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APPLICATION NUMBER:

209604Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	July 17, 2017
From	Anamitro Banerjee, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	209604
Type of Application	505(b)(2)
Applicant	Accord Healthcare Inc.
Date of Receipt	October 13, 2016
PDUFA Goal Date	August 13, 2017
Proposed Proprietary/Established Name	N/A/ gemcitabine injection
Dosage forms / Strength	Injection/ 100 mg/mL in 2 mL, 10 mL, 15 mL and 20 mL
Route of Administration	Intravenous injection
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. • as a single agent for the treatment of pancreatic cancer.
Recommended:	**APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Drug Substance (Haripada Sarker), dated June 26, 2017
- Drug Product (Paresma Patel), dated June 14, 2017
- Microbiology (Yarery Smith), dated May 22, 2017
- Manufacturing Facilities (Wenzheng Zhang), dated July 07, 2017
- Manufacturing Process (Huiquan Wu), dated July 10, 2017
- Quality Biopharmaceutics (Parnali Chatterjee), dated March 09, 2017

- Clinical (Lee Pai-Scherf); in DARRTS, dated July 07, 2017
- Pharmacology/Toxicology (Stephanie L. Aungst); in DARRTS, dated July 17, 2017
- OPDP (Nazia Fatima), in DARRTS, dated June 16, 2017
- CMC Biostatistics (Meiyu Shen); in DARRTS, dated June 08, 2017
- DMEPA (Otto Townsend), dated February 28, 2017 and May 02, 2017
- OSIS (Li-Hong Yeh); in DARRTS, dated May 19, 2017
- Clinical Pharmacology (Edwin Chow), dated July 12, 2017

1. Introduction

The proposed Gemcitabine Injection is a clear, colorless to yellow, sterile solution filled in a clear glass vial available in 100 mg/mL concentration presented in 2 mL, 10 mL, 15 mL, and 20 mL fill volumes. The drug product is intended for dilution (with 0.9% sodium chloride) into infusion solution and intravenous administration. This submission (NDA 209604) is a 505(b)(2) application, referencing the lyophilized powder formulation, GEMZAR® (NDA 020509). The listed drug (LD) GEMZAR® is available in 200 mg and 1 g (b) (4) vials. The LD requires an additional reconstitution step with 0.9% sodium chloride solution prior to dilution into infusion solution. While the therapeutic active moiety (gemcitabine), salt form, and route of administration are the same as LD, the proposed product differs in dosage form, strength, and drug content.
The applicant included two pharmacokinetic bioequivalence trials with 10 mL configuration of the proposed product and the 1g/vial configuration of the LD; and a waiver of in vivo bioequivalence (BE) request for remaining three fill volumes of the proposed product with same concentrations.
The applicant is relying on FDA's finding on safety and efficacy for the listed drug GEMZAR®.

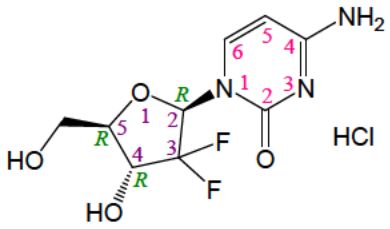
2. Background

The current application relies on the Agency's determination of human safety and efficacy for the gemcitabine lyophilized powder for injection (GEMZAR®0, which has been previously approved for marketing under NDA 020509.

The applicant is seeking approval of gemcitabine solution for injection for the same indication granted for GEMZAR®. GEMZAR® 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; and as a single agent for the treatment of pancreatic cancer.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance for NDA 209604 is gemcitabine hydrochloride. Labeling and strength designation is on the basis of the gemcitabine free base, consistent with the listed product, GEMZAR®. The FDA salt nomenclature policy is adopted for labeling purposes.
Chemical Name: 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer).



Gemcitabine
4-amino-1-((2*R*,4*R*,5*R*)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one hydrochloride
Chemical Formula: $C_9H_{12}ClF_2N_3O_4$
Molecular Weight: 299.66

The gemcitabine drug substance is non-hygroscopic, white to off white crystalline powder that is soluble in aqueous and slightly soluble in methanol, but practically insoluble in alcohol (ethanol) and other polar organic solvents. Polymorphism is not known for this drug substance. The drug substance has three chiral centers with a specific rotation of +43° – +50° at 20°C and melting point of 287 – 292 °C.

