CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210063Orig1s000

CLINICAL REVIEW(S)

NDA #	210063
Pathway submitted	505(b)(2)
Submit Date	02/19/2019
Product	Fulvestrant Injection
Therapeutic Class	Hormone antagonist
Formulation/Route of administration	250 mg per 5 mL in single-dose prefilled syringe for intramuscular injection
Recommended dosing regimen	500 mg IM injection on days 1, 15, 29 and once monthly thereafter
Cross-Referenced NDA(s)	NDA 021344 (Faslodex®)
Proposed Indication	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.
Sponsor	Teva Pharmaceuticals USA, Inc.
Primary Reviewer	Sakar Wahby, PharmD
Secondary Reviewer	Harpreet Singh, MD

1 SUMMARY OF APPLICATION

Teva Pharmaceuticals USA, Inc. originally submitted NDA 210063 on December 28, 2016 for Fulvestrant Injection for approval under Section 505(b)(2) as an alternative formulation of the Listed Drug (LD) Faslodex®. Upon review of the original submission and based on non-clinical, product quality, and device related deficiencies, FDA issued a Complete Response letter on October 26, 2017. The deficiencies in the Complete Response letter were from non-clinical, drug product and process, device characterization (CDRH ODE review for device quality) and manufacturing (CDRH OC review for device manufacturing). For a complete list of the deficiencies, refer to the CR letter in DARRTS dated October 26, 2017.

On February 19, 2019, Teva Pharmaceuticals USA, Inc. submitted complete responses to the FDA deficiencies. This application intends to rely for approval on FDA's finding of safety and effectiveness for the LD (Faslodex®) NDA 21344, that led to approval for the following indications:

- 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.

On the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book)'s exclusivity listing for Faslodex® (Fulvestrant) injection NDA 21344, the LD upon which this 505(b)(2) NDA 210063 relies, Exclusivity I-749 expires August 25, 2020 described as:

> 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

(b) (4)

The proposed drug's active ingredient (fulvestrant), strength, dosage form, the route of the administration (IM), and the indications are the same as those of the LD (Faslodex®). The only difference between the LD and the proposed drug is the excipients used in the formulation. No clinical efficacy or safety data were submitted in support of this 505(b)(2) application. In the current resubmission, the applicant provided complete responses to all outstanding deficiencies issued in the CR letter dated October 26, 2017. The responses have been reviewed by each discipline in the non-clinical, OPQ team, as well as the CDRH consult team and the deficiencies have been adequately addressed and the NDA is recommended acceptable by all disciplines. Refer to DARRTS for each discipline's complete review.

The annotated label compared with the reference drug (Faslodex®) provided by the applicant has been reviewed and has no changes from the LD product label. The carton and immediate container labels were reviewed by DMEPA and all issues were resolved. The Office of Medication Error Prevention and Risk Management (OMEPRM)/OSE evaluated the physical comparison, labeling comparison, and comparative task analysis submitted under this NDA for Fulvestrant Injection to determine whether the sponsor needs to submit the results of a human factors validation study or a comparative human factor study as part of preapproval marketing submission because this is a combination product with a

proposed prefilled syringe device constituent part that is intended to treat breast cancer. Based on OMEPRM review of the applicant's submitted use-related risk analysis (URRA), comparative analyses, and justification, OMEPRM have determined that a human factors validation study is not needed to be submitted for Agency review.

Recommendation:
Based on the review of Teva Pharmaceuticals complete responses to the nonclinical, CMC, and CDRH deficiencies, as well as the submitted documentation, this 505(b)(2) application is recommended for approval for all indications for which Faslodex® has been approved. This application has been cleared for full approval by the FDA 505b2 committee.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAKAR M WAHBY
08/09/2019 08:11:49 AM

B HARPREET SINGH
08/13/2019 03:17:34 PM

Cross-Discipline Team Leader Review

Date	October 17, 2017
From	Laleh Amiri-Kordestani, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	210063
NDA Type	505(b)(2)
Reference NDA	Faslodex, NDA 021344, AstraZeneca Pharmaceuticals
Applicant	Teva Pharmaceuticals USA, Inc.
Date of Submission	December 28, 2016
PDUFA Goal Date	October 28, 2017
Proprietary Name / Non-Proprietary Name	Fulvestrant Injection, pre-filled syringe
Dosage form(s) / Strength(s)	250 mg /5 mL single-dose pre-filled syringe
Applicant Proposed Indication(s)/Population(s)	• 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.
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	*N/A*

