CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210326Orig1s000

SUMMARY REVIEW

Addendum-Division Director Summary Review for Regulatory Action

Date	06/28/2018
From	Laleh Amiri-Kordestani, MD
Subject	Addendum-Division Director Summary Review
NDA#	210326
Applicant	Fresenius Kabi USA, LLC
Date of Submission	08/31/2017
PDUFA Goal Date	06/30/2018
Proprietary Name	Fulvestrant Injection
Established or Proper Name	Fulvestrant
Dosage Form(s)	Liquid for intramuscular use
Applicant Proposed Indication(s)/Population(s)	• Treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy. • Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. • Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.
Applicant Proposed Dosing Regimen(s)	500 mg intramuscular (IM) injection on days 1, 15, 29 and once monthly thereafter
Recommendation on Regulatory Action	*Tentative Approval*
Recommended Indication(s)/Population(s) (if applicable)	• Treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy. • Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. • Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.
Recommended Dosing Regimen(s) (if applicable)	*500 mg IM injection on days 1, 15, 29 and once monthly thereafter*

Addendum

Fresenius Kabi USA, LLC has chosen to retain all indications and requested Tentative Approval. All patent/exclusivity deficiencies have been satisfied for a tentative approval action under 21 CFR 314.105. The listed drug upon which this application relies is subject to a period of patent protection and exclusivity protection and, therefore final approval of this application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective at this time.
In conclusion, final approval cannot be granted at this time because of the unexpired exclusivity on the listed drug upon which this application relies and a waiver of that exclusivity which is not yet effective. For further details on regulatory issues, please see the Tentative Approval letter.

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/s/

LALEH AMIRI KORDESTANI
06/28/2018

Division Director Summary Review for Regulatory Action

Date	6/14/2018
From	Amna Ibrahim MD
Subject	Division Director Summary Review
NDA #	210326
Applicant	FRESENIUS KABI USA LLC
Date of Submission	08/31/2017
PDUFA Goal Date	06/30/2018
Proprietary Name	Fulvestrant injection
Dosage Form(s)	Liquid for intramuscular use
Applicant Proposed Indication(s)/Population(s)	Fulvestrant is an estrogen receptor antagonist indicated for the: • Treatment of hormone receptor (HR)-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. • Treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.
Action or Recommended Action:	Pending resolution of patent and exclusivity issues
Approved/Recommended Indication(s)/Population(s) (if applicable)	Fulvestrant Injection is an estrogen receptor antagonist indicated for the: • Treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy. • Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. • Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Schechter, Genevieve A
Pharmacology Toxicology Review	Chang, Ching-Jey G.
Biopharmaceutics Review	Chatterjee, Parnali A.
Product Quality Review	Adams, William M./ Sarker, Haripada
Product Quality Microbiology Review	Morgan, Jason K.
Clinical Pharmacology Review	Hamed, Salaheldin
OPDP	Lidoshore, Ruth/Wright, Kevin
CDTL Review	Balasubramaniam, Sanjeeve
OSE/DMEPA	Gao, Ting Ting
Other	

OND=Office of New Drugs
DMPP= Division of Medical Policy Programs
OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

1. Benefit-Risk Assessment

Fresenius Kabi, USA, LLC submitted NDA 210326 in accordance with Section 505(b)(2) of the FD&C Act for Fulvestrant Injection, 250 mg/5mL Prefilled Syringe. The Listed Drug (LD) is FASLODEX, 250 mg/5mL Prefilled Syringe (NDA 021344), which is manufactured by AstraZeneca Pharmaceuticals LP.

2. Background

Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and downregulates the ER protein in human breast cancer cells. FASLODEX, the LD, was initially approved for:

i. *the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.*

FASLODEX was subsequently was approved for

ii. *the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy (2016)*

iii. *the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy (2017)*

iv. *the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with abemaciclib in women with disease progression after endocrine therapy (2017)*

In the study supporting the approval in combination with abemaciclib, pre/perimenopausal women enrolled in the study received the gonadotropin-releasing hormone agonist goserelin. Of note, the indications in combination with palbociclib and abemaciclib were based on studies conducted that led to the approval of the two NMEs.

FASLODEX 500 mg is recommended intramuscularly into the gluteal area on days 1, 15, 29 and once monthly thereafter. The additional dose of FASLODEX given two weeks after the initial dose allows for steady state concentrations to be reached within the first month of dosing. Hepatic impairment requires dose modification on fulvestrant.

FASLODEX patents expire in 2021 for all indications. Per Orange book, accessed on 6/13/2018, it also has exclusivity for the following indications:

- for the treatment of hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in combination therapy with palbociclib and fulvestrant in women with disease progression following endocrine therapy (until 2/19/2019).

- monotherapy for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer in postmenopausal women not previously treated with endocrine therapy (until 2020).

IRs have been sent in consultation with the FDA legal team to resolve patent issue. The action on the NDA will depend on the recommendation of the FDA legal team. No other review issues have been identified.

3. Product Quality

Fulvestrant is a white powder. The drug product, Fulvestrant Injection, 250 mg/5 mL (50 mg/mL), is a clear, colorless to yellow viscous liquid supplied in a sterile single-use prefilled syringe for intramuscular injection. The formulation includes inactive ingredients: benzyl alcohol, dehydrated alcohol, polysorbate 80, alpha-tocopherol, (b) (4) castor oil and (b) (4). Per the CMC review, the difference between the LD, FASLODEX and Fulvestrant for injection is the change in co-solvent benzyl benzoate in the LD to polysorbate 80 and α-tocopheral. The (b) (4) were adequate. 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 drug product will be marketed in two syringes, each with 5 ml of the drug product. The device was deemed acceptable by CDRH.

