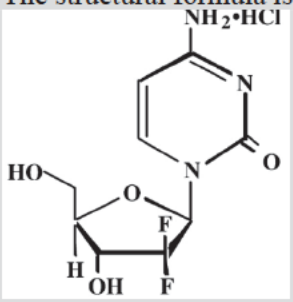
The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ • HCl and the molecular weight is 299.66.
Gemcitabine HCl is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

[redacted] (b) (4)

Reviewer's Assessment: *Adequate.*
The following suggested edits were sent to the applicant.

11 DESCRIPTION

Gemcitabine is a nucleoside metabolic inhibitor [redacted] (b) (4). Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer).
The structural formula is [redacted] (b) (4).



Gemcitabine HCl is a white to off white crystalline powder. The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ • HCl and the molecular weight is 299.66.
Gemcitabine HCl is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.

[redacted] (b) (4)

(b) (4)

The applicant made the suggested edits to the Description Section of the PI, and the revised PI was submitted on 15-June-2017 (SD 16).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gemcitabine Injection is a clear colorless to pale yellow solution available in sterile multiple-dose vials containing:

Vial	NDC number
200 mg/2 mL (100 mg/mL)	16729-391-30
1 g/10 mL (100 mg/mL)	(b) (4)
1.5 g/15 mL (100 mg/mL)	
2 g/ 20 mL (100 mg/mL)	

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); (b) (4) excursions permitted between 15° C and 30°C (59°F and 86°F). (b) (4) .

After initial puncture, Gemcitabine Injection multiple-dose vials are stable for 28 days when stored at room temperature, (b) (4)

Reviewer's Assessment: *Adequate.*

The following suggested edits were sent to the applicant: the table was reformatted to remove the lines, and the storage conditions were revised to be consistent with USP Controlled Room Temperature.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gemcitabine Injection is a clear colorless to pale yellow solution available in sterile multiple-dose vials containing:

Vial	NDC number
200 mg/2 mL (100 mg/mL)	16729-391-30
1 g/10 mL (100 mg/mL)	(b) (4)
1.5 g/15 mL (100 mg/mL)	
2 g/ 20 mL (100 mg/mL)	

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); ~~and that allows for~~ excursions permitted between 15° C and 30°C (59°F and 86°F). (b) (4)

Gemictabine is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

After initial puncture, Gemcitabine Injection multiple-dose vials are stable for 28 days when stored at room temperature, (b) (4)

The applicant was asked to remove the in-use storage conditions because they are available in the Dosage and Administration section of the PI. The applicant submitted revised labeling on 15-June-2017 (SD 16) and suggested leaving the in-use storage conditions in Section 16 of the PI in addition to Section 2, which is acceptable from a CMC perspective. The applicant was asked to remove the (b) (4) statement to be consistent with the carton/container labels and the stability data provided in the NDA submission.

Primary Labeling Reviewer Name and Date:

Paresma Patel, Ph.D.
June 22, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, Ph.D.
June 22, 2017

Paresma Patel

Digitally signed by Paresma Patel
Date: 6/22/2017 11:20:18AM
GUID: 5646367e005f4dee2a4ed91154b786ac

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 6/22/2017 11:28:31AM
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BIOPHARMACEUTICS REVIEW Office of New Drug Products/Office of Pharmaceutical Quality/Division of Biopharmaceutics			
Application No.:	NDA 209604	**Biopharmaceutics Reviewer:** Parnali Chatterjee, PhD	
Submission Date:	10/13/2016		
Division:	Division of Oncology Products (DOP)	**Acting Biopharmaceutics Lead:** Okpo Eradiri, PhD	
Applicant:	Accord Healthcare Inc.	**Acting Brach Chief:** Angelica Dorantes, PhD	
		Date Assigned:	10/21/2016
Generic Name:	Gemcitabine Injection 100 mg/mL	**Date of Review:**	12/07/2016
Indication:	Indicated for the treatment of breast, ovarian, non-small cell lung, and pancreatic cancer	**Type of Submission: Original submission**	
Dosage Form/ Strengths	Ready to use solution 100 mg/ mL supplied as 2mL, 10 mL, 15 mL, and 20 mL vials		
Route of Administration	Intravenous infusion		
Type of Review	Address the Applicant's request for a biowaiver in the original submission Module 1.12.15		

SUMMARY OF BIOPHARMACEUTICS REVIEW:

