CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209604Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 209604	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: GEMCITABINE injection, for intravenous use Dosage Form: injection Strengths: 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)		
Applicant: Accord Healthcare, Inc.		
Date of Receipt: October 13, 2016		
PDUFA Goal Date: August 13, 2017	Action Goal Date (if different): August 11, 2017	
RPM: Anuja Patel, OHOP, DOP 2		
Proposed Indication(s): 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. (1.3) • as a single agent for the treatment of pancreatic cancer.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Gemzar (Gemcitabine for Injection) NDA 020509	Clinical
Gemzar (Gemcitabine for Injection) NDA 020509	Nonclinical
Drug Master File DMF (b) (4) for Drug Substance Manufacturing	Drug Substance Manufacturing Process

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

This NDA relies on FDA's prior findings of safety and effectiveness for the listed drug, Gemzar, in route of administration and indications. The proposed product is a 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.

Bioequivalence studies were conducted by the Applicant to bridge their product with the reference listed product; specifically, two bioequivalence studies were conducted and the final study reports were contained in this NDA submission:

- Protocol 311-13 entitled "A multicentre, randomized, open label, two-period, two-treatment, two-way crossover, single dose bioequivalence study comparing Gemcitabine Injection 100 mg/mL (10 mL) (Manufactured by: Intas Pharmaceuticals Ltd.) to the reference listed drug Gemzar 1g/vial (Gemcitabine for Injection 1g/vial, Lilly USA, LLC, Indianapolis, IN 46285, USA) in patients with Pancreatic or Ovarian Cancer."

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Gemzar (gemcitabine for Injection)	020509	Y (per Cover letter, Patent Certification and Form 356h)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a new dosage form, the drug product is a clear, colorless to pale yellow solution filled in a clear glass multiple-dose vials available in 100 mg/mL concentration presented in 2 mL, 10 mL, 15 mL, and 20 mL fill volumes. The Listed Drug GEMZAR® (gemcitabine for injection), NDA 020509, is a lyophilized powder available in 200 mg/vial and 1 g/vial as a single use vials.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note *that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

APPEARS THIS WAY ON ORIGINAL

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/s/

ANUJA PATEL
07/18/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 16, 2017

To: Anuja Patel, MPH
Sr. Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **GEMCITABINE injection, for intravenous use**
NDA 209604

Office of Prescription Drug Promotion comments on the proposed Carton/Container Labeling

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Office of Prescription Drug Promotion (OPDP) has reviewed the draft carton/container labeling for GEMCITABINE injection, for intravenous use (gemcitabine) as requested by Division of Oncology Products (DOP2) in the consult dated November 01, 2016.

OPDP's review of the proposed carton/container labeling is based on the draft carton/container labels titled, "draft-carton-container-labels.pdf" send by electronic mail on June 16, 2017 to OPDP (Nazia Fatima) from DOP2 (Anuja Patel). OPDP has reviewed the carton/container labeling and has no comments.

If you have any questions, please feel free to contact, Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on this PI. Thank you!

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NAZIA FATIMA
06/16/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 16, 2017

To: Anuja Patel, MPH
Sr. Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products

From: Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **GEMCITABINE injection, for intravenous use**
NDA 209604

Office of Prescription Drug Promotion comments on proposed prescribing information (PI)

Office of Prescription Drug Promotion (OPDP) has reviewed the draft prescribing information (PI) for GEMCITABINE injection, for intravenous use (gemcitabine) as requested by Division of Oncology Products (DOP2) in the consult dated November 01, 2016.

OPDP's review of the proposed PI is based on the draft PI titled, "Accord Response to FDA preliminary edits sent 53017_SD15.docx" send by electronic mail on June 16, 2017 to OPDP (Nazia Fatima) from DOP2 (Anuja Patel). OPDP has reviewed the proposed PI and does not have any comments.

If you have any questions, please feel free to contact, Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov. OPDP appreciates the opportunity to provide comments on this PI. Thank you!