Disciplines and Consultants	Names	
Regulatory Project Management	RPMs:	Sakar Wahby
	CPMS/TL:	Alice Kacuba
Clinical	Reviewer:	Sara Horton
	TL:	Laleh Amiri-Kordestani
Clinical Pharmacology	Reviewer:	Salaheldin Hamed
	TL:	Pengfei Song
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Eias A. Zahalka
	TL:	Todd R Palmby
Product Quality (CMC) Review Team:	ATL:	Xiao H. Chen
	RBPM:	Kristine Leahy
• Drug Substance	Reviewer:	Haripada Sarker
• Drug Product	Reviewer:	Amit Mitra
• Process	Reviewer:	Feiyan Jin
• Facility	Reviewer:	Frank Wackes
• Biopharmaceutics	Reviewer:	Parnali Chatterjee
• Microbilogy	Reviewer:	Koushik Paul
CDRH	Reviewer:	Sarah B. Mollo
	TL:	Alan M. Stevens
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Tingting Gao
	TL:	Chi-Ming (Alice) Tu

- **Benefit-Risk Assessment**

Benefit-Risk Summary and Assessment

This New Drug Application, NDA 210,063 for Fulvestrant Injection, 250 mg/5 mL was submitted by Teva Pharmaceuticals USA, Inc. under the provisions of section 505(b)(2) of the Federal, Food, Drug, and Cosmetic Act. Fulvestrant Injection, Pre-Filled Syringe is a Single Entity Combination Drug Product. The application relies on FDA's previous findings of safety and efficacy for the listed drug (LD), Faslodex (fulvestrant) injection, for intramuscular use, 250 mg/5mL (50 mg/mL) manufactured by AstraZeneca Pharmaceuticals. The listed drug, Fasolodex, was approved in 2002 under NDA 021344. The proposed Fulvestrant Injection strength, dosage form, and route of administration are similar to Faslodex Injection the LD, but several of the inactive ingredients are different (b) (4) (b) (4)

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. Faslodex is 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, or
- HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
- HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

There are a number of concerns with Fulvestrant Injection Pre-Filled Syringe application which will need to be addressed by the Applicant prior to marketing this product. Key issues are listed below:

- The safety of the proposed level of the medium chain triglycerides excipient in the drug product to be administered by intramuscular injection was not adequately justified.
- Major product quality and stability issues.
- Applicant has not submitted any design requirements and/or specifications for the prefilled syringe.

Recommended Regulatory Action: A Complete Response is recommended.

- # Background

This New Drug Application, NDA 210,063 for Fulvestrant Injection, 250 mg/5 mL was submitted by Teva Pharmaceuticals USA, Inc. under the provisions of section 505(b)(2) of the Federal, Food, Drug, and Cosmetic Act. The application relies on FDA's previous findings of safety and efficacy for the listed drug, Faslodex (fulvestrant) injection, for intramuscular use, 250 mg/5mL (50 mg/mL) manufactured by AstraZeneca Pharmaceuticals. The listed drug (LD), Fasolodex, was initially approved in 2002 under NDA 021344. The proposed Fulvestrant Injection strength, dosage form, and route of administration are similar to Faslodex Injection the LD, but several of the inactive ingredients are different. Fulvestrant Injection Pre-Filled Syringe is a Single Entity Combination Drug Product.

The recommended dose for Fasolodex is 500 mg (two 5 ml injections of 250 mg/5 ml) administered intramuscularly one in each buttock (gluteal area), on days 1, 15, 29 and once monthly thereafter.

Faslodex is 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, or
- HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.
- HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.