Background:

Accord Healthcare Inc., is seeking approval for Gemcitabine Injection 100 mg/mL for the treatment of breast, ovarian, non-small cell lung, and pancreatic cancer under the 505 b (2) path. The reference listed drug (RLD), Gemzar® was approved under NDA 020509 for the following strengths, 200 mg base/vial and 1 gm base/vial. Since the proposed drug product is for intravenous use, there is no biopharmaceutics issue to assess in this Application. However, the Applicant included a biowaiver request in Section 1.12. The objective of this review is to evaluate the Applicant's request for the waiver of in vivo bioequivalence (BE) testing for three fill volumes 2 mL (200 mg/2 mL), 15 mL (1.5 g/15 mL), and 20 mL (2g/ 20 mL).

Submission:
In this submission, the Applicant has requested waiver of in vivo bioequivalence (BE) testing for three fill volumes 2 mL (200 mg/2 mL), 15 mL (1.5 g/15 mL), and 20 mL (2g/ 20 mL) based on demonstration of BE of the 10 mL (1g/10 mL) fill volume. Since the concentration of gemcitabine in all fill volumes is the same, the biowaiver request is granted, provided bioequivalence of the 10 mL fill volume to the listed drug is demonstrated.

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 209604 for gemcitabine injection, 100 mg/mL, is recommended for APPROVAL.

Signature

Parnali Chatterjee, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Signature

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Okponanabofa Eradiri

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Date: 3/09/2017 12:13:47PM
GUID: 50bdfe8d00003559ede66be3fd299f65

Parnali Chatterjee

Digitally signed by Parnali Chatterjee
Date: 12/07/2016 10 32:51AM
GUID: 57fe9bf6008e2949beb0cef2b7631eca

MICROBIOLOGY

Product Background

NDA: 209604

Drug Product Name
Proprietary: N/A
Non-proprietary: Gemcitabine Injection
Strength: 100 mg/mL – 2 mL, 10 mL, 15 mL and 20 mL

Route of Administration: Intravenous

Applicant Name: Accord Healthcare Inc.

Manufacturing Site:
Intas Pharmaceuticals Limited,
Plot No. 457/ 458, Village – Matoda,
Bavla Road, Ta. Sanand,
Dist. Ahmedabad – 382 210, Gujarat, India.

Method of Sterilization: (b) (4)

Supporting/Related Documents:
Microbiology reviews 40-716a1.doc (M. Stevens Riley, dated 04/11/07) and 203153.doc (J. Wells, 10/28/2011), 205574.doc and 205574a1.doc (L. Shelton, 03/19/2014 and 09/29/2015, respectively) are referenced for relevant information regarding the validation of the subject (b) (4)

Remarks: This is a 505b(2) application. Gemcitabine Injection is new formulation with new strength of 100 mg/mL available as ready to add to infusion solution containing 200 mg/2 mL, 1 g/10 mL, 1.5 g/15 mL or 2 g/ 20 mL.

Review Summary: The submission is recommended for approval on the basis of sterility assurance.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
10/13/2016	10/13/2016	N/A	10/20/2016
03/21/2017*	03/21/2017	N/A	03/22/2017
04/25/2017*	04/25/2017	N/A	04/26/2017
05/18/2017*	05/18/2017	N/A	05/18/2017

*IR Response

P.1 Description of the Composition of the Drug Product

- **Drug product composition –**

Ingredients	Function	Quantity [mg per mL]	Quantity [mg per vial)]			
			2 mL	10 mL	15 mL	20 mL
Gemcitabine Hydrochloride§ [USP] equivalent to Gemcitabine	Active	113.85[1] 100.00	227.70 200.00	1138.50 1000.00	1707.75 1500.00	2277.00 2000.00
PEG-300 [USNF]	(b) (4)	250.00	500.00	2500.00	3750.00	5000.00
Propylene Glycol [USP]		150.00	300.00	1500.0	2250.00	3000.00
Sodium Hydroxide [USNF]		16.00	32.00	160.00	240.00	320.00
Sodium Hydroxide [USNF]	pH adjusting agent			(b) (4)		
Hydrochloric acid [USNF]	pH adjusting agent					
Dehydrated Alcohol [USP]	(b) (4)	q.s to 1 mL	q.s to 2 mL	q.s to 10 mL	q.s to 15 mL	q.s to 20 mL
(b) (4)						

§113.85 g of Gemcitabine Hydrochloride is equivalent to 100.00 mg of Gemcitabine, Molecular weight of Gemcitabine Hydrochloride and Gemcitabine Base is 299.66 and 263.198 respectively.

