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RESEARCH**

APPLICATION NUMBER:

210326Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	05/30/2018
From	Sanjeeve Balasubramaniam, MD, MPH
Subject	Cross-Discipline Team Leader 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)	250 mg per 5 mL syringe for intramuscular injection
Applicant Proposed Indication(s)/Population(s)	<ol style="list-style-type: none"> 1. Treatment of hormone receptor (HR)-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. 2. Treatment of HR-positive, human epidermal growth factor receptor 2 (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	<i>Approval</i>
Recommended Indication(s)/Population(s) (if applicable)	<ol style="list-style-type: none"> 1. Treatment of HR-positive, HER2-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy. 2. Treatment of HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy. 3. 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)	<i>500 mg IM injection on days 1, 15, 29 and once monthly thereafter</i>

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Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
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
OSI	
CDTL Review	Balasubramaniam, Sanjeeve
OSE/DMEPA	Gao, Ting Ting
Other	

1. **Benefit-Risk Assessment**

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

[Fulvestrant is a steroidal estrogen receptor antagonist administered via intramuscular injection. Faslodex, the Listed Drug for this 505(b)(2) application, was approved in 2002 for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy at a dose of 250 mg IM montly. In August, 2017, Fresenius Kabi, USA, LLC submitted this 505(b)(2) application for Fulvestrant Injection. The application contained data for chemistry, manufacturing, and controls (CMC); two nonclinical studies in rabbits; and one bioequivalence study in 266 healthy female subjects; as well as the proposed prescribing information and additional regulatory documentatation.

Metastatic breast cancer is common, with more than 150,000 women in the US currently living with the disease. In 2017, mBC remains incurable with a 5-year survival of approximately 20%. The current standard of care for women with HR-positive, HER2-negative mBC is to administer sequential lines of endocrine-based therapy and then, once endocrine therapy options have been exhausted or endocrine resistance is confirmed, to rely on chemotherapy. Available therapy for postmenopausal women with HR-positive mBC includes: monotherapy with tamoxifen; an aromatase inhibitor (AIs) such as anastrozole, exemestane, or letrozole; or fulvestrant; or the combination of endocrine therapy with a cyclin-dependent kinase (CDK) inhibitor or an mTOR inhibitor. Endocrine therapy for premenopausal women includes tamoxifen, and there are data to support the use of AI and fulvestrant regimens in premenopausal women with concurrent suppression of ovarian function. For women with HR-positive, HER2-negative mBC whose disease has become refractory to endocrine therapy, cytotoxic therapy with paclitaxel, capecitabine, vinorelbine, eribulin, or gemcitabine is commonly used.

On April 25, 2002, based on the results of two randomized phase 3 trials and 24 supportive clinical trials, AstraZeneca received the initial marketing approval for fulvestrant. In the pivotal trials, postmenopausal women with advanced breast cancer who had recurrence or progression of disease and required treatment because of either relapse after adjuvant tamoxifen therapy or progression after first-line treatment with tamoxifen for advanced disease were randomized to treatment with monthly fulvestrant 250 mg IM for a median of 6 months or anastrozole tablets. The initial trial was designed to detect superiority in time to disease progression (TTP), but an interim analysis failed to show a significantly longer TTP in the fulvestrant group; at this point, the statistical analysis plan was amended to analyze the data to demonstrate noninferiority in response rates between the two treatment groups, since noninferiority in TTP is not established as a regulatory endpoint for marketing approval. In this updated analysis, TTP was considered a supportive endpoint.

Superiority in any endpoint was not shown for fulvestrant over anastrozole. FDA-adjudicated response rates in the European trial were 20.3% in the fulvestrant arm and 14.9% in the anastrozole arm. In the North American trial, FDA response rates in both arms were 17%. A deficiency in response rate of greater than 10% for the fulvestrant arm was not supported statistically, thereby achievieng the acceptance criterion for noninferiorty.

In 2017, two new indications were added to the LD: 1) monotherapy for the treatment of HR positive, HER2-negative advance breast cancer in postmenopausal women not previously treated with endocrine therapy; 2) for 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. Because the LD is still protected by exclusivity for this second indication until February, 2019, the applicant submitted a letter of consent from the manufacturer of the LD, AstraZeneca, for the

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marketing of Fulvestrant Injection.