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/s/

NAZIA FATIMA
06/16/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 2, 2017
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 209604
Product Name and Strength:	Gemcitabine Injection, 200 mg/2 mL, 1 g/10 mL, 1.5 g/15 mL, and 2 g/20 mL (100 mg/mL)
Applicant/Sponsor Name:	Accord Healthcare, Inc.
Submission Date:	March 29, 2017 and April 26, 2017
OSE RCM #:	2016-2401-1
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Deputy Director (acting):	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Gemcitabine injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 BACKGROUND

On March 29, 2017, Accord submitted revised labeling in response to a "Preliminary Comments on Carton and Container Labeling Memorandum" issued by DOP2. One of our recommendations from our previous review was for Accord to change the product codes of the National Drug Code (NDC) numbers so the product codes for each strength was not sequential. During review of the revised labeling submitted March 29, 2017, we noted that the product codes had been updated to be non-sequential; however, the new product codes were not printed on the top panels of the carton labeling for the 1 g, 1.5 g, and 2g strengths. In addition,

[a] Townsend, O. Label and Labeling Review for Gemcitabine (Accord – NDA 209604). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 FEB 28. RCM No.: 2016-2401.

the Office of Pharmaceutical Quality noted the equivalency statement for free base gemcitabine compared to gemcitabine hydrochloride was not included on carton labeling. These deficiencies were communicated to Accord via electronic mail and Accord submitted the revised carton labeling on April 26, 2017. We find the applicant has implemented all of our recommendations in the April 26, 2017 submission.

3 CONCLUSION

The revised container labels submitted on March 29, 2017 and the carton labeling submitted on April 26, 2017 for gemcitabine are acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

OTTO L TOWNSEND
05/02/2017

DANIELLE M HARRIS
05/02/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 28, 2017
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 209604
Product Name and Strength:	Gemcitabine Injection, 200 mg/2 mL, 1 g/10 mL, 1.5 g/15 mL, and 2 g/20 mL (100 mg/mL)
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Accord Healthcare, Inc.
Submission Date:	October 13, 2016 and January 16, 2017
OSE RCM #:	2016-2401
DMEPA Primary Reviewer:	Otto L. Townsend, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As part of the review of this 505(b) (2) submission, DOP2 requested that we review the Prescribing Information, container labels, and carton labeling for Gemcitabine Injection from a medication errors perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C– N/A
ISMP Newsletters	D– N/A
FDA Adverse Event Reporting System (FAERS)*	E– N/A
Other	F– N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

This 505(b) (2) application from Accord references Gemzar (gemcitabine, NDA 020509) as the listed drug. Gemzar is available as a lyophilized powder for injection, which following reconstitution results in a concentration of 38 mg/mL. There are several generic gemcitabine for injection products available as powders with resultant concentrations of 38 mg/mL after reconstitution. In addition, there are gemcitabine injection products available as solutions in concentrations of 38 mg/mL. Accord is proposing a gemcitabine injection that would be available in a concentration if 100 mg/mL, which is more than twice the concentration of the listed product and other commercially available gemcitabine products. If the same volume of Accord's proposed product is administered, the patient would receive an overdose. For example, if a patient is prescribed a dose of 1,500 mg, the volume of Gemzar required would be 39.47 mL. This same volume of the proposed product would provide 3,947 mg, which is more than double the prescribed dose.