The submitted stability study data is sufficient to support the applicant's proposal of an initial shelf life of 30 months stored at (b) (4) ^{0}C. After discussion with the applicant, the following storage conditions were found acceptable by the FDA CMC team:

Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F) [USP Controlled Room Temperature].
Fulvestrant Injection can also be stored at refrigerated conditions: 2°C-8°C (36°F-46°F).

Because of the compliance history and the proposed manufacturing, no preapproval inspection was performed.

Office of Pharmaceutical Quality found this NDA acceptable from their perspective.

4. Nonclinical Pharmacology/Toxicology

In a non-GLP pharmacokinetic study in female rabbits, multiple fulvestrant formulations, including the formulation proposed for marketing (fulvestrant concentration of 50 mg/mL), were administered and it showed similar bioavailability and exposure with relatively comparable injection site lesions. In addition, in a GLP local tolerance toxicology study in female rabbits, a single intramuscular dose of Fulvestrant or FASLODEX at 12.5 mg/kg were tolerated in female rabbits.

Fulvestrant Injection is recommended for approval for the proposed indications from the pharmacology/toxicology perspective.

5. Clinical Pharmacology

The applicant submitted a 266-patient PK study to support bioequivalence. This was an open-label, two-treatment, single period, parallel, single-dose, randomized, fasting, bioequivalence study of fulvestrant after intramuscular administration to healthy, non-smoking post-menopausal female subjects. PK for Fulvestrant Injection 50 mg/mL were compared to those of FASLODEX Injection, 50 mg/mL. The geometric mean ratios of the PK parameters (CMAX and AUC) along with 90% confidence intervals were within the range.

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

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

No clinical studies were submitted to support this NDA. The efficacy of this drug relies on the efficacy of the LD.

8. Safety

No clinical studies were submitted to support this NDA. The safety of this drug relies on the safety of the LD.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

There is unexpired pediatric exclusivity for listed FASLODEX in the Orange Book

11. Other Relevant Regulatory Issues

- Exclusivity or patent issues of concern: please see section 2 of this review for exclusivity and patent issues on which resolution is pending.
- Office of Scientific Investigations and Surveillance (OSIS) Audits: The Division of New Drug Bioequivalence Evaluation (DNDBE), 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.
- Financial Disclosure: the applicant certified that they had not entered in any financial arrangements with the listed clinical investigators.

12. Labeling

- Labeling will be based on the label for the LD and will depend on the indications in the action letter

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Other Postmarketing Requirements and Commitments

None.

There are no unresolved review issues. The remaining issues are legal and action will depend on how the patent and exclusivity issues are resolved. An amendment to this summary review will be provided at the time of action.

Amna Ibrahim MD
Deputy Director
Division of Oncology Products 1

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/s/

AMNA IBRAHIM
06/14/2018

Division Director Summary Review for Regulatory Action

Date	05/17/2019
From	Amna Ibrahim MD
Subject	Deputy Division Director Summary Review
NDA #	210326
Applicant	FRESENIUS KABI USA LLC
Date of Submission	03/20/2019
PDUFA Goal Date	05/20/2019
Proprietary Name	Fulvestrant injection
Dosage Form(s)	Liquid for intramuscular use
Action or Recommended Action:	Approval
Approved/Recommended Indication(s)/Population(s) (if applicable)	• Treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy. • Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. • HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib, as initial endocrine based therapy or following disease progression on endocrine therapy. • Treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.

Fresenius Kabi, USA, LLC submitted NDA 210326 in in 2017 in accordance with Section 505(b)(2) of the FD&C Act for Fulvestrant Injection, 250 mg/5mL Prefilled Syringe. The Listed Drug (LD) is FASLODEX, 250 mg/5mL Prefilled Syringe (NDA 021344), which is manufactured by AstraZeneca Pharmaceuticals LP.

Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and downregulates the ER protein in human breast cancer cells. FASLODEX, the LD, was initially approved for:

> *The treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.*

FASLODEX is currently approved for the treatment of

- *Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.*
- *HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.*
- *HR-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women in combination with ribociclib, as initial endocrine based therapy or following disease progression on endocrine therapy.*
- *HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib or abemaciclib in women with disease progression after endocrine therapy.*

FASLODEX 500 mg is recommended intramuscularly into the gluteal area on days 1, 15, 29 and once monthly thereafter. The additional dose of FASLODEX given two weeks after the initial dose allows for steady state concentrations to be reached within the first month of dosing. Hepatic impairment requires dose modification on fulvestrant.

Please refer to my previous detailed summary from June 14, 2019, which discusses the findings of the various disciplines involved. All review disciplines had found the NDA approvable from their perspective. Also refer to Dr Amiri's addendum on June 28, 2018 which outlines the unexpired exclusivity as the basis for the Tentative Approval letter issued in June 2018.

The applicant resubmitted the application but withdrew it in March 2019. The application was resubmitted on March 20, 2019 as a class I submission.

Per the OPQ summary review, CMC information remains unchanged from the original NDA submission except that the applicant added an alternate drug product packaging/labeling site. The acceptability of the new packaging/labeling site has been reviewed by the process/facility reviewer and found acceptable. The product quality review team recommends approval for this NDA.

A new indication has been added to the label, which was reviewed by the team and William Pierce, the Associate Director for labeling. No information was submitted for any other discipline and there are no remaining review issues. There are also no remaining legal issues. An Approval Action will be taken.

Amna Ibrahim MD
Deputy Director
Division of Oncology Products 1

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/s/

AMNA IBRAHIM
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