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**VIA ELECTRONIC SUBMISSION**

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

# CITIZEN PETITION

Teva Pharmaceuticals USA, Inc. ("Teva") submits this Petition to the Food and Drug Administration ("FDA") in accordance with 21 C.F.R § 10.25(a) and § 10.30[1] and pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act ("FDC Act"). For the reasons discussed below, Teva respectfully requests that FDA assign a Therapeutic Equivalence Evaluation Code ("TE Code") for the company's Fulvestrant Injection, 250 mg/5 ml (50 mg/ml) which FDA approved on August 19, 2019 under New Drug Application ("NDA") 210063. NDA 210063 was submitted by Teva to FDA pursuant to FDC Act § 505(b)(2). Teva's Fulvestrant Injection, 250 mg/5 ml (50 mg/ml) was 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.

## I. FDA ACTION REQUESTED

Teva requests that FDA assign in the Agency's Orange Book a TE code of "AO" to Teva's Fulvestrant Injection, 250 mg/5 ml (50 mg/ml). As demonstrated below, Teva's

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[1] In the Preface to FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), the Agency states that "[a] person seeking to have a therapeutic equivalence rating for a drug product approved in a 505(b)(2) application may petition the Agency through the citizen petition procedure (*see* 21 CFR 10.25(a) and 21 CFR 10.30.)" Orange Book Preface (39th ed., 2019), at xxiv.

Fulvestrant Injection, 250 mg/5 ml (50 mg/ml) meets all applicable requirements for a TE Code with respect to AstraZeneca Pharmaceuticals LP's ("AstraZeneca") FASLODEX® (fulvestrant) Injection, 50 mg