We noted this concentration difference during our review of the Pre-NDA meeting package submitted by the Sponsor on August 3, 2015 under IND 107393. In the meeting preliminary comments conveyed to the Sponsor on August 28, 2015, we provided the following comment:

In the NDA submission, include a plan to mitigate the potential risk of overdose due to concentration confusion (38 mg/mL vs. 100 mg/mL) if the proposed 100 mg/mL concentration gemcitabine product is introduced to the market.[a]

The Sponsor requested further guidance on the risk assessment parameters to be included. During a teleconference between the Agency and the Sponsor, we provided clarification and advised the Sponsor on ways to differentiate their product, including the use of distinct colors for each strength presentation.[b] To address the risk of confusion between their proposed 100 mg/mL concentration product and the products that are currently available as 38 mg/mL, the Applicant proposed the use of a flag on the carton labeling that states, "New Concentration and Preparation". In their Annotated Draft Labeling Text document included with their submission, in reference to the flag, the Applicant states, "Additional information for Accord's proposed generic is included to differentiate it from the RLD's lyophilized formulation for Injection and thus minimizing the risk of medication errors." A similar strategy was employed by the Applicant with their tentatively approved cabazitaxel product (NDA 207949) that's also more concentrated than currently marketed cabazitaxel product.

The Applicant also proposed to repeat the total strength per total volume on the upper right side of the PDP and back panel on carton labeling in addition to the total strength per total volume followed by the concentration per milliliter in center of PDP and back panel. This format is trade dress for this Applicant and has been approved for their other products. Therefore, we do not object to this format. Also, the proposed container labels and labeling contains the statement "Do not refrigerate". We normally discourage use of negative statements but because other currently marketed Gemcitabine Injections (e.g. Gemcitabine Injections by Actavis and Hospira) require refrigeration, we do not object to the inclusion of this negative statement.

In the Filing Communication letter to the Applicant, the Agency included labeling comments related to the Prescribing Information and a request to resubmit labeling that addressed the issued identified.[c] The Applicant addressed some of the issues by relocating information and reformatting with the use of bullets, but did not delete duplicate information. For example, the Agency recommended the use of subheadings and bullets in the Dosage and Administration section. The Applicant included the subheadings, but did not delete duplicate information. In addition, the Agency recommended the use of command language, but the Applicant did not fully implement this recommendation.

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[a] Accord Healthcare. Preliminary Comments for Type B Pre-NDA meeting: IND 107393. Gemcitabine injection. Durham (NC): Accord Healthcare; 2015 AUG 28.

[b] Accord Healthcare. Memorandum of Type B Pre-NDA meeting minutes: IND 107393. Gemcitabine injection. Durham (NC): Accord Healthcare; 2015 SEP 1.

[c] Accord Healthcare. Filing Communication Letter: NDA 209604. Gemcitabine injection. Durham (NC): Accord Healthcare; 2016 DEC 16.

4 CONCLUSION & RECOMMENDATIONS

There are elements of the proposed Gemcitabine Injection labels and labeling that are vulnerable to medication errors. These elements can be improved to promote the safe use of the proposed product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Revise Section 2.6 (Preparation and Administration) to improve clarity of

(b) (4)

"Inspect solution and discard vial if particulate matter or discoloration is observed." to reflect the requirement that the solution contained in the vial must be inspected prior to use.

ii. "Dilute Gemcitabine Injection with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL"
to read,

(b) (4)

iii. "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."
to read,

(b) (4)

iv. "…room temperature 20° to 25°C (68° to 77°F)…"
to read,
"…room temperature 20°C to 25°C (68°C to 77°F)…" to include the unit of measurement after each number in the temperature range.

2. In Section 2.6 (Preparation and Administration)
   i. Since the product is (b) (4), delete the statement, (b) (4)

ii. Delete the duplicative information, [redacted]

iii. Delete the duplicative statements, [redacted]

4.2 RECOMMENDATIONS FOR ACCORD

We recommend the following be implemented prior to approval of this NDA:

A. General Comment (Container Labels and Carton Labeling)

1. Revise the NDC so the product codes (middle digits) are differentiated and not sequential. Injectable products might contain the same product concentration but contain a different total amount of drug in the container because of differences in the fill volume (e.g., 20 mg/2 mL (10 mg/mL), 40 mg/4 mL (10 mg/mL)). When the same product code number is used for all of the different containers, healthcare practitioners have had difficulty distinguishing the difference in total drug content.
2. Since the vials are intended for multiple doses and should be discarded 28 days after initial puncture, revise the statement [redacted] to read "Discard 28 days after initial puncture".

