# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210063Orig1s000

# SUMMARY REVIEW

# Division Director Summary Review for Regulatory Action

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| **Date** | August 19, 2019 |
| **From** | Amna Ibrahim MD |
| **Subject** | Division Director Summary Review |
| **NDA #** | 210063, class 2 resubmission |
| **Applicant** | Teva Pharmaceuticals USA Inc |
| **Date of Submission** | 02/19/2019 |
| **PDUFA Goal Date** | 08/19/2019 |
| **Proprietary Name** | Fulvestrant Injection |
| **Established or Proper Name** | Fulvestrant Injection |
| **Dosage Form(s)** | Injection for intramuscular use |
| **Action or Recommended Action:** | Approval |
| **Approved/Recommended Indication(s)/Population(s)** (if applicable) | • Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer in postmenopausal women not previously treated with endocrine therapy.<br>• HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy.<br>• 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.<br>• 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 | Wahby, Sakar M. |
| Pharmacology Toxicology Review | Eias A Zahalka |
| OPQ Review | Chen, Xiao Hong |
| Clinical Pharmacology Review | Hamed, Salaheldin |
| OPDP | Serlemitsos-Day, Maritsa |
| CDTL Review | Chen, Xiao Hong |
| OSE/DMEPA | Gao, Tingting N. |

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| OFFICE OF DEVICE EVALUATION and CDRH/OC memo | Wolloscheck, David |

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
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. Background

Fulvestrant is an antiestrogenic agent that binds – in a competitive manner – to estrogen receptor (ER). NDA 210063 for Fulvestrant Injection was submitted as a 505b2 application and it relies for safety and efficacy findings on the listed drug (LD) FASLODEX® (fulvestrant) injection (NDA # 021344) of AstraZeneca Pharmaceuticals LP. This application initially received a Complete Response (CR) letter on 10/26/2017. The applicant resubmitted the NDA and was designated a class 2 submission. The CR letter listed multiple deficiencies relating to non-clinical, drug product and process, device characterization (CDRH ODE review for device quality) and manufacturing (CDRH OC review for device manufacturing).

Please refer to the summary review for the original submission. Also refer to the CDTL review for further details for this class 2 submission.

# 2. Product Quality

Fulvestrant, USP is a white powder for intramuscular administration. The sterile injection solution is a clear, colorless to yellow viscous liquid supplied in two 5 mL single-dose prefilled syringes each containing 250 mg fulvestrant/5 mL for intramuscular administration. The API and its concentration, the route of the administration (IM), dose and the indications are the same as those of the LD. The only difference between the LD and the proposed drug is the excipients used in the formulation. The proposed Fulvestrant Injection contains benzyl alcohol and dehydrated alcohol, castor oil, medium chain triglycerides, and nitrogen as inactive ingredients.

The product quality deficiencies were pertaining to the drug product, manufacturing process, as well as deficiencies for device (CDRH) and its manufacturing (CDRH OC). In the current resubmission, the applicant provided complete response to all outstanding product quality deficiencies. The applicant conducted a long term (refrigerated) leachability study to cover the shelf life of the drug product. The acceptance criteria were adequate. The manufacturing steps of the proposed drug product (DP) were acceptable. To address the plunger rod issue, the applicant stated that fulvestrant injection 50 mg/ml (250 mg/5 ml) combination product includes a prefilled syringe and no reconstitution is required, according to its intended use. Therefore, specification for tensile and elongation of the plunger rod is considered not applicable and no verification of tensile and elongation of the plunger is required, as part of the

design verification and validation tests". Per the OPQ and CDRH reviewer, since there is no guidance or regulation for unassembled component testing of pre-filled syringe components such as "plunger rods" within CDER and CDRH, the applicant's response is adequate.

(b) (4)

The master batch record has been updated accordingly. This was considered acceptable.

The extractables/leachables studies were performed on the (b) (4) and the study reports were provided. The toxicological risks on the leachables were assessed and found to be low. The firm's response was considered acceptable.

(b) (4)

The responses have been reviewed by each discipline in the OPQ team as well as CDRH consult team and the deficiencies have been adequately addressed and the NDA is recommended as acceptable.

## 3. Nonclinical Pharmacology/Toxicology

In the original submission, 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. This deficiency has been adequately addressed in this submission. Teva's fulvestrant formulation containing MCT was compared to the listed drug in a repeat-dose toxicology study in rats. Both test articles showed comparable local and systemic toxicity profiles. Non-clinical review finds that the deficiency has been adequately addressed and recommends approval of the NDA.

## 4. Clinical Pharmacology

OCP recommended approval from their perspective in the first cycle of submission review.

## 5. Clinical Microbiology

NA

## 6. Clinical/Statistical-Efficacy

No clinical data submitted. The application relies on the efficacy of FASLODEX®.

## 7. Safety

No clinical data submitted. The application relies on the safety of FASLODEX®

## 8. Advisory Committee Meeting

NA

## 9. Pediatrics

NA

## 10. Other Relevant Regulatory Issues

- DMEPA: Based on the review of the use-related risk analysis (URRA), comparative analyses, and justification, DMEPA reviewer determined that a human factors validation study is not needed.

- CDRH and OC: the deficiencies were addressed by the applicant and the CDRH/OC memo finds the NDA approvable from their perspective.

- (b) (4)

- Office of Scientific Investigations (OSI) Audits: NA
- Financial Disclosure: NA
- Other Good Clinical Practice (GCP) issues: NA

## 11. Labeling

Labeling was amended from that of the LD as appropriate after discussions with the team

## 12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

None

- Other Postmarketing Requirements and Commitments

NDA 210062
Fulvestrant Injection
Class 2 Resubmission
None

Amna Ibrahim MD
Deputy Director, DOP1
OHOP, OND, CDER

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/s/

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