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RESEARCH**

APPLICATION NUMBER:

210326Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	210326
Submission Type; Code:	505(b)(2)
Applicant Name:	Fresenius Kabi USA, LLC.
Submission Dates:	08/31/2017
Brand Name:	Fulvestrant Injection, for intramuscular use
Listed Drug Name:	FASLODEX [®] (fulvestrant); NDA 21344
Dosage Form:	Solution for intramuscular (IM) injection
Dosage Strengths:	250 mg/5 mL (50 mg/mL)
Dosing Regimen:	500 mg (2 X 250 mg injection) on days 1, 15, 29 and once monthly thereafter
Proposed Indication:	<ul style="list-style-type: none">• Treatment of hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer in postmenopausal women not previously treated with endocrine therapy• Treatment of HR+ advanced breast cancer in postmenopausal women with disease progression following endocrine therapy, and• Treatment of HR+/HER2- advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy
OCP Division:	Division of Clinical Pharmacology V
Primary Reviewer:	Salaheldin Hamed, Ph.D.
Team Leader:	Pengfei Song, Ph.D.

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1 EXECUTIVE SUMMARY

This application is a 505(b)(2) NDA submission by Fresenius Kabi USA, LLC, requesting the approval of 50 mg/mL Fulvestrant Injection for intramuscular use for all the indications of Listed drug (LD), FASLODEX®.

The Applicant submitted bioequivalence study data in 266 healthy adult female subjects comparing the proposed product to the LD to support the approval. Study results demonstrated that the proposed product and the LD have similar area under the curve (AUC) and maximum plasma concentration of fulvestrant (C_{MAX}).

Table 1: Summary of Relative BA Findings

Parameter	Ratio (%Ref)	90% CI
AUC _{INF}	97.32	93.77-101.00
AUC _{0-T}	99.05	95.04-103.22
C _{MAX}	105.86	96.37-116.29

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the NDA 210326 and recommends the approval of Fulvestrant Injection 50 mg/mL from a clinical pharmacology perspective.

1.2 Summary of Important Clinical Pharmacology Findings

This application is an NDA for Fulvestrant Injection 50 mg/mL that was submitted under section 505 (b)(2) of the Act. This application is referencing Listed Drug (LD) FASLODEX, which is approved under NDA21344 as a monotherapy – for the treatment of HR+/HER2- advanced breast cancer in postmenopausal women not previously treated with endocrine therapy and the treatment of HR+advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy – and in combination with palbociclib or abemaciclib – for the treatment of HR+/ HER2-advanced or metastatic breast cancer in women with disease progression after endocrine therapy.

Fulvestrant Injection, 250 mg/5 mL (50 mg/mL), is a clear to yellow solution supplied in a sterile single-use prefilled syringe for intramuscular injection. The formulation includes inactive ingredients: benzyl alcohol, polysorbate 80, alpha-tocopherol, and (b) (4) castor oil. The Fulvestrant Injection formulation differs qualitatively and quantitatively from the LD formulation. This application provided relative bioavailability data of the proposed product to the LD to support a recommendation for the approval of the proposed product.

The Applicant conducted an open-label, two-treatment, single period, parallel, single-dose, randomized, fasting, lab-blinded bioequivalence study of Fulvestrant Injection 50 mg/mL versus Faslodex Injection, 50 mg/mL, after intramuscular administration in normal, healthy, non-smoking post-menopausal female subjects (Study FULV-006-CP1). The study compared the PK profile of a 250-mg dose of Fulvestrant Injection to 250-mg dose of FASLODEX up to 238 days post-injection. The geometric mean ratios of the PK

parameters (C_{MAX} and AUC) along with 90% confidence intervals were within the range of bioequivalence (**Table 1**).

The Office of Study Integrity and Surveillance (OSIS) recommended accepting data without on-site inspection because the site had been inspected and the outcome was classified as no action indicated (Section 3.1).