B. Carton Labeling

1. Delete the statement [redacted] as it crowds the carton labeling and is duplicative with the statement "Must Be Diluted Before Use". The statement "Must Be Diluted Before Use" on the PDP and back panel already instructs end users that the drug product must be [redacted].

2. Change the statement, [redacted] to read, "See Prescribing Information for complete dilution information."

3. Change the statement, [redacted] to read, "Usual Adult Dose: See Prescribing Information."

4. Include the unit of measurement after each number in the temperature range. For example, change "…room temperature 20° to 25°C (68° to 77°F)…" to read, "…room temperature 20°C to 25°C (68°C to 77°F)…".

5. The flag, "New Concentration and Preparation" may only remain in place for six months.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gemcitabine Injection that Accord submitted on January 17, 2017, and the listed drug (LD).

Table 2. Relevant Product Information for Gemcitabine Injection and the Listed Drug

Product Name	**Gemcitabine Injection**	**Gemzar (NDA 020509)**
Initial Approval Date	N/A	May 22, 1996
Active Ingredient	gemcitabine hydrochloride	gemcitabine hydrochloride
Indication	Ovarian, Breast, Non-small Cell Lung, and Pancreatic Cancer	
Route of Administration	Intravenous	
Dosage Form	Injection	
Strength	200 mg/2 mL, 1 gm/10 mL, 1.5 gm/15 mL, and 2 gm/20 mL	200 mg and 1 gm
Dose and Frequency	**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/m2 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.	
How Supplied	**Multiple-dose Vials:** 200 mg/2 mL (100 mg/mL) 1 g/10 mL (100 mg/mL) 1.5 g/15 mL (100 mg/mL) 2 g/ 20 mL (100 mg/mL)	**Single-Use Vials:** 200 mg 1 gm
Storage	Store at 20°C to 25°C (68°F to 77°F) and that allows for excursions between 15° C and 30°C (59°F and 86°F).	
Container Closure	Clear glass vials with rubber stopper.	Clear glass vials with (b) (4) stoppers.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Gemcitabine Injection labels and labeling submitted by Accord on October 13, 2016 and January 16, 2017.

- Container labels
- Carton labeling
- Prescribing Information

G.2 Label and Labeling Images

(b) (4)

[redacted]

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

OTTO L TOWNSEND
02/28/2017

CHI-MING TU
02/28/2017

M E M O R A N D U M

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

DATE: 12/19/2016

TO: Division of Oncology Products (DOP2)
Office of Hematology and Oncology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209604

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Nirmal Hospital Pvt Ltd.	Ring Road, Civil Street, Nr. Kadiwala School, Surat, 395002, Gujarat, India
Clinical	City Cancer Centre	No. 33-25-33, Venkta Krishnayya Street, Suryaraopet, Vijayawada, 520002 Andhra Pradesh, India
Clinical	Meenakshi Mission Hospital & Research Centre	Lake Area, Melur Road, Madurai, 625107, Tamil Nadu, India
Clinical	Curie Manavata Cancer Centre	Opp. Mahamarg Bus Stand, Mumbai Naka, Nashik, Maharashtra, India

M E M O R A N D U M

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

DATE: 12/19/2016

TO: Division of Oncology Products (DOP2)
Office of Hematology and Oncology Products

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 209604

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

Although the last inspections was classified as a VAI, based on the inspectional outcome and our recommendation to the review division, an inspection is not needed at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Srinivasam Cancer Care Hospitals India Private Limited	No. 236/1, 2nd Floor, Vijayshree Layout, Arekere, Bannerghatta Road, Banglore, Kamataka, India
		(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHILA S NKAH
12/20/2016

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209604

Application Type: 505(b)(2)

Drug Name(s)/Dosage Form(s): Gemcitabine injection, for intravenous use, 100 mg/mL vials

Applicant: Accord Healthcare Inc.

