CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209604Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA209604/SDN1
Link to EDR	\\CDSESUB1\evsprod\NDA209604\209604.enx
Submission Date	NDA
Submission Type	*Standard Review*
Brand Name	Gemcitabine Injection
Generic Name	Gemcitabine
Dosage Form and Strength	Sterile solution for injection with100 mg/mL strength in four filled volumes of 2 mL, 10 mL, 15 mL, and 20 mL
Route of Administration	Intravenous infusion
Proposed Indication	For intravenous use as a 30 minute infusion in: • Ovarian Cancer at 1000 mg/m^2 on Days 1 and 8 of each 21 day cycle • Breast Cancer at 1250 mg/m^2 on Days 1 and 8 of each 21 day cycle • Non-Small Cell Lung Cancer at 1000 mg/m2 on Days 1, 8 and 15 of each 28 day cycle or 1250 mg/m^2 on Days 1 and 8 of each 21 day cycle • Pancreatic Cancer at 1000 mg/m^2 once weekly for up to 7 weeks, followed by a week of rest from treatment. Subsequent cycles should consist of infusions once weekly for 3 consecutive weeks out of every 4 weeks.
Applicant	Accord Healthcare Inc.
Associated IND	*IND107393*
OCP Review Team	*Edwin Chiu Yuen Chow, Ph.D.* *Jeanne Fourie Zirkelbach, Ph.D.*

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1. EXECUTIVE SUMMARY

In accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Accord Healthcare Inc. submitted an original New Drug Application (NDA 209604/S-0000) for Gemcitabine Injection® 100 mg/mL. Accord Healthcare Inc. proposed that Gemcitabine Injection® has the same active ingredient, route of administration (i.v. infusion), and indications as the listed drug product, Gemcitibine HCl for injection (Gemzar®). However, unlike Gemzar, which is formulated as a sterile lyophilized powder containing 200 mg or 1 g of gemcitabine HCl as well as mannitol and sodium acetate as excipients, Gemcitabine Injection® is a formulated as a clear colorless to pale yellow solution containing gemcitabine HCl (100 mg/mL) as well as PEG-300, propylene glycol and sodium hydroxide in dehydrated alcohol as excipients.

Based on the comparison to the listed drug (Gemcitibine HCl for injection (Gemzar®; NDA20509), Accord Healthcare Inc. requested a waiver of *in vivo* bioequivalence assessment for Gemcitabine Injection® in accordance with 21 CFR 320.22(b). This request was denied based on FDA concerns regarding (b) (4) As a result, the current 505(b)2 application includes two pharmacokinetic bioequivalence trials. However, (b) (4) of Study 655-10, only the later study (Study 311-13) was reviewed for clinical pharmacology acceptability.

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 C_{max} and AUC falling within 80-125% limits.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology V has reviewed the information contained in NDA 209604/S-0000. This application is acceptable from a clinical pharmacology perspective.

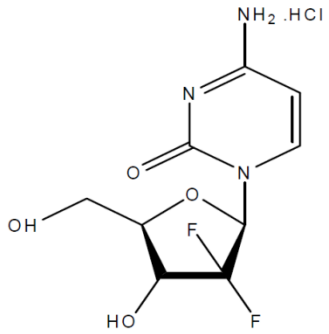
1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

As per drug product label of Gemzar® for Injection, gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is denoted as 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer). The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ .HCl. The salt form has a molecular weight of 299.66 g/mol. Gemcitabine HCl is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.



Gemcitabine HCl

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant's proposed Gemcitabine Injection is supplied in a sterile form for intravenous use only. The proposed drug product is available in a 100 mg/mL strength with four filled volumes of 2 mL, 10 mL, 15 mL and 20 mL, and excipients include (b) (4) (PEG) 300, (b) (4)% propylene glycol, and (b) (4)% dehydrate alcohol. The pH of the final solution for injection is adjusted by sodium hydroxide and hydrochloric acid to pH (b) (4)

The aqueous solubility of gemcitabine hydrochloride studied in purified water is 70.2 mg/mL.