2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Drug Substance:

Fulvestrant (C₃₂H₄₇F₅O₃S) is a white powder with a molecular weight of 606.77 (**Figure 1**) that is practically insoluble in water.

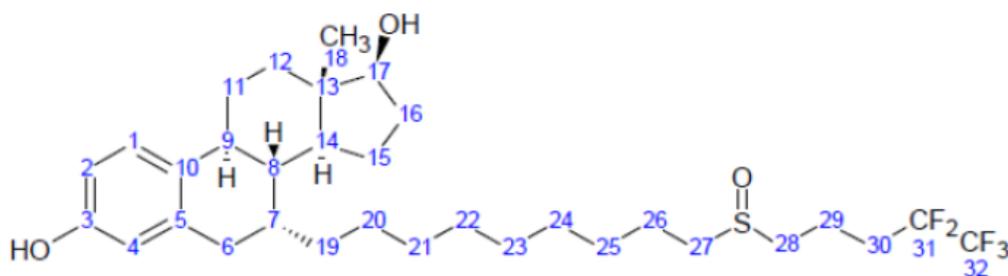


Figure 1: Structure of Fulvestrant

Drug Product:

Fulvestrant Injection, 250 mg/mL, is a clear colorless to yellow viscous sterile liquid, supplied in a sterile single-use prefilled syringe for intramuscular injection, each containing 250 mg fulvestrant. The formulation includes inactive ingredients: alcohol, benzyl alcohol, polysorbate 80, alpha-tocopherol, and (b) (4) castor oil.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Fulvestrant is an antiestrogenic agent that binds – in a competitive manner – to estrogen receptor (ER). Fulvestrant inhibits the growth of estrogen-sensitive and tamoxifen-resistant human breast cancer cells *in vitro*.

Fulvestrant Injection is indicated for the treatment of HR+/HER2- advanced breast cancer in post-menopausal women not previously treated with endocrine therapy and the treatment of HR+ (b) (4) advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. Fulvestrant is also indicated for the treatment of HR+/HER2-advanced breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

2.1.3 What are the proposed dosages and routes of administration?

Fulvestrant Injection is supplied as two 5 mL prefilled syringes each containing 250 mg fulvestrant. The recommended dose is 500 mg to be administered intramuscularly into the buttocks (gluteal area) slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29 and once monthly thereafter.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

To support this 505(b)(2) NDA, the Applicant conducted a pivotal bioequivalence study and a pilot relative bioavailability study. The two studies are summarized in **Table 2**.

Table 2: Summary of Clinical Pharmacology Studies

Study	Description	Design
FULV-006-CP1	Pivotal BE study	Parallel design in healthy female volunteers receiving 250 mg of FASLODEX [®] (n=133) vs. test product (n=133)
FULV-005-CP1	Pilot BE study	Parallel study in healthy subjects (n=15 per cohort) comparing PK (up to 126 days) and safety of the proposed formulation to FASLODEX [®] .

The Applicant conducted a pilot BE study that was an open label, randomized, two-treatment, parallel group, single-dose bioequivalence study (FULV-005-CP1) to test the relative bioavailability of the proposed product in comparison to the LD. The objective of the study was to characterize the variability in PK parameters of the proposed product to determine the adequate sample size for the pivotal study, assess pain at the site of injection, and monitor safety of the study subjects.

The pivotal BE study (FULV-006-CP1) was an open-label, randomized, parallel group, single dose, bioequivalence study of Fulvestrant injection 50 mg/mL in healthy, adult, non-smoking female subjects in fasting conditions. The secondary objectives were to assess pain at the site of injection and monitor safety of the study subjects.

2.2.2 What are the PK characteristics of the drug?

The following information is obtained from the currently approved label of the listed drug, FASLODEX[®].

Absorption – the single dose and multiple dose PK parameters of the 500 mg dosing regimen with an additional dose (AD) at day 15, to allow for reaching steady-state concentrations, are summarized in **Table 3**.