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. In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen-resistant, as well as estrogen-sensitive human breast cancer (MCF-7) cell lines. In in vivo tumor studies, fulvestrant delayed the establishment of tumors from xenografts of human breast cancer MCF-7 cells in nude mice. Fulvestrant inhibited the growth of established MCF-7 xenografts and of tamoxifen-resistant breast tumor xenografts. (Faslodex drug label)

Teva Fulvestrant Injection is not a new molecular entity. The inactive ingredients for the proposed drug product are different both qualitatively and quantitatively from that of the listed drug product. Teva Fulvestrant injection contains the following inactive ingredients in each 5 mL syringe: benzyl alcohol 500 mg (10% w/v) and dehydrated alcohol 500 mg (10% w/v) (b) (4) (b) (4); castor oil 3000 mg (60% w/v) (b) (4) (b) (4), medium chain triglycerides q.s. to 5 mL (b) (4)% w/v), and nitrogen q.s. (ref: proposed Teva fulvestrant label). In contrast, each injection of Faslodex (LD) contains as inactive ingredients: 10% w/v Alcohol, USP, 10% w/v Benzyl Alcohol, NF, and 15% w/v Benzyl Benzoate, USP, as co-solvents, and made up to 100% w/v with Castor Oil, USP as a co-solvent and release rate modifier (ref: Fasoldex label).

This application is limited to chemistry, manufacturing, and controls information, nonclinical studies, a bioequivalence study and proposed product labeling. The application relies on FDA's findings of safety and effectiveness with the listed drug, Faslodex, for clinical safety and efficacy data and published litreture. The proposed indications of administration of Teva Pharmaceuticals USA, Inc.'s Fulvestrant Injection, pre-filled syringe are the same as the listed drug, Faslodex.

Teva Pharmaceuticals USA, Inc. held no meetings with the Agency during their product development or prior to the NDA submission.

• Product Quality

Source: CMC Review

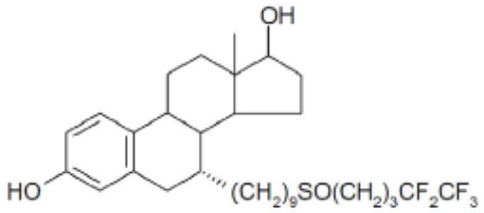
Final CMC Team Recommendation: A complete response action is recommended.

Drug Substance: (*Drs. Haripada Sarker and Benjamin Stevens)*

International Non-proprietary Name (INN): Fulvestrant

Chemical Name: Estra-1,3,5(10)-triene-3,17-diol,7-[9-[(4,4,5,5,5-pentafluoropentyl)sulfinyl]nonyl]-,(7α,17β)
Or
7α-[9-[(4,4,5,5,5-Pentafluoropentyl)sulfinyl]nonyl]estra-1,3,5(10)-triene-3,17β-diol

Structure:



Molecular Weight: 606.77

Fulvestrant is a synthetic organic substance, and has USP monograph. Fulvestrant USP is manufactured by (b) (4) and is supplied to be used in the manufacture of Fulvestrant for Injection (b) (4). The Applicant, Teva Pharmaceuticals, receives the DS from (b) (4). From drug substance perspective, the quality information supports the NDA 210063 is found to be Acceptable.

Drug Product: (*Drs. Amit Mitra and Anamitro Banerjee)*

The proposed commercial primary packaging is a 5 ml clear, prefilled syringe with a grey rubber plunger similar to that of the listed drug.

Each pre-filled syringe contains 250 mg fulvestrant, USP. The inactive ingredients are dehydrated alcohol, USP (500 mg), benzyl alcohol, NF (500 mg), castor oil, USP (b) (4) , and medium chain triglyceride, NF (qs. to 5.0 ml). The LD is Falsodex (fulvestrant) Injection and it is also available in a 5 ml pre-filled syringe. Each 5 ml contains 250 mg fulvestrant, USP. The inactive ingredients for the LD in 5 ml are: Alcohol, USP (500 mg), benzyl alcohol, NF (500 mg), benzyl benzoate, USP (750 mg), castor oil, USP (qs. to 5.0 ml). The LD does not contain medium chain triglycerides. Therefore, the proposed drug product is different from that of the LD qualitatively and quantitatively.

Outstanding Deficiencies/Comments Regarding Drug Product:

- Provide long term leachability data including the safety evaluation report of the leachable from the syringe components to cover the shelf life period. Alternatively, you may include the data from accelerated leachable studies.
- Adopt specification for tensile and elongation of the plunger rod covering the shelf life as a part of quality control.