2.2.2 Therapeutic individualization

This section is not applicable for this NDA.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

There are no significant content changes to the relevant clinical pharmacology sections in the label proposed by Accord Healthcare Inc. Based on the current Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products[1], Section 7 (Drug Interactions) was removed from the label since there is no significant clinical meaningful interaction between gemcitabine, cisplatin, paclitaxel, or carboplatin. The pharmacokinetic contents in Section 12.3 was re-organized according to the published Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

[1]https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm109739.pdf

3.1 Overview of the Product and Regulatory Background

On March 12, 2010, the applicant (IND107393) met with FDA to discuss the proposed product (Gemcitabine Injection) for submission as a 505(b)(2) application. FDA stated that a bio-waiver for in vivo bioequivalence to the listed drug cannot be granted due to [(b) (4)] On July 2014, a summary of in vivo bioequivalence study results (Study#655-10) [(b) (4)] was submitted with the IND Annual Report (Amendment 11). The study failed to meet the bioequivalence (BE) acceptance criteria. [(b) (4)] As a result, Accord submitted a new BE protocol (Study # 311-13) [(b) (4)] with clear specification of gemcitabine infusion within the specified time of 30 minutes (±5 min) and to exclude patient data from the final analysis in cases where there is deviations from the specified infusion time. The new proposed study was to enroll 44 patients. On October 29, 2014, an FDA Advice letter communicated that Accord needs to re-estimate their sample size in Study 311-13. However, on December 17, 2014, Accord stated that the expiry date of the PLD (Gemzar 1g /vial) had expired [(b) (4)] and only 32 out of 44 planned patients were enrolled. On March 3, 2015, FDA provided Accord with two alternative options: (1) if the available data from 30 patients showed bioequivalence, the study will be stopped and will not proceed to accrue additional patients to Study 311-13; (2) Accord will obtain a new lot of Gemzar and complete the study with a total of 44 patients. On June 8, 2015, Accord agreed to comply with FDA option 1 and completed the study with 30 patients. Overall, Accord completed Study#311-13 in 32 patients with ovarian or pancreatic cancer. However, only data from 30 patients were used in statistical analyses. Two patients were excluded from the BE analysis due to withdrawal of consent and a protocol deviation.

3.2 General Pharmacological and Pharmacokinetic Characteristics

As stated in the current approved gemcitabine package insert, gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine is generally administered as intravenous infusion for 30 minutes. The volume of distribution was increased with infusion length. Following intravenous infusions lasting <70 minutes, volume of distribution of gemcitabine was reported to be around 50 L/m^2. For long infusions, the volume of distribution rose to 370 L/m^2. Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible. Within one week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2′-deoxy-2′,2′-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours. Clearance of gemcitabine was affected by age and gender. The lower clearance in [(b) (4)] the elderly results in higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table [(b) (4)] shows the plasma clearance and half-life of gemcitabine following short infusions for patients by age and gender.

Table (b) (4) : Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men ($L/hr/m^2$)	Clearance Women ($L/hr/m^2$)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a] Half-life for patients receiving <70 minute infusion.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

This section is not applicable for this NDA.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

No formal studies were conducted for the proposed general dosing regimen appropriate for this NDA.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No formal studies were conducted to evaluate the intrinsic factors for this NDA.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No formal studies were conducted for food-drug or drug-drug interactions for this NDA.

4. APPENDICES

4.1 Bioanalytical Method Report

Plasma concentrations of gemcitabine in patients were measured using a high performance liquid-chromatography tandem mass spectrometry (LC-MS/MS) method with Gemcitabine $^{13}C^{15}N_2$ used as an internal standard (ISTD). Briefly, 0.1 mL plasma samples, spiked with ISTD, were precipitated with methanol and centrifuged to separate the precipitates. The supernatant was transferred and used for analytical analyses. The method was validated for measuring the total gemcitabine concentration only. The validation summary is shown below (Table 2).

Table 2: Summary of LC-MS/MS method parameters from validation report

Validation Parameters	**Results**
Linearity (Range)	0.102-35.007 µg/mL
Coefficient of determination	>0.99
Limit of quantification	0.102 µg/mL
Limit of detection	0.020 µg/mL
Dilution integrity	105.079 µg/mL diluted 5 fold
Selectivity	No interference at the retention time and transition of drug and internal standard

Between-batch (inter-day precision)	0.9-4.2%
Within-batch (Intra-day precision)	0.6-2.7%
Between-batch (Inter-day accuracy)	97.4-106.4%
Within-batch (Intra-day accuracy)	97.8-107.1%
Recovery (Gemcitabine) for low quality control (LQC), medium quality control (MQC) & high quality control (HQC)	75.1%, 74.7%, and 75.3%
Average recovery of ITSD	80.4%
Bench-top stability	11 hours at room temperature
Processed stability	101 hours within 2-8°C 2 hours at room temperature
Freeze-thaw stability (cycles)	5 cycles (at -65 ± 10°C)
Long-term stability of gemcitabine in human plasma	181 days at -65 ± 10°C & -22 ± 5°C