Table 3: Summary of Fulvestrant PK Parameters [gMean (CV%)] in Postmenopausal Advanced Breast Cancer Patients after Intramuscular Administration 500 mg + AD Dosing Regimen

		C _{max} (ng/mL)	C _{min} (ng/mL)	AUC (ng.hr/mL)
500 mg + AD	Single dose	25.1 (35.3)	16.3 (25.9)	11400 (33.4)
	Multiple dose steady-state	28.0 (27.9)	12.2 (21.7)	13100 (23.4)

Distribution – the apparent volume of distribution at steady-state is approximately 3 to 5 L/kg. Distribution is largely extravascular. Fulvestrant is highly bound (99%) to plasma proteins; VLDL, LDL, and HDL lipoprotein fractions appear to be the major binding components.

Metabolism – Fulvestrant biotransformation involves a number of pathways: oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulphate. The identified metabolites are either less active or exhibit similar activity to fulvestrant in antiestrogen models. Cytochrome P450 3A4 (CYP 3A4) is the only P-450 isoenzyme involved in the oxidation of fulvestrant.

Excretion – Fulvestrant is rapidly cleared by the hepatobiliary route with excretion via the feces (~90%). Renal elimination was negligible (less than 1%). After an intramuscular injection of 250 mg, the clearance (Mean \pm SD) is 690 \pm 226 mL/min with an apparent half-life of 40 days.

2.3 General Biopharmaceutics

2.3.1 What is the relative bioavailability of the proposed product to approved reference product?

At the planned 238 days of PK sampling, Fulvestrant Injection was found to be equivalent, in terms of AUC as well as C_{MAX} , to the FASLODEX[®] at 250 mg injection.

FULV-006-CP1 was an open-label, randomized, parallel group, single dose, bioequivalence study of Fulvestrant Injection 50 mg/mL in healthy, adult, non-smoking female subjects under fasted conditions. PK sampling was performed up to day 238 days post-dose.

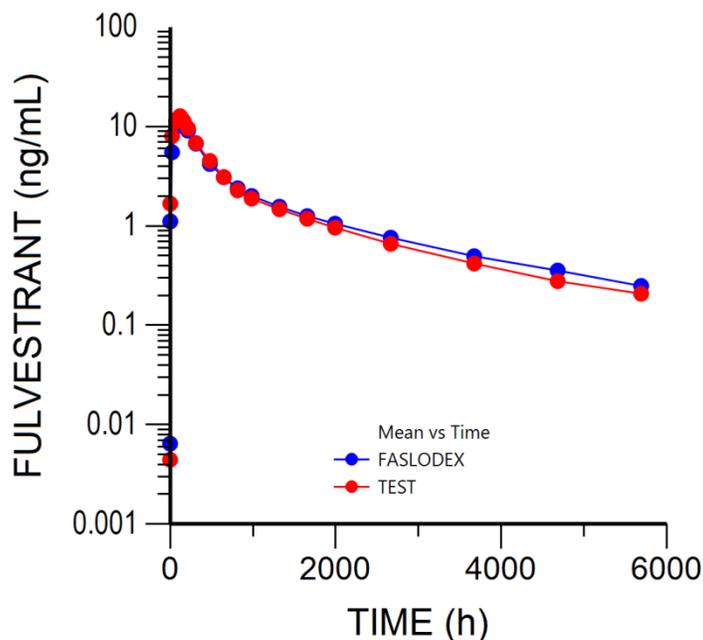


Figure 2: Mean PK profiles of the proposed product (red) and FASLODEX[®] (blue)

The proposed formulation was found to be bioequivalent to the reference formulation (Figure 2 and Table 1). The geometric mean ratio of the PK parameters of proposed formulation to those of the LD along with the 90% confidence intervals fell within the 80% to 125%.

2.4 Analytical Section

2.4.1 How are the active moieties identified and measured in the plasma?

A high-performance liquid chromatography mass spectrometric method was employed for measuring fulvestrant in plasma. The sample preparation was accomplished by liquid liquid extraction technique.