The drug substance is manufactured by (b) (4) The applicant refers to the DMF (b) (4) for the drug substance manufacturing process. The DMF was reviewed and was found adequate to support this NDA. The drug substance specifications are consistent with the USP monograph. The drug substance is packaged in (b) (4) (b) (4) The applicant referred to the DMF for further information. The batch analysis data and the stability conform to the specifications. The proposed retest period of (b) (4) for the drug substance proposed by the applicant may be granted.
The applicant included a (b) (4)

The drug product formulation contains the API, PEG 300 (b) (4), Propylene glycol (b) (4), sodium hydroxide ((b) (4) and pH adjusting agent), hydrochloric acid (pH adjusting agent), dehydrated alcohol ((b) (4)), and (b) (4). All the ingredients are compendial grade. No novel excipients or excipients with human or animal origin are used.
The drug product is manufactured (b) (4) The drug product manufacturing process involves (b) (4)
The in-process controls indicated in the submission were found adequate for this type of dosage form. The commercial scale is (b) (4) L for the (b) (4) mL presentation and (b) (4) L for the other presentations.

The proposed drug product specifications include routine testing needed for this type of product. The drug product specifications include testing for description, identification, pH, (b) (4) volume in container, particulate matter, sterility, bacterial endotoxin, chromatographic purity, assay, alcohol content, (b) (4) clarity, color and achromicity, (b) (4) and (b) (4) Batch data for several exhibit batches of each strength (about (b) (4) the commercial scale) provided in this NDA conform to the proposed specifications.

Stability data, inverted as well as upright, for several batches for each strength under 36 M long term (25°C/60% RH), and 6M accelerated (40°C/75%RH) conditions provided in this submission are acceptable. Post approval stability protocol and commitment is adequate. The proposed shelf life of 24 months may be granted for the drug product when stored under controlled room temperature: 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F). The applicant provided adequate data to demonstrate that a vial may be stored for 28 days at room temperature after the initial puncture.

Considering that the applicant demonstrated that the 10 mL fill volume is bioequivalent to the listed drug, the biowaiver request for the proposed drug product for all the fills are granted as the concentrations for all the presentations are the same.

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

Facilities
All the facilities are currently acceptable.

Overall CMC recommendation
The Office of Pharmaceutical Quality recommends approval action for NDA 209604.

4. Pharmacology/Toxicology
The applicant identified two new impurities ((b) (4) specific to this product originating from the excipients (b) (4) The applicant proposed acceptance limits for (b) (4) (NMT (b) (4) %) and (b) (4) (NMT (b) (4) %) based on a dose of (b) (4) mg/m^2 rather than the maximum dose of 1250 mg/m^2 approved for the breast cancer indication. On agency's request, the applicant lowered the acceptance limits for these impurities to NMT (b) (4) % and NMT (b) (4) % respectively based on the maximum dose of 1250 mg/m^2. No other impurities were identified in this product.

The Pharmacology/Toxicology Reviewer recommends approval of the application.

5. Clinical
No clinical safety or efficacy data were submitted in this NDA application. The team recommended multiple revisions to the applicant's proposed package insert for clarity, brevity, and consistency with the listed drug package insert.

The clinical team recommends approval of this product contingent upon satisfactory reviews by other FDA disciplines.

6. Clinical Pharmacology

The applicant's request for waiver of in vivo bioequivalence assessment was denied based on FDA concerns that (b) (4) As a result, the current 505(b)2 application includes two pharmacokinetic bioequivalence trials. However, due to (b) (4) of Study 655-10, only the later study (Study 311-13) was reviewed. The study 311-13 compares the 10 mL fill configuration of the proposed product with the 1 g/vial configuration of the LD.

In the Study 311-13, the applicant conducted a multicenter, randomized, open label, two-period, two treatment, two-way crossover, single dose bioequivalence study in patients with pancreatic or ovarian cancer. The study was planned to be conducted on 44 patients with pancreatic or ovarian cancer, but only 32 patients were treated. Only 30 patients were included in statistical analysis. Two patients were excluded due withdrawal of informed consent or infusion interruptions.

Study 311-13 showed that Gemcitabine Injection was bioequivalent to the listed drug, with the 90% confidence intervals of the geometric mean ratios of gemcitabine Cmax and AUC falling within 80-125% limits.

The Agency's statistical team (Review by Dr. Meiyu Shen dated June 08, 2017) has verified that the smaller number of subjects in the study is acceptable.

The Office of Clinical Pharmacology found the information provided in the application acceptable.

7. Advisory Committee Meeting

N/A

8. Pediatrics

Full waiver from the pediatric studies request under IND 107393 was reviewed by the PeRC and it was granted on March 29, 2017

9. Other Relevant Regulatory Issues

None

10. Labeling

Several labeling comments were conveyed to the applicant during the course of the review of this application. The applicant accepted all the edits recommended by the agency.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

No deficiencies are pending at this time that precludes approval of this NDA. This NDA is recommended for APPROVAL.

- **Risk Benefit Assessment**

Please refer to NDA 020509.

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/s/

ANAMITRO BANERJEE
07/18/2017

JOSEPH E GOOTENBERG
07/18/2017

I concur with the conclusions reached by the CDTL, as embodied in this review, that no deficiencies are pending at this time that preclude approval of this NDA. I recommend this NDA for APPROVAL.