Receipt Date: October 13, 2016

Goal Date:

PDUFA (12 month- Standard Review): August 13, 2017

1. Regulatory History and Applicant's Main Proposals

Gemcitabine Injection, is a sterile, clear, colorless to pale yellow solution in a multi-dose clear glass vial formulated as 100 mg/mL gemcitabine freebase with USP/NF grade PEG- 300, propylene glycol and dehydrated alcohol. Sodium hydroxide and hydrochloric acid are added to obtain pH (b) (4). Clinical presentations are 2 mL, 10 mL, 15 mL and 20 mL vials with (b) (4) stopper and color-coded (b) (4) seal. Drug product is intended to be admixed with 0.9% sodium chloride, USP for intravenous infusion over 30 minutes.

The Reference Listed Drug (RLD) for the proposed 505 (b)(2) application is GEMZAR® [Gemcitabine for Injection (Lyophilized)], a product of Eli Lilly and Company Limited, USA.

The proposed formulation differs from the formulation of the LD in terms of its form (ready to use formulation as compared to the lyophilized formulation of the LD). IND 107393 was first submitted on October 17, 2011, with clinical study # 655-10, entitled "A Multi-Center, Randomized, Open-Label, Two-Period, Two-Treatment, and Two-Way Crossover, Single Dose Bioequivalence Study Comparing Gemcitabine Injection (Manufactured by Intas Pharmaceuticals Ltd.) to the reference listed drug Gemzar injection (Eli Lilly and Co) in patients with Pancreatic or Ovarian Cancer", intended to support a 505(b)(2) application for Gemcitabine Injection. A summary of the study results submitted on July 2014 with the IND Annual Report (amendment 11) indicated that the study failed to meet the bioequivalence acceptance criteria.

On August 19, 2013, Accord submitted a second bioequivalence (BE) protocol, study # 311-13 entitled, "A Multicenter, Randomized, Open-Label, Two-Period, Two-Treatment, Two-Way Crossover, Single Dose Bioequivalence Study Comparing Gemcitabine Injection 100 mg/ml (manufactured by Intas Pharmaceuticals Ltd) to the Listed Drug Gemzar 1g/vial (Lilly USA, LLC) in Patients with Pancreatic or Ovarian Cancer". Results from study 311-13 are intended to support this 505(b)(2) application for Gemcitabine Injection.

On September 1, 2015 a type B, pNDA meeting teleconference was held to discuss the completeness and appropriateness of the submitted information intended to support NDA approval. The meeting minutes issued on September 23, 2015.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 16, 2017. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *No comments*

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *No comments*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment: *No comments*

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment: *No comments*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: *No comments*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *No comments*

YES

7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment: *No comments*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment: *No comments*

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment: *No comments*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment: *Product title is bolded; however the product title should be, "Gemcitabine injection, for intravenous use", with lower case as indicated.*

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *No comments*

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment: *No boxed warning is proposed.*

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment: *No comments*

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment: *No comments*

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.****"*)

Comment: *No comments*

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment: *No comments*

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment: *No comments*

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment: *No comments*

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment: *Only one dosage form proposed in different strengths which are bulleted.*

Selected Requirements of Prescribing Information

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment: *No comments*

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment: *No comments*

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment: *No comments*

Revision Date in Highlights

NO 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment: *Revision Date should be on one line and right justified.*

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment: *No comments*

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment: *No comments*

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment: *There is no proposed black box warning.*

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment: *No comments*

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment: *No comments*

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *No comments*

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment: *No comments*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Subsections 8.1, 8.2, and 8.3 are pertinent to applications required to convert to the Pregnancy and Lactation Labeling Rule (PLLR).*

- *FDA published the Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,*

referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR or final rule) at https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