Based on the review of the CMC, nonclinical, and bioequivalence studies, as well as submitted documentation, this 505(b)(2) application is recommended for approval for all indications for which Faslodex has been approved.

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> It is estimated that over 150,000 women in the US are living with metastatic breast cancer in 2018, which is an incurable disease with a 5-year survival of approximately 20%. 	<p>Locally advanced and metastatic breast cancer are serious and life-threatening conditions.</p>
Current Treatment Options	<ul style="list-style-type: none"> As it is not curable, the goals of treating MBC are palliative in nature with an aim to prolong the time until disease progression, reduce cancer-related symptoms, and improve survival. Available endocrine based therapies for postmenopausal women with HRpositive MBC include tamoxifen, aromatase inhibitors (AIs) such as anastrozole, exemestane, and letrozole, and fulvestrant. Endocrine therapies in combination with CDK 4/6 inhibitors and mTOR inhibitors are also available agents. Endocrine therapy options for premenopausal women also include tamoxifen, and there are data to support the use of AIs and fulvestrant in premenopausal women with concurrent ovarian function suppression. For patients with HR-positive, HER2-negative MBC whose disease has progressed on endocrine therapy, chemotherapy is an additional treatment option. These therapy options include paclitaxel, capecitabine, vinorelbine, eribulin, and gemcitabine. 	<p>Despite numerous available therapies, all patients with HR+, HER2- metastatic breast cancer eventually develop endocrine resistance and succumb to their disease. Therefore, there is an unmet medical need to improve the outcomes of patients with this disease.</p>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> The benefit of fulvestrant, the LD for this application, was demonstrated in clinical trials leading to marketing approval for Faslodex in 2002 and 2017; this 505(b)(2) application bases the evidence for approval on the clinical studies performed in support of the LD. 	<p>Bioequivalence, nonclinical safety, and CMC data submitted in this 505(b)(2) application supports the conclusion that Fulvestrant Injection may rely on the same clinical findings as demonstrated for the LD for demonstration of safety and efficacy in the intended population.</p>
Risk and Risk Management	<ul style="list-style-type: none"> The safety profile of fulvestrant as a single agent and fulvestrant in combination with palbociclib or abemaciclib is acceptable for the intended population and is well known. Toxicities are manageable with appropriate treatment interruption and/or dose modifications, listed in the prescribing information. 	<p>The safe use of fulvestrant for the intended population can be managed through appropriate labeling and routine oncology care. No REMS is indicated.</p>

2. Background

NDA 210362 submitted by Fresenius Kabi USA, LLC, for Fulvestrant Injection was submitted on August 31, 2017 for approval under Section 505(b)(2) as an alternative formulation of the Listed Drug (LD) Faslodex. This application intends to rely for approval on FDA's finding of safety and effectiveness for the LD that led to approval on April 25, 2002 for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy. Two additional indications were added in 2017: 1) 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; and 2) for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with abemaciclib in women with disease progression after endocrine therapy. This is the first application submission for this product.

The applicant has re-formulated fulvestrant in a formulation that substitutes polysorbate 80 and alpha tocopherol to replace the LD's use of benzyl benzoate. Fulvestrant Injection also has a slightly higher castor oil content than the LD. Fulvestrant Injection has the same active ingredient (fulvestrant), strength, route, dosage, and dosing regimen as the LD. The LD is supplied in sterile pre-filled syringes containing 50 mg/mL fulvestrant administered intramuscularly as two concurrent 5 mL injections on day 1, 15, 29 and once monthly thereafter. Currently, there are no approved therapeutic equivalents for Faslodex. The applicant listed Patent IV certifications for unexpired patents in accordance with 21 CFR 314.50(i) and notified all patent owners by November 2, 2017. A copy of the court order dismissal for the patent lawsuit was provided on May 4, 2017. ***Pending: A copy of a letter from drug innovator providing consent for full approval of NDA 210326.***

3. Product Quality

Fulvestrant is a white powder. Drug substance review was based on review of Drug Master File (DMF) (b) (4), reviewed in 2017, and found to be Adequate for an ANDA. No other significant amendment is noted for the DMF for this application, so the drug substance information is found to be acceptable.