In Study 311-13, gemcitabine total plasma concentrations were determined though the same LC-MS/MS method as described above and analyzed by (b) (4). A total of 14 sample analysis batches were performed. Of the 14 analysis batches, 1 run failed due to blank QC samples not meeting prespecified analytical run acceptance criteria, but the batch was re-ran and met the analysis criteria. Incurred sample reproducibility was performed on 103 samples and 95.1% of samples met the prespecified criteria. Samples were stored at -65°C until time of analysis. The maximum sample storage duration between collection and analysis for all samples was 140 days, which was within the established stability interval of 181 days. A summary of the LC-MS/MS method results are show in Table 3.

Table 3: Summary of LC-MS/MS method parameters from Study 311-13

Matrix	Human Plasma
Reference or analytical standard	Lot 9-DHL-154-2 (From (b) (4); 98% purity)
Minimum dilution	1
Standard curve concentrations (µg/mL)	0.102, 0.203, 1.753, 5.264, 17.547, 26.308, 31.506, 35.007 µg/mL
Limit of detection	NA
LLOQ	0.102 µg/mL
ULOQ	35.007 µg/mL
Standard Curve Precision (%CV)	1.3 to 3.3%
Standard Curve Accuracy (%)	91.0 to 105.4%
Inter-assay Precision (%CV)	HQC (27.002 µg/mL): 3.9% MQC (15.526 µg/mL): 5.7% LMQC (5.279 µg/mL): 3.8% LQC (0.301 µg/mL): 6.7%
Inter-assay Accuracy (%)	HQC (27.002 µg/mL): 105.2% MQC (15.526 µg/mL): 98.6% LMQC (5.279 µg/mL): 95.4% LQC (0.301 µg/mL): 101.3%

4.2 Clinical PK/PD Assessments

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. (b) (4). Patients were administered Gemcitabine Injection (either test or reference product as per randomization schedule) at a dose of 1000 mg/m^2 over 30 minutes (-3 minutes and + 5 minutes) on Day 1 (Period 1) and Day 8 (Period 2) of the 21 day cycle in case of ovarian cancer patients and on Day 1 and Day 8 of the chosen week in case of pancreatic cancer patients. Carboplatin was administered intravenously on Day 1 after Gemcitabine administration for ovarian cancer patients. A total of 16 blood samples, (3 samples during infusion and 12 samples post infusion of 2 mL each & 1 pre-dose sample of 4 mL) were collected from each patient in each period (except for discontinued / withdrawn patients and missing samples). The timepoints taken were predose, -25 min before end of infusion (EOI), -15 min EOI, EOI, 5, 10, 20, 30, and 45 min, 1, 1.5, 2, 4, 6, 8, and 10 hr post EOI.

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. One patient was excluded from the analysis due to withdrawal of informed consent. The other patient had an infusion interruption at around 16 minutes and was discontinued from the study.

A summary of the PK parameters by study drug is shown in Table 4.

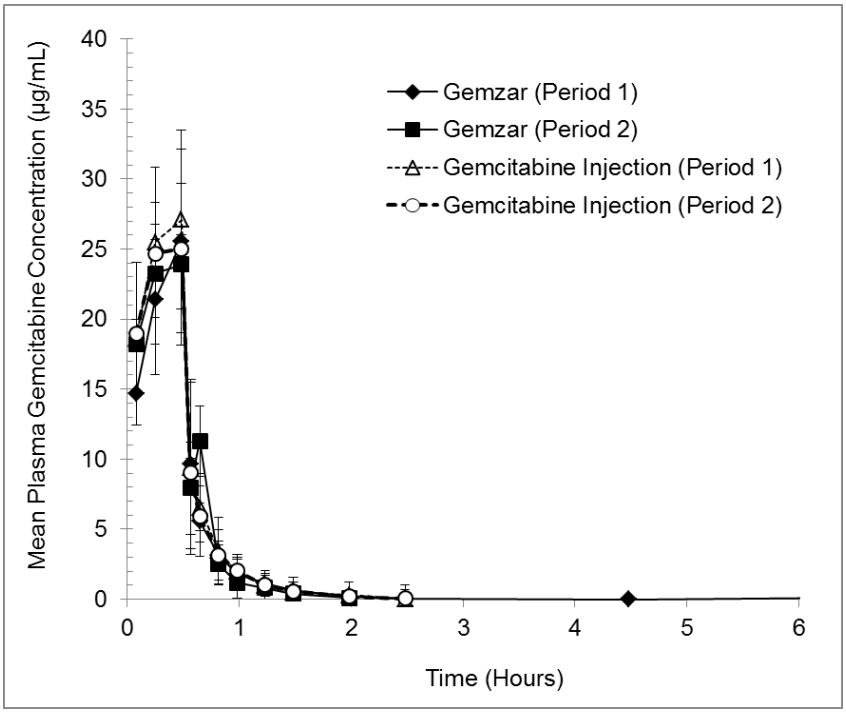
Table 4: Summary of PK Parameters (Study 311-13)