Drug Product Process (*Drs. Feiyan Jin and Maotang Zhou)*

Outstanding Deficiencies/Comments Regarding Drug Product Process:

- (b) (4)
- We acknowledge that you provided the extractables/leachables study protocol for the (b) (4). Provide the study reports with data.
- (b) (4)
-
-

- (b) (4)

Outstanding Deficiencies/Comments Regarding Combination Product

(b) (4)

(b) (4)

Biopharmaceutics: Per reviewers' assessment (Drs. Parnali Chatterjee and Okpo Eradiri), because the drug product is a clear and sterile solution for intramuscular injection, in vitro drug release tesing is not a requirement for batch release or stability testing of the proposed drug product in the current submission. The Aplication does not contain biopharmaceutics data that requires assessment. Biopharmaceutics review activity is therefore not necessary for this NDA.

Environmental assessment: Per reviewers' assessment (*Drs. Paresma Patel and Anamitro Banerjee*) the Applicant's claim for categorical exclusion is acceptable.

Facility reviews/inspection: Per facility reviewers' assessment *(Drs Frank Wackes and Christina Capacci-Daniel)*, while there are no drug manufacturing concerns, this facility is not acceptable for the intended commercial operations stated in NDA 210063 based upon deficiencies identified by CDRH (see CDRH section below).

- **CDRH**

Source: CDRH Review (Drs. Sarah B. Mollo and Alan M. Stevens)

The drug product is provided in a pre-filled syringe. CDRH was consulted for the review of the syringe.

Outstanding CDRH Deficiencies/Comments

- The NDA does not include any design requirements and/or specifications for your prefilled syringe. The essential performance requirements should be included within the NDA. This should include, but is not limited to: the expelled volume (accuracy), breakloose force, glide force, and tip cap removal force. You may reference a master file or 510(k) for the actual verification testing (test reports, protocols, etc). However, the expelled volume (dose accuracy), breakloose force, and glide force of the pre-filled syringe should be performed on the combination product including the drug product and the safety needle (i.e. same gauge and length) that is provided with the pre-filled syringe. Provide the design requirements and/or specifications for your prefilled syringe.

- The table below represents the information needed to complete an adequate review of the device constituents. Provide this information, preferably in tabular format, for each

essential performance requirement as specified in your design requirement documentation or provide a justification for why the testing is not necessary. The device requirements should include but are not limited to: deliverable volume (dose accuracy), break loose, glide force, and tip cap removal force.

Essential Performance Requirement	**Specification**	**Verification**	**Validation**	**Aging / Stability (Y/N)**	**Shipping/ Transportation (Y/N)**	**Lot Release Testing (Y/N)**
Dose Accuracy	Ex: No less than 10 mL	{Insert Document Number}	{Insert Document Number or title of completed clinical study}	{Insert Yes if specification was verified after aging the device to the labeled date of expiry}	{Insert Yes if specification was validated after shipping or simulated shipping}	{Insert Yes if specification is a part of the lot release testing of the final finished combination product}
Needle Connection Type	Ex: ISO 11608-2	….	….	….	….	….
Break loose						
Glide force						
Cap Removal Force	Ex: ≤ 15 N	….	….	….	….	….
….	….	….	….	….	….	….

- The syringes are presented in a tray with polystyrene plunger rod and SafetyGlide needles. You state that the BD Safety Glide™ Needle, is a Class II, 510(k) Medical Device cleared by the Center Devices and Radiological Health, U.S. FDA CDRH, under 510(k)#: K951254 and that therefore, no letter of access is needed for a 510(k) cleared Medical Device." However, the needle is being supplied with the syringe and is therefore part of the combination product. The following information regarding the needle was not included within the submission:

- Include the design requirements and specifications in the NDA (i.e. length, gauge, connection type, material).

- You may reference a master file or 510(k) for the verification testing; however, for the Agency to review the information within the K951254, you need to submit a letter of authorization (LOA) to review the information within the 510(k) to support the NDA.