2.4.2 For all moieties measured, is free, bound, or total measured?

The total concentration of fulvestrant was measured in the pivotal BE study (FULV-006-CP1).

2.4.3 What bioanalytical methods are used to assess concentrations?

The concentration of fulvestrant was measured using a high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) assay.

2.4.3.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What is curve fitting technique?

The standard curve spanned a range of concentration from 0.052 ng/mL to 40 ng/mL. The concentration range covered the mean observed C_{MAX} (~13 ng/mL) and the mean concentration at the last PK sampling timepoint (0.2 ng/mL at day 238). Weighted ($1/x^2$) linear regression was used for back calculation of fulvestrant concentration.

2.4.3.2 What are the lower and upper limits of quantitation?

The LLOQ was 0.054 ng/mL and the ULOQ was 40 ng/mL.

2.4.3.3 What are the accuracy, precision, and selectivity at these limits?

The accuracy ranged from 90.6% to 100.8% and precision ranged from 1.8% to 5.5% at the LLOQ and ULOQ.

2.4.3.4 What is the sample stability under conditions used in the study?

The stability of QC samples was assessed at room temperature, freeze thaw cycles (4 cycles), conditions of use (at least 148 hours), short term stability (at least 6 hours at 25 °C), and long-term stability (at least 417 days at -70 °C)

2.4.3.5 What is the QC sample plan?

QC samples at LLOQ (0.054 ng/mL), low (~ 0.15 ng/mL), low to medium (~ 4.5 ng/mL), medium (~ 18 ng/mL), and high (~30 ng/mL) were included in each run. The accuracy and precision values within runs and between runs were well within the regulatory acceptance criteria (Table 4).

Table 4: Bioanalytical Method Validation Summary

Information Requested	Data
Analyte	Fulvestrant (MW = 606.77 g/mol)
Internal standard (I.S.)	Fulvestrant D5 (MW = 611.81 g/mol)
Method description	Liquid-liquid Extraction
Limit of quantitation	0.053 ng/mL
Average recovery of drug	99.6 % (LQC), 100.2% (MQC), and 97.4% (HQC)
Average recovery of IS	100.0 %
Standard curve concentrations	0.052 ng/mL to 40 ng/mL
QC concentrations	[0.053 ng/mL (LLOQ QC), 0.154 ng/mL (LQC), 4.392 ng/mL (LMQC), 17.925 ng/mL (MQC), 30.042 ng/mL (HQC), 116.16 ng/mL (DQC)]
QC Intraday precision range	1.8 % to 4.9 %
QC Intraday accuracy range	92.6 % to 110.2 %
QC Interday precision range	1.9 % to 8.6 %
QC Interday accuracy range	99.6% to 109.5 %
Bench-top stability	At least 16 hours @ room temperature
Stock stability	At least 13 weeks @ -25 ± 10 °C
Processed stability	148 hours @ 7°C in Autosampler tray
Freeze-thaw stability	4 cycles
Long-term storage stability	At least 413 days below -70°C
Dilution integrity	119.36 ng/mL diluted up to 5-fold
Selectivity	No interfering peaks observed in 8 blank plasma batches screened

3 APPENDICES

3.1 OSIS report

MEMORANDUM

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

DATE: 11/30/2017

TO: Division of Oncology Products (DOP1)
Office of Hermatology 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 210326

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	Lambda Therapeutic Research, Inc.	460 Comstock Road, Toronto, Ontario, Canada
Clinical	BioPharma Services, Inc.	4000 Weston Road, Toronto, Canada
Clinical	Algorithme Pharma, Inc.	1200 Beaumont Avenue, Mount-Royal, Quebec, Canada
Analytical	(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/

SALAHELDIN HAMED
05/22/2018

PENGFEI SONG
05/22/2018

NAM ATIQR RAHMAN
05/22/2018
I concur with the recommendation.