PK parameters	**Geometric Mean (% CV)**			
	Test		**Reference**	
	Period 1	**Period 2**	**Period 1**	**Period 2**
C_{Max} (µg/mL)	28.7 (18.4%)	26.4 (17.4%)	25.0 (26.5%)	27.5 (45.1%)
AUC_{0-t} (µg /mL·hr)	14.2 (17.5%)	14.2 (18.8%)	13.0 (22.9%)	13.1 (26.9%)
AUC_{0-Inf} (µg/mL·hr)	14.3 (16.9%)	14.3 (18.7%)	13.1 (23.1%)	13.2 (26.8%)
V_c (L/m^2)	24.8 (42.7%)	28.3 (49.1)	32.3 (65.5%)	33.4 (36.2%)
CL (L/hr/m^2)	70.4 (20.8%)	69.1 (20.2%)	75.2 (27.1%)	76.1 (28.0%)
$t_{1/2}$ (hr)	0.244 (12.6%)	0.284 (33.7%)	0.298 (28.0%)	0.304 (30.6%)

Test: test product (Gemcitabine Injection); Reference: reference listed product (Gemzar)

As shown in Figure 2, the PK profiles of Gemzar and Gemcitabine Injection were similar.

Figure 1: Plasma gemcitabine concentration vs. time profile in study drugs



Bioequivalence analyses were performed on data of 30 patients using Phoenix 64 (V7.0.0.2535). The pharmacokinetic parameters of gemcitabine were summarized in Table 5.

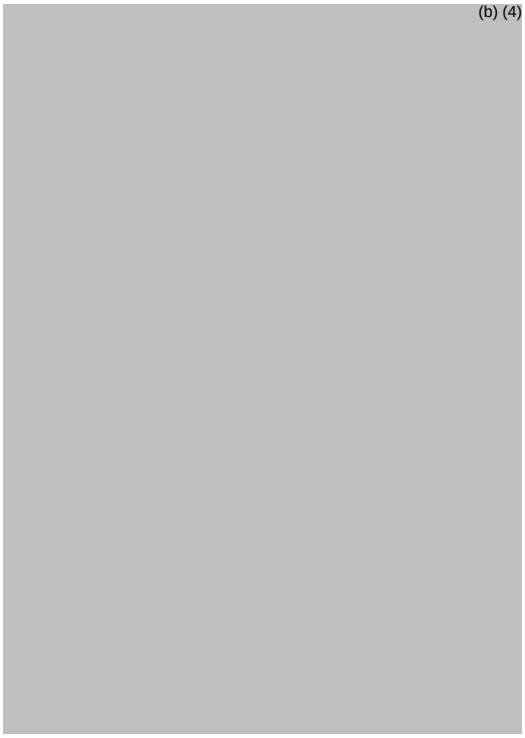
Table 5: Bioequivalence analyses of gemcitabine

	Geometric Mean Ratio (T/R)	**Lower Bound**	**Upper Bound**
$LogC_{max}$	105.2	94.4	117.2
$LogAUC_{0-t}$	108.6	101.9	115.7
$LogAUC_{0-inf}$	108.4	101.7	115.5

T: test product (Gemcitabine Injection); R: reference listed product (Gemzar)

The bioequivalence result showed that Gemcitabine Injection is bioequivalent to reference listed product. The same individual patient had received a single dose of Gemcitabine Injection and the reference listed product, which eliminate a potential deviation of differences in total gemcitabine clearance between male and female patients. The washout period between the two dosing periods (Day 1 and Day 8) of the crossover design study is acceptable since the half life of gemcitabine is between 42-94 min.