- In addition to performance testing per standards addressing the needle requirements (e.g. ISO 7864, ISO 9626, ISO 23908), the 510(k) should include a clinical use study mimics actual clinical use by patient substitutes rather than actual patients and helps evaluate the sharps injury prevention feature. The clinical use study helps to isolate problems with the device, optimize the device design, identify deficiencies in labeling and evaluate the type of training needed for device user. If the 510(k) does not provide a simulated use study, provide documentation of a clinical use study per FDA guidance document "Guidance for Industry and FDA Staff: Medical devices with Sharps Injury Prevention Features", August 9, 2005. A sample size of 500 with zero failures of the protection feature is recommended. The clinical use study will help FDA evaluate the devices sharps injury preventions feature for its safety and effectiveness. For more information please refer to http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071663.htm

- The 510(k) should include a biocompatibility evaluation of the final finished needle component of the pre-filled syringe per the Agency guidance, Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". The endpoints evaluated should be based on the type and duration of contact. As your device is intended to deliver fluids systemically, the Agency recommends that the following endpoints are addressed: cytotoxicity, sensitization, and irritation, acute systemic toxicity, hemolysis, and material-mediated pyrogenicity. If the 510(k) does not evaluate the appropriate endpoints, additional testing may be needed.

- The release specifications submitted under section 3.2.P.5.1 do not include the breakloose and glide force. These specifications should be included in the release testing for the combination product. Update your release specifications to include the breakloose and glide force.

- The stability testing does not include the testing of the essential performance requirements of the device constituent of the combination product. Provide stability data supporting the proposed shelf-life of the combination product including testing of the expelled volume (i.e. dose accuracy), breakloose, and glide force of the combination product.

- The Agency was unable to locate a risk assessment of the combination product. Provide the risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential

system failure states. This should include planned mitigations of these risks, verification of risk mitigations, as well as the acceptability of remaining risks.

- A description of materials including the material composition (trade name and common name), material supplier, and whether the material is drug and/or patient contacting was not provided. Provide this information and include any additives, processing agents, colorants, etc.

• Nonclinical Pharmacology/Toxicology

Source: Pharmacology and Toxicology Review (Drs. Eias A. Zahalka and Todd Palmby)

Final Pharmacology/Toxicology Team Recommendations: Complete Response action is recommended.

For nonclinical support, the Applicant relied on the Agency's finding of safety and effectiveness for Faslodex (LD). In addition to reliance on the LD, the Applicant submitted two reports of nonclinical studies in two species, and relied upon literature to support the safety of an inactive ingredient, medium chain triglycerides (MCT), which was used in the formulation of the drug product (Fulvestrant Injection). However, these studies were not adequate to qualify the excipient. The study reports did not list MCT as a component of the formulation/vehicle administered to the animals in both studies. In addition, the Applicant did not provide explanation for why the study reports did not list MCT as a component of the vehicle used in those studies or why the Certificates of Analysis did not report MCT levels. As such, the potential safety concern in regard to MCT local tissue effects was not addressed.

Outstanding Nonclinical Deficiency

- The safety of the proposed level of the medium chain triglycerides (MCT) excipient in the drug product to be administered by intramuscular injection was not adequately justified. The potential impact of this excipient on local tissue toxicities as it compares to the listed drug was not adequately addressed. You may not rely on information from the Summary Basis of Approval (SBA) or FDA reviewers' public summaries to justify a safe level of an excipient. MCT were not listed as a component of the vehicle or in the Certificate of Analysis in the reports for the rat and rabbit toxicology studies conducted with fulvestrant intramuscular injection and submitted to your NDA. The levels and fatty acid composition of the MCT administered to rats and rabbits in your fulvestrant injection studies were not provided. Therefore, these studies were inadequate to assess the safety of intramuscular injection of the proposed levels of MCT present in your to be marketed Fulvestrant Injection drug product. Provide an adequate justification for the safety of the proposed levels of MCT in your drug

product administered by intramuscular injection. We recommend that you submit a final report from a GLP nonclinical bridging toxicology study in a single species comparing your Fulvestrant Injection formulation to the listed drug product (Faslodex) at a clinically relevant dose. This study should include assessment of local tissue effects (macro and microscopic) and toxicokinetics following repeated intramuscular injections.

• Clinical Pharmacology

Source: Clinical Pharmacology Review (Drs. Salaheldin Hamed and Pengfei Song)

Final Clinical Pharmacology Team Recommendations: Approval

This application relied on the findings of safety and efficacy for the listed drug (LD) product Faslodex (fulvestrant) injection, for intramuscular use, 250 mg /5mL (50 mg/mL) of AstraZeneca Pharmaceuticals. The proposed Fulvestrant Injection strength, dosage form, and route of administration are similar to Faslodex Injection the LD, but several of the inactive ingredients are different (medium chain triglycerides replacing benzyl benzoate, dehydrated alcohol replacing ethanol).