- *Refer to the FDA website for Pregnancy and Lactation Labeling (Drugs) Final Rule at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm*
- *Refer to "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry (December 2015)" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf Refer to Appendix A: ORGANIZATION AND FORMAT FOR PREGNANCY, LACTATION, 775 AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL SUBSECTIONS*

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment: *No comments*

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment: *No comments*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment: *No comments*

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment: *No comments*

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment: *No comments*

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment: *There is a Contraindication listed for this product .*

Selected Requirements of Prescribing Information

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *No comments*

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: No comments

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: No comments

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *No comments*

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ANUJA PATEL
12/12/2016

MONICA L HUGHES
12/13/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209604/0 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: N/A Established/Proper Name: GEMCITABINE Dosage Form: injection Strengths: 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)		
Applicant: Accord Healthcare Inc. Agent for Applicant (if applicable): N/A		
Date of Application: October 13, 2016 Date of Receipt: October 13, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: August 13, 2017	Action Goal Date (if different): August 11, 2017	
Filing Date: December 12, 2016	Date of Filing Meeting: November 17, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): 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.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?	☒	☐		

If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.				
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☐	☒	☐	RPM sent email to document room on12.4.16, requesting the following updates: requesting removal of Regulatory Pathway 505b(1); and addition of type 3 classification
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☒	☐		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product	☐	☐	☒	

considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD	☒	☐	☐	

guidance?[1] **If not,** explain (e.g., waiver granted).				
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		Accord Healthcare, Inc. ("Accord") is a wholly owned subsidiary of Intas Pharmaceuticals Limited, and has a place of business at 1009 Slater Road, Suite 210-B, Durham, NC 27703.
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	Beginning on **12/5/2016**, an NDA applicant or NDA holder must submit patent information to its NDA on the revised Forms FDA 3542a or 3542, as appropriate. The forms have been updated to conform to regulatory changes made by the final rule and to facilitate electronic completion.
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	Electronic Submission
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		PERC meeting scheduled for March 8, 2017
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	Initial Agreement letter issued August 12, 2016under IND 107393
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Request for full waiver of pediatric studies included with NDA

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	NDA is a 505b2
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015:	☐	☒	☐	Comments will be

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☐	☒	☐	included in the Day 74 letter
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	Consult uploaded 11/1/16
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	Consult uploaded 11/7/16
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☐	☐	Consult uploaded 11/7/16
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT	☒	☐	☐	NDA contains BE

study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** Office of Study and Integrity and Surveillance ***OSIS consult submitted 11/7/16***				studiestherefore OSIS was consulted
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 1, 2015 teleconference, Type B, IND 107393	☒	☐		On September 1, 2015 a type B, pNDA meeting teleconference was held under IND 107393 to discuss the completeness and appropriateness of the submitted information intended to support NDA approval. The meeting minutes issued on September 23, 2015.
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 17, 2016

BACKGROUND: Gemcitabine Injection, is a sterile, clear, colorless to pale yellow solution in a multi-dose clear glass vial formulated as 100 mg/mL gemcitabine freebase with USP/NF grade PEG-300, propylene glycol and dehydrated alcohol. Sodium hydroxide and hydrochloric acid are added to obtain pH (b) (4). Clinical presentations are 2 mL, 10 mL, 15 mL and 20 mL vials with (b) (4) stopper and color-coded (b) (4) seal. Drug product is intended to be admixed with 0.9% sodium chloride, USP for intravenous infusion over 30 minutes.

The Listed Drug (LD) for the proposed 505 (b)(2) application is GEMZAR® [Gemcitabine for Injection (Lyophilized)], a product of Eli Lilly and Company Limited, USA.

The proposed formulation differs from the formulation of the RLD in terms of its form (ready to use formulation as compared to the lyophilized formulation of the RLD).