The two-way crossover bioequivalence study with 30 patients conducted by Accord appears acceptable. The between subject coefficient of variation (CV%) of gemcitabine clearance was reported to be between 17.1-31%. Intra-subject coefficient of variation is less than between subject variation. Assuming the intra-subject variability of gemcitabine is between 10-25%, a standard two-way crossover comparison between test and reference product showed that no more than 17 patients are needed to achieve 80% power for bioequivalence (see Table below).



In addition, the FDA statistical team has verified that the smaller number of subjects in the study is acceptable. See biometric review (REV-BIOMETRICS-01, 06/08/2017).

4.3 Exposure-Response

No formal studies were conducted for exposure-response for this NDA.

4.4 Co-Development of Drug and Companion Diagnostic

No formal studies were conducted for Co-development of drug and companion diagnostic for this NDA.

4.5 Influence of Genetic Markers on PK, Efficacy, or Safety

No formal studies were conducted for influence of genetic marker on PK, efficacy, or safety for this NDA.

4.6 PBPK Modeling and Simulation

No formal studies were conducted for PBPK modeling and simulation for this NDA.

4.7 Enrichment and Stratification

No formal studies were conducted for enrichment and stratification for this NDA.

4.8 Population PK Analysis

No formal studies were conducted for population PK analysis for this NDA.

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/s/

EDWIN C CHOW
07/12/2017

JEANNE FOURIE ZIRKELBACH
07/12/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA Number	209604	**SDN**	1
Applicant	Accord Healthcare Inc.	**Submission Date**	10/13/2016
Generic Name	Gemcitabine	**Brand Name**	Gemcitabine Injection
Drug Class	A prodrug of nucleoside metabolic inhibitor		
Indication	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		
Dosage Regimen	For intravenous use only. Ovarian Cancer: 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Breast Cancer: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Non-Small Cell Lung Cancer: 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. Pancreatic Cancer: 1000 mg/m^2 over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.		
Dosage Form	**Reference:** Gemcitabine HCl equivalent to 200 mg or 1 g gemcitabine sterile lyophilized powder in a single dose glass vial **Test:** Gemcitabine Injection 100 mg/mL, 2 mL, 10 mL, 15 mL and 20 mL	**Route of Administration**	Intravenous (IV) infusion
OCP Division	DCPV	**OND Division**	DOP2

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Edwin Chow	Jeanne Fourie-Zirkelbach
Pharmacometrics	NA	NA
Genomics	NA	NA

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	12/12/2016	**24-Day Letter Date**	12/26/2016
Review Due Date		**PDUFA Goal Date**	8/11/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☐ No

If yes explain: Pivotal bioequivalence trial.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☑ Bioequivalence		2	Comparison of PK of Gemzar® and Gemcitabine Injection in Study 311-13 & 655-10
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☑ Single Dose	2	Phase 1 Studies (311-13 & 655-10) on PK of Gemzar® and Gemcitabine Injection
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			

☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☑ Patients	2	Phase 1 Studies (311-13 & 655-10) on PK of Gemzar® and Gemcitabine Injection
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	***In Vitro***	0	***In Vivo***	2
Total Number of Studies to be Reviewed		0		2

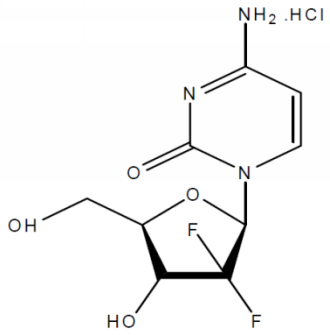
Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	Reference listed drug product as "R" and test drug product as "T"
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	Bioequivalence (BE) study (311-13 & 655-10); note only study 311-13 will be evaluated
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	BE study (311-13 & 655-10); note only Study 311-13 will be evaluated
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	Submission contains method validation report and bioanalytical report for Study 311-13 & 655-10
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports	☑Yes ☐No ☐N/A	Only PK data (concentrations and PK parameters) was submitted in

items 1 to 6 above (in .xpt format if data are submitted electronically)?		Study 311-13 & 655-10
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	Submitted BE Summary Data Tables
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	Tmax, Cmax, AUC, and PK concentrations
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		

8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

Gemzar (gemcitabine for injection, USP) is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is denoted as 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer). The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ .HCl. The salt form has a molecular weight of 299.66 g/mol. Gemcitabine HCl is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents.