(b) (4)

USP: United States Pharmacopoeia.
USNF: United States National Formulary.
PEG-300-Polyethylne Glycol 300

- **Description of container closure system –**

Component	Presentation/Fill volume	Description	Manufacturer name and address
Container	2 mL	2 mL USP type I clear glass vial	(b) (4)
	10 mL	10 mL USP type I clear tubular glass vial	
	15 mL	15 mL USP type I clear tubular glass vial	
	20 mL	20 mL USP type I clear (b) (4) glass vial	
Closure	2 mL	*13 mm (b) (4) rubber stopper	
		**13 mm (b) (4) rubber stopper	
	10 mL 15 mL 20 mL	*20 mm (b) (4) rubber stopper **20 mm (b) (4) rubber stopper	
Seal	2 mL	$13 mm (b) (4) seal	
	10 mL	$20 mm (b) (4) seal	
	15 mL	$20 mm (b) (4) seal	
	20 mL	$20 mm (b) (4) seal	

*Rubber stopper used in exhibit batches
**Rubber stopper used in exhibit batches and proposed for commercial batches
$For commercial batches meant for US market we are proposing (b) (4) as per USP <1> requirement.

(b) (4)

26 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer's Assessment: Sufficient information has been provided regarding the validation of the sterility test for release of commercial batches.

Acceptable

(b) (4)

[redacted]

(b) (4)

[redacted]

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q)
MODULE 1
2.A. Package Insert
(Module 1, draft-labeling-text.pdf)

Storage temperature: 20-25 °C (68-77 °F); Route of administration: IV; Container: Multi-dose

The package insert indicates that after initial puncture, Gemcitabine Injection multiple-dose vials are stable for 28 days when stored at room temperature, (b) (4).

Reconstituted/Further Diluted Drug Product

Further product dilution:
Each vial contains a gemcitabine concentration of 100 mg/mL. Hence, withdrawing 2 mL, 10 mL, 15 mL or 20 mL of the vial contents will provide 200 mg, 1 g, 1.5 g or 2 g of gemcitabine, respectively. The appropriate amount of drug should be further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL. When prepared as directed, diluted gemcitabine solutions are stable for 24 hours at controlled room temperature (20° to 25°C). Discard unused portion.

In-use stability studies of Diluted solution (microbiological data)
(Section P.2, pharmaceutical-development.pdf, pages 68, 239-299 of 306)

A study (ASGTIPU4D/DSP-01) was performed by spiking the drug product solution at a concentration of (b) (4) mg/mL and (b) (4) mg/mL after dilution with 0.9 % sodium chloride solution at (b) (4) °C with (b) (4) CFU/mL) of compendial microorganisms to demonstrate that the diluted product solution will not support microbial growth during the proposed storage period.

Study details:

(b) (4)

Reviewer's Assessment: Although the proposed labeling indicates that after initial puncture, the drug product multiple-dose vials are stable for 28 days when stored at room temperature, with

(b) (4) the microbiological studies in support of the referenced storage time and temperature could not be located in the application. However, assuming that the applicant will resolve the deficiencies issued in section P.2 of this review, the results from the USP <51> AET would cover this storage period. Thus, no additional information will be requested.

Acceptable

Post-Approval Commitments: None

Lifecycle Management Considerations: None

List of Deficiencies:
No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

Primary Microbiology Reviewer Name and Date: Yarery Smith, Ph.D., 05/22/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed): I concur with the primary reviewer's assessment. Jesse Wells, Ph.D., 5/24/2017

END

Yarery Smith

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Jesse Wells

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Date: 5/30/2017 06:50:30AM
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ATTACHMENT I: Final Risk Assessments

Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4) (b) (4)	Acceptable	None
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable	None
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	None
Assay (b) (4)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable	None
Assay (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	None
Uniformity of Dose (Fill volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable	None

(b) (4)

Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Acceptable	None
pH (High)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Acceptable	None
pH (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Acceptable	None
Particulate Matter	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M	Acceptable	None
Leachables extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Acceptable	None
Appearance (color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Acceptable	None
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	Acceptable	None

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
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