In support of this NDA application, the Applicant conducted an open label, randomized, parallel group, single dose, bioequivalence study of Fulvestrant Injection 50 mg/mL in 252 healthy adult female subjects comparing the proposed product to the LD. The study ACT15160 compared the PK profile of a 250 mg dose of Fulvestrant Injection to 250 mg dose of FASLODEX® up to 56 days post-injection. 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}).

Reviewer comment: Per clinical pharmacology team's review, there was a concern that absorption of Teva fulvestrant was incomplete at day 55. However, considering that the effective half-life was approximately 28 days, 75% of the relevant AUC was characterized in 55 days and the products were bioequivalent. I agree with the team's conclusion that the study results appear adequate to support the bioequivalence of the two products.

The Office of Study Integrity and Surveillance (OSI) conducted an inspection of Study ACT15160 and observed no objectionable findings and concluded that the data from the study are reliable.

• Microbiology

Per the microbiology reviewers' assessment (Drs. Koushik Paul, and Erika Pfeiler), there are no outstanding microbiology product quality issues that preclude approval.

- **Clinical**

Final Clinical Team Recommendations: A complete response action is recommended.

The application relies on FDA's previous findings of efficacy and safety for the listed drug, Faslodex, under NDA 021344 held by AstraZeneca Pharmaceuticals. The Teva product contains the same amount of active ingredient, in the same concentration as the Listed Drug, Faslodex, but several of the inactive ingredients are different. Application relied upon a BE study and literature to support the safety of the change in the inactive ingredients.

1. To characterize the differences in inactive ingredients (dehydrated alcohol replacing ethanol, and medium chain triglycerides (MCT) replacing benzyl benzoate), Applicant conducted a BE study to assess whether the changes in excipients imply any changes in product bioavailability. Based on the results of this BE study Teva's product is bioequivalent to the Faslodex® (fulvestrant injection) 250mg/5mL (50mg/mL) manufactured for AstraZeneca.

Reviewer comment: This reviewer agrees with Applicant's conclusion that it appreas that changes in the inactive ingredient in the Teva product does not impact the product bioavailability in this BE study in healthy, adult human female subjects under fasting conditions.

2. Applicant stated that there are currently other FDA approved drug products containing MCT and ensuring a much higher parenteral exposure than the Fulvestrant formulation (for example, SMOFLIPID 20% from FRESENIUS KABI, NDA no 207648 ensures a daily MCT exposure of up to 36 grams).

Reviewer comment: This does not justify the safety of the proposed levels of MCT in Teva fulvestrant as this product is administered by intramuscular injection.

3. Application also relied upon literature to support the safety of the change in the inactive ingredients, including medium chain triglycerides. Per nonclinical reviewer's assessment who reviewed the nonclinical litreture (*Drs. Eias A. Zahalka and Todd Palmby),* these studies were not adequate to qualify the MCT excipient.

Reviewer comment: This reviewer agrees with the nonclinical team that the safety of the chronic intramuscular use of Teva fulvestrant specifically inactive ingredient MCT is not established.

- ## Advisory Committee Meeting

This 505(b)(2) application was not referred to an advisory committee because it has the same active ingredient, same route of administration, and same proposed indications as the listed drug and relies on FDA's finding of safety and efficacy for the listed drug.

- ## Pediatrics

Teva Pharmaceuticals USA, Inc. requested a full waiver for submission of pediatric use information in this submission.

Reviewer Comment: Because Fulvestrant Injection, 250 mg/5 mL (50 mg/mL) does not involve a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration, this application does not trigger PREA.

- ## Other Relevant Regulatory Issues

Not applicable.

- ## Labeling

FDA performed no formal labeling review of the Applicant's proposed prescribing information this cycle.

- ## Postmarketing Recommendations

Not applicable.

- ## Recommended Comments to the Applicant

Please refer to the Complete Response letter.

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

/s/

LALEH AMIRI KORDESTANI
10/24/2017

AMNA IBRAHIM
10/26/2017
Also see the CMC Team Leader review