Gemcitabine HCl

Mechanism of Action: The main mechanism of action of gemcitabine is to induce cell apoptosis by blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is first metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

Indication: Gemzar is approved for use (1) in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum- based therapy (2) in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated (3) in combination with cisplatin, for the treatment of non-small cell lung cancer (4) and as a single agent, for the treatment of pancreatic cancer.

Drug Product: Gemzar is supplied in a sterile form for intravenous use only. For the reference listed drug (RLD) product (NDA#020509), vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. For Gemcitabine Injection drug product, it is available in 100 mg/mL strength with four filled volumes of 2 mL, 10 mL, 15 mL and 20 mL, containing excipients that include (b)(4)% polyethylene glycol (PEG) 300, (b)(4)% propylene glycol, and (b)(4)% dehydrate alcohol and is adjusted by sodium hydroxide and

hydrochloric acid to pH [redacted]

Proposed Recommended Dosage: The proposed recommended intravenous dose of Gemzar is as follows:
Ovarian Cancer: 1000 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle.
Breast Cancer: 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle.
Non-Small Cell Lung Cancer: 1000 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 28-day cycle or 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle.
Pancreatic Cancer: 1000 mg/m^2 over 30 minutes once weekly for the first 7 weeks, then one week rest, then once weekly for 3 weeks of each 28-day cycle.

Regulatory History

- IND 107393 was initiated on December 3, 2009, and a Type B Pre-IND meeting was held on March 12, 2010. The FDA response that a bioequivalence study will be required for Gemcitabine Injection because [redacted]
- On October 17, 2011, Bioequivalence (BE) Study # 655-10 protocol, 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", was submitted for the intend to support a 505(b)(2) application for Gemcitabine Injection.
- A summary of study results (Study#655-10) submitted on July 2014 with the IND Annual Report (Amendment 11) indicated that the study failed to meet the bioequivalence acceptance criteria. [redacted]
- On August 19, 2013, Accord submitted a second bioequivalence (BE) protocol, which is Study # 311-13 [redacted] (1) Clear specification of gemcitabine infusion within the specified time of 30 minutes (+5 min) and exclude patient data from analysis if any deviation from the specified infusion time (2) Study sample size based on an adaptive sequential design [redacted]
- On August 6, 2014, a teleconference was held between FDA and Accord concerning the acceptability of the study design and the overall development plan for Study #311-13. Accord stated that the study was open for accrual and estimated that approximately 44 patients would be enrolled by the end of October 2014. FDA informed Accord that an agreement concerning the sample size re-estimation for the new Study protocol # 311-13 had not been reached, and that the [redacted] was not acceptable, [redacted].
- On December 17, 2014, Accord submitted a Type C Written Response Only meeting request to seek guidance regarding a path forward for the ongoing bioequivalence 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 a 505(b)(2) application for Gemcitabine Injection, manufactured by Intas, LD. Intas stated that the expiry date of the RLD (Gemzar 1 g/vial) used in study 311-13 was [redacted] and that only 30 out of 44 planned patients in stage-I of the study have been enrolled.
- On March 3, 2015, FDA issued final written response and also asked the sponsor to address the issue of controlling type I error rate in the sample size re-estimation.
- On June 8, 2015, FDA held an informal teleconference with the company for an update on Study # 311-13 and to confirm whether they intend to stop enrolling patients with the present 30 patients, as indicated in their March 20, 2015, Amendment, and that Accord will analyze the data based on Option 2 of our

March 3, 2015, minutes. Intas acknowledged and confirmed that the data will be analyzed with the 30 patients and that no new patients will be enrolled. FDA further instructed Accord to include in their NDA application a detailed regulatory history and an overall summary with top line data for both BE studies conducted under the IND.

- On July 28, 2015, FDA issued an Advice letter reiterating the agreements made during the June 8, 2015, teleconference and reminded Intas that Intas must submit an Initial Pediatric Study Plan (iPSP) no less than 210 days prior to submission of the 505(b)(2) marketing application for Gemcitabine injection and that failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

Reference Listed Drug (Gemzar) Pharmacokinetics from Package Insert: The volume of distribution was increased with infusion length. Following intravenous infusions lasting <70 minutes, volume of distribution of gemcitabine was reported to be around 50 L/m^2. For long infusions, the volume of distribution rose to 370 L/m^2. Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible. Within one week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2′-deoxy-2′,2′-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma.
The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours. Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 1 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

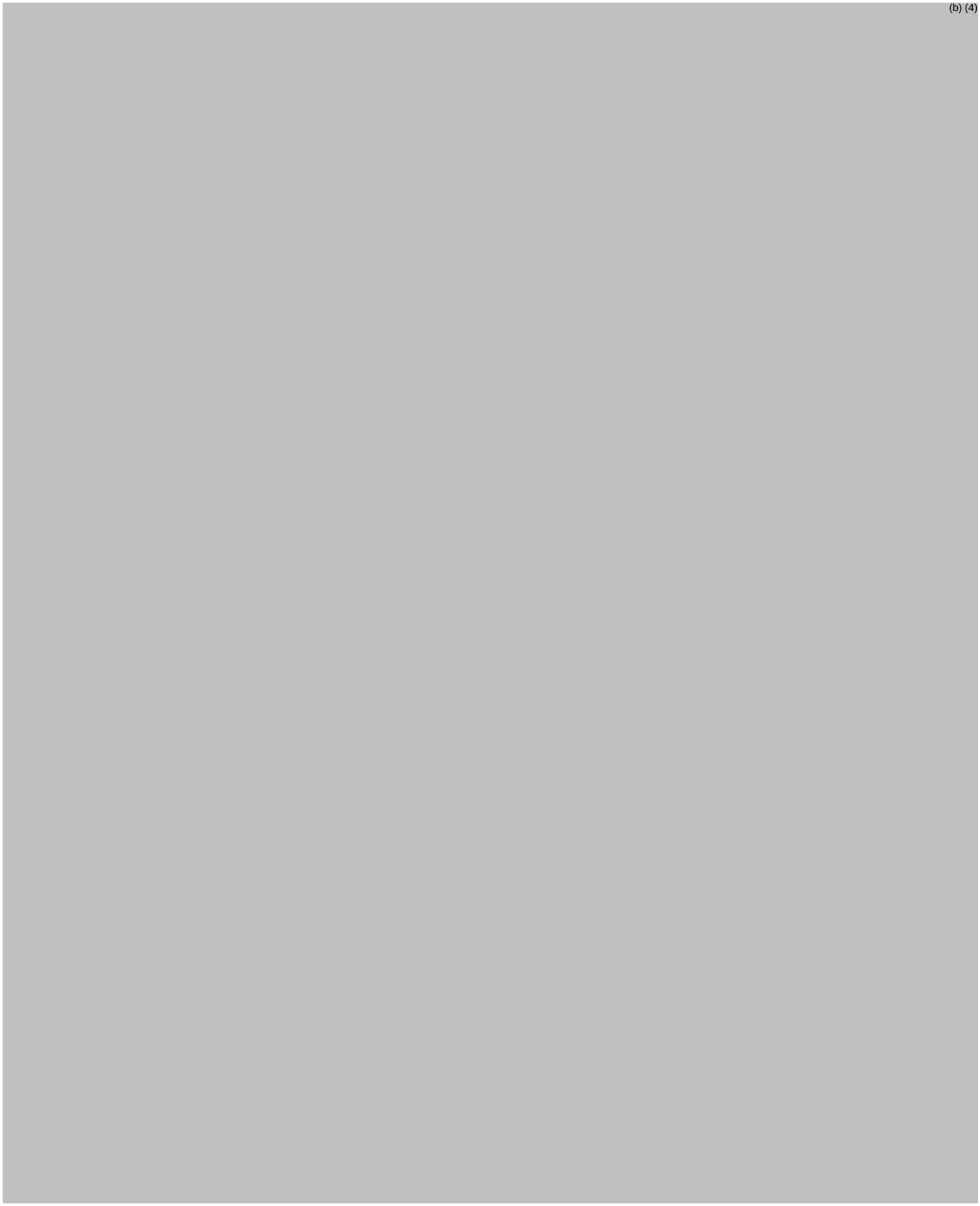
Table (b) (4): Gemcitabine Clearance and Half-Life for the "Typical" Patient

Age	Clearance Men (L/hr/m^2)	Clearance Women (L/hr/m^2)	Half-Life[a] Men (min)	Half-Life[a] Women (min)
29	92.2	69.4	42	49
45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

[a] Half-life for patients receiving <70 minute infusion.

Justification for to file a 505(b)(2) application for Gemcitabine Injection
The sponsor states that the proposed Gemcitabine Injection drug product contains identical amounts of the same active ingredient as gemcitabine and is given by the same route of administration as Gemzar. Both drug products are converted to the same dosage form (i.e. clear solution for injection) prior to administration to patients. The proposed Gemcitabine Injection is a clear solution for injection whereas Gemzar is reconstituted into a clear solution for injection. The sponsor has conducted two BE trials (Study 655-10, then Study 311-13 &) for approval.
Study 655-10: The sponsor 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 (b) (4)

The pharmacokinetic parameters of Gemcitabine were summarized in Table 2.



[redacted] (b) (4)

Study 311-13: The sponsor conducted another multicenter, randomized, open label, two-period, two-treatment, two-way crossover, single dose bioequivalence study in patients with pancreatic or ovarian cancer. [redacted] (b) (4) The study was planned to be conducted on 44 patients with pancreatic or ovarian cancer, but only 32 patients were treated. Of the 32 patients enrolled and treated, 4 (12.50%) were males and 28 (87.50%) were females. The mean ± SD for age of these 32 patients (ITT) was 49.4 ± 9.14 years. The mean ± SD for BMI (Body Mass Index) was 23.8 ± 5.00 kg/m^2 and the mean body surface area (BSA) was 1.5 ± 0.15 m^2. The racial make-up of the study was 100% Asian. Only 30 patients were included in statistical analysis. Patients were administered Gemcitabine Injection (either test or reference product as per randomization schedule) at a dose of 1000 mg/m^2 over 30 minutes (-3 minutes and + 5 minutes) on Day 01 (Period-I) and Day 08 (Period-II) of the 21 day cycle in case of ovarian cancer patients and on Day 01 and Day 08 of the chosen week in case of pancreatic cancer patients. Carboplatin was administered intravenously on Day 01 after Gemcitabine administration for ovarian cancer patients. A total of 16 blood samples, (3 samples during infusion and 12 samples post infusion of 2 mL each & 1 pre-dose sample of 4 mL) were collected from each patient in each period (except for discontinued / withdrawn patients and missing samples). The timepoints taken were predose, -25 min before end of infusion (EOI), -15 min EOI, EOI, 5, 10, 20, 30, and 45 min, 1, 1.5, 2, 4, 6, 8, 10 hr post EOI. The pharmacokinetic parameters of Gemcitabine were summarized in Table 5.

Table 5: Descriptive Statistics of Formulation Means for Gemcitabine (N = 30)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product-T	Reference Product-R
T_{max} (h)#	0.467 (0.250 - 0.517)	0.467 (0.083 - 0.700)
C_{max} (µg/mL)	27.987 ± 5.0742	28.313 ± 15.9095
AUC_{0-t} (µg.h/mL)	14.372 ± 2.5677	13.426 ± 3.5023
$AUC_{0-\infty}$ (µg.h/mL)	14.509 ± 2.5237	13.356 ± 3.4354*
λ_z (1/h)	2.621 ± 0.7209	2.392 ± 0.6374*
$t_{½}$ (h)	0.284 ± 0.0772	0.315 ± 0.1053*
AUC_%Extrap_obs (%)	0.992 ± 2.1230	0.752 ± 0.5353*
V_d (L/m^2)	29.190 ± 10.0475	35.833 ± 14.7434*
Cl (L/h/m^2)	70.934 ± 12.1102	79.007 ± 17.7879*

#T_{max} is represented as median (min-max) value. *N = 29.

Note: Patient F01 had AUC_%Extrap_obs > 20% in Period-I (Reference Product-R). Hence, the same was not considered for the computation of descriptive statistics for the related elimination phase pharmacokinetic parameters.

The bioequivalence analyses of C_{max}, $InAUC_{0-t}$ and $InAUC_{0-\infty}$ were summarized in Table 6. The statistical result showed that the test was bioequivalent compared to reference drug product. The result from the analyses showed that the test appeared to be bioequivalent compared to reference listed drug product.

Table 6: **Relative Bioavailability Results for Gemcitabine (N = 30)**

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Patient CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	28.028	26.773	104.7	94.13 - 116.43	24.4	96.4
$lnAUC_{0-t}$	14.363	13.281	108.1	101.43 - 115.30	14.6	100.0
$lnAUC_{0-\infty}$	14.496	13.328*	108.8	101.83 - 116.17	14.7	100.0

*N = 29.

11 adverse events were reported after administration of test drug product and 19 adverse events were reported after administration of reference listed drug product.

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/s/

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12/02/2016

JEANNE FOURIE ZIRKELBACH
12/02/2016