The drug product is a sterile solution of 250 mg/5 mL filled in a 5 cc Type I glass syringe. It contains the following USP/NF compendial excipients: benzyl alcohol, dehydrated alcohol, polysorbate 80, alpha-tocopherol, castor oil, and (b) (4). No excipient exceeds the IIG limits for this route of administration. The proposed indication, the route of administration, and the dose are the same as those of the LD. The difference between the LD, Faslodex and Fulvestrant Injection is the change in co-solvent benzyl benzoate in the LD to polysorbate 80 and α -tocopherol.

The specification for drug product batch release and stability testing addresses appearance, key packaging attributes, chemical identity, assay for drug substance and co-solvents; chemical impurities, microbiological purity, and USP <1> requirements.

The (b) (4) of the drug product manufacturing process has been demonstrated through equipment qualification, (b) (4),

(b) (4) and manufacturing process validation studies. The microbiology information provided for the NDA is found to be acceptable.

CMC information provided in NDA 210326 for Fulvestrant Injection has been reviewed by the product quality review team in the Office of Pharmaceutical Quality, and is found to be acceptable. The review team recommended Approval for the NDA from the product quality standpoint.

Reviewer Comment: I concur with the CMC review team that the chemistry, manufacturing, and controls data submitted in support of this application are adequate to recommend approval for Fulvestrant Injection for the same indications as fulvestrant.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology team reviewed two nonclinical studies provided in this application. 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 in female New Zealand White rabbits and showed similar bioavailability and exposure with relatively comparable injection site lesions. The study was previously reviewed under IND-122336.

In a GLP local tolerance toxicology study in female rabbits, a single intramuscular dose of FK Fulvestrant or Faslodex at 12.5 mg/kg was tolerated in female rabbits with no significant findings between the two fulvestrant formulations.

Based on these two studies, Fulvestrant Injection was recommended for approval from a pharmacology/toxicology perspective.

Reviewer Comment: I concur with the pharmacology/toxicology review team that the two nonclinical studies performed in support of this application are adequate to recommend approval for Fulvestrant Injection for the same indications as fulvestrant.

5. Clinical Pharmacology

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.

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.

Reviewer Comment: I concur with the Office of Clinical Pharmacology review team that the bioequivalence study performed in support of this application is adequate to recommend approval for Fulvestrant Injection for the same indications as fulvestrant.

6. Clinical Microbiology

Not applicable for this application.

7. Clinical/Statistical- Efficacy

No clinical efficacy data were submitted in support of this 505(b)(2) application.

8. Safety

No clinical safety data were submitted in support of this 505(b)(2) application.

9. Advisory Committee Meeting

No advisory committee meeting was held.

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

- Because of unexpired exclusivity or patent issues for the relevant indications, this application will be granted tentative approval under 21 CFR 314.107.
- DSI Audits: No clinical data were submitted for this application. OSIS recommended accepting data without an onsite inspection, since OSIS had recently inspected manufacturing sites for this product and the outcome was classified as No Action Indicated (NAI).
- Other consult: Kevin Wright from DDMAC had no comments in his review of the PI. Tingting Gao states in her review that DMEPA found the PI to be adequate and made some recommendations for the carton and container labels.

- Fresenius Kabi, USA, LLC, provided certification that it did not and will not use in any capacity the services of any person debarred under Subsections (a) and (b) of Section 335a of the Federal Food, Drug, and Cosmetic Act in connection with this application for Fulvestrant Injection, NDA 210326.
- Fresenius Kabi, USA, LLC, provided certification that there were no financial arrangements with the listed investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. Each listed clinical investigator was required to and disclosed that they did not have a proprietary interest in this product or a significant equity in the sponsor. None of the listed investigators were the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). Additionally, there were no clinical effectiveness/safety studies performed in conjunction with this application.

12. Labeling

- Proprietary name: N/A
- Physician labeling: all major issues were resolved.
- Carton and immediate container labels: all major issues were resolved.
- Patient labeling/Medication guide: all major issues were resolved.

13. Postmarketing Recommendations

N/A

14. Recommended Comments to the Applicant

None.

Sanjeeve Balasubramaniam, MD, MPH
Clinical Team Leader
DOP1, OHOP, CDER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANJEEVE BALASUBRAMANIAM
06/26/2018