IND 107393 was first submitted on October 17, 2011, with clinical study # 655-10, entitled "A Multi-Center, Randomized, Open-Label, Two-Period, Two-Treatment, and Two-Way Crossover, Single Dose Bioequivalence Study Comparing Gemcitabine Injection (Manufactured by Intas Pharmaceuticals Ltd.) to the reference listed drug Gemzar injection (Eli Lilly and Co) in patients with Pancreatic or Ovarian Cancer", intended to support a 505(b)(2) application for Gemcitabine Injection. A summary of the study results submitted on July 2014 with the IND Annual Report (amendment 11) indicated that the study failed to meet the bioequivalence acceptance criteria. On August 19, 2013, Accord submitted a second bioequivalence (BE) protocol, study # 311-13 with similar design to 655-10.

Refer to DARRTS IND 107393 for detailed regulatory history, including advice letters and issued communications.

Summary of Discussion: There were no filing issues identified by the review division during this meeting. The nonclinical review team stated that only a labeling review will be conducted for this application. CMC stated that no facility inspections will be needed for this application

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Anuja Patel	Y
	CPMS/TL:	Monica Hughes	Y
Cross-Discipline Team Leader (CDTL)	Anamitro Banerjee		Y
Division Director/Deputy	Joseph Gootenberg		Y

Office Director/Deputy	N/A		
Clinical	Reviewer:	Lee Pai Scherf	Y
	TL:	Gideon Blumenthal	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Edwin Chow	Y
	TL:	Jeanne Fourie Zirkelbach	Y
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	N/A	
	TL:	N/A	

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Stephanie Aungst	N
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Anamitro Banerjee	Y
	RBPM:	Steven Kinsley	Y
• Drug Substance	Reviewer:	Haripada Sarkar	Y
• Drug Product	Reviewer:	Paresma Patel	Y
• Process	Reviewer: Branch Chief:	Huiquan Wu Rakhi Shah	N Y
• Microbiology	Primary Reviewer:	Yarery Smith	N

	Secondary Reviewer:	Jesse Wells	N
• Facility	Primary Reviewer: Secondary Reviewer:	Wendy Zhang Christina Cappaci-Daniel	N N
• Biopharmaceutics	Primary Reviewer: Secondary Reviewer:	Parnali Chatterjee Okpo Eradiri	Y Y
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Nazia Fatima	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Janine Stewart	N
	TL:	Alice Tu Chi Ming	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			

	*For additional lines, right click here and select "insert rows below"	

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO From CMC Filing Review: The Applicant has provided data from two BE studies (311-13 and 655-10) to demonstrate BE between Test and Reference; results from the 2 studies will be assessed by Office of Clinical Pharmacology.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The drug is not first in its class
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: Nonclinical will review the label and provided comments as needed.	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? **Comments**: Per Application Team Leader: The facility decision will be based on profile rather than an inspection of the facility. This is an assessment made by the facility reviewer based on recent inspection profile and a risk assessment.	☐ Not Applicable ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Joseph Gootenberg **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): March 16, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): • **Day 60:** Monday, December 12, 2016 • **Deficiencies Identified letter (Day 74):** Monday, December 26, 2016 **(Target Date is December 19, 2016 due to Holiday)** • **Primary Reviews Due:** Sunday, July 9, 2017 **(Target Date: Friday July 7, 2017)** • **Secondary Review Due:** Sunday, July 16, 2017 **(Target Date: Friday, July 14, 2017)** • **CDTL Review Due:** Sunday, July 23, 2017 **(Target Date: July 21, 2017)** • **Deputy Director Review Due:** Sunday, August 13, 2017 **(Target Date: Friday, August 11, 2017)** • **Final Action Letter Due:** Sunday, August 13, 2017 **(Target Date: Friday, August 11, 2017)** **Comments**: Wrap Up Meeting scheduled for June 19, 2017	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)

☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANUJA PATEL
12/12/2016

MONICA L HUGHES
12/13/2016