CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209604Orig1s000

CLINICAL REVIEW(S)

ADDENDUM to CLINICAL REVIEW OF NDA 209604

Date	July 20, 2017
Clinical Reviewer	Lee Pai-Scherf, Medical Officer, DOP2/OHOP/CDER Erin Larkins, Acting Team Leader, DOP2/OHOP/CDER
NDA	209604
Application type	505(b)(2)
Date of Submission	October 13, 2016
PDUFA Goal Date	August 11, 2017
Applicant	Accord Healthcare, Inc.
Drug Product	Gemcitabine Injection 100 mg/mL
Drug Substance	Gemcitabine Hydrochloride USP
Dosage Forms/Strength/Route of Administration	Solution for infusion/100 mg/mL, 2mL, 10mL, 15mL and 20 mL/Intravenous
Proposed Indications 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	

This addendum provides the Financial Certification and Disclosure information submitted by Accord to NDA 209604.

The Applicant submitted Certification of Financial Interests and Arrangements of Clinical Investigators (Form 3454) for studies 311-13 and 655-10 and a list of all investigators who participated in the studies.

Accord Healthcare Inc. states that none of the listed investigators for studies 311-13 and 655-10 had financial conflicts of interest as defined in 21 CFR 54.2(a), 21 CFR 54.2(b), and 21 CFR 54.2(f).

Reviewer's Comment: based on the information provided, the investigators for studies 311-13 and 655-10 had no financial conflicts of interest that would affect the outcome of the study.

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/s/

LEE HONG PAI SCHERF
07/20/2017

CLINICAL REVIEW OF NDA 209604

Date	July 5, 2017
Clinical Reviewer	Lee Pai-Scherf, Medical Officer, DOP2/OHOP/CDER Erin Larkins, Acting Team Leader, DOP2/OHOP/CDER
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This NDA was submitted by Accord Healthcare, Inc. under the provisions of 505(b)(2) and relies on FDA's prior findings of safety and effectiveness for listed drug Gemzar® (gemcitabine for injection, Eli Lily), which was approved on May 15, 1996 under NDA 020509.

The Applicant is seeking approval for the above listed indications, for which Gemzar® (gemcitabine for injection) is approved.

Accord's proposed drug product is Gemcitabine Injection 100 mg/mL, 2mL, 10 mL, 15mL, and 20 mL solution form for intravenous infusion after dilution, while the reference listed drug, Gemzar® (gemcitabine for injection) is in the form of lyophilized powder for intravenous infusion after reconstitution and dilution.

Bioequivalence Study in Support of the NDA

No efficacy or safety data was submitted for review under this NDA. Please refer to the detailed review of the adequacy of the bioequivalence 311-13 study design and PK findings by FDA's Clinical Pharmacology Review Team, Drs. Edwin Chow and Jeanne Fourie Zirkelbach.

The application includes the results from two bioequivalence pharmacokinetic studies: Study 655-10 and Study 311-13. As per agreement reached during pre-NDA communication with the FDA, results from study 655-10 would not be reviewed for clinical pharmacology acceptability due to (b) (4) during the conduct of the study, which rendered the results uninterpretable.

Study 311-13 is a multicenter, 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® 1 g/vial (gemcitabine for injection 1 g/vial), by Lilly USA, LLC, Indianapolis, IN 46285, USA) in patients with pancreatic or ovarian cancer.

The primary endpoint of the study is to characterize the PK profile of the test formulation relative to that of reference formulation in patients and to assess the bioequivalence. The secondary endpoint is to monitor the safety of the patients, who are exposed to the investigational medicinal product.

All patients received single dose of either the test gemcitabine or reference gemcitabine 1000mg/m^2 intravenously over 30 minutes as per randomization schedule, with a gap of 7 days between the dose administration in Period-I and Period-II. Patients with ovarian cancer received gemcitabine on day 1 (Period I) and day 8 (Period II) of the 21 day cycle and carboplatin (AUC 5) on day 1 of each cycle. Patients with pancreatic cancer received gemcitabine on day 1 (Period I) and day 8 (Period II). Blood sample for pharmacokinetic assessment were collected at the pre-specified time points after each dese.

From July 4, 2014 thru November 19, 2014 a total of 32 patients were enrolled in 6 investigational sites in India. The mean age was 49 year-old (range 30 to 63), 90% were female (N=28), 100% Asian (N=32), 78% (N=25) of the patients had ovarian cancer and 22% (N=7) pancreatic carcinoma.

Pharmacokinetic results from 30 patients who completed the two-way crossover portion per protocol were submitted and reviewed by the Clinical Pharmacology review team. The team concluded that the application is acceptable from a clinical pharmacology perspective. The PK data showed that the 90% confidence intervals of the test gemcitabine and reference gemcitabine were within 80-125%.

The applicant states that a total of 30 adverse events (AEs) were reported by 15 patients during the conduct of the study. The most frequent AEs were constipation (N=6), vomiting (N=5) and diarrhea (N=3). One serious AE was reported (constipation). There were no deaths during the study.

Pediatric Study Plan

On March 11, 2016, Accord submitted an Initial Pediatric Study Plan (iPSP) and a request for a full waiver of the pediatric studies requirements for Gemcitabine injection, 100 mg/mL (IND 107393). FDA issued an Agreed Initial Pediatric Study Plan (Agreed iPSP) for Gemcitabine Injection 100 mg/mL letter on April 12, 2016. On March 29, 2017, PeRC members met and

agreed with granting a full waiver for Gemcitabine Injection for the proposed population since available data indicates that conducting studies in pediatric population is impossible or highly impractical because of the small number of pediatric patients with ovarian cancer, metastatic breast cancer, non-small cell lung cancer and pancreatic cancer.

Labeling

The review team recommended multiple revisions to the Applicant's proposed Packaged Insert for clarity, brevity and consistency with the reference drug Package Insert. These recommendations were communicated to Accord on May 30, 2017. Accord accepted FDA's recommendations to the label.

Recommendation

The clinical review team recommends approval of NDA 209604, contingent upon satisfactory review of Gemcitabine Injection (100mg/mL) by all FDA disciplines. The recommendation is based FDA's Clinical Pharmacology Review team's findings indicating comparative bioequivalence between Accord's drug product and the reference listed drug Gemzar®.

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/s/

LEE HONG PAI SCHERF
07/07/2017

ERIN A LARKINS
07/07/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 209604 **Applicant: Accord HealthCare Inc.** **Stamp Date: October 13, 2016**

Drug Name: Gemcitabine; Injection Solution **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
10.	Has the applicant submitted a benefit-risk analysis for the product?			X	
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?	X			GEMZAR® (gemcitabine for injection)
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	X			
14.	Describe the scientific bridge (e.g., BA/BE studies)	X			BE studies
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size:			X	BE studies

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Treatment Arms: Location in submission:				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	This 505(b)(2) application is supported by two bio-equivalence studies (311-13 and 655-10)
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			The BE studies submitted to support this application are acceptable (refer to filing review by the Clinical Pharmacology Review team)
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The BE studies submitted to support this application are acceptable (refer to filing review by the Clinical Pharmacology Review team)
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			X	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			Only PK data sets were submitted, per agreement.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?			X	
38.	For the major derived or composite endpoints, are all of the			X	

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

There are no comments to be forwarded to the Applicant at this time.

Lee Pai-Scherf, MD, DOP2/OHOP — December 8, 2016

Reviewing Medical Officer — Date

Gideon Blumenthal, MD, DOP2/OHOP

Clinical Team Leader — Date

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/s/

LEE HONG PAI SCHERF
12/08/2016

GIDEON M BLUMENTHAL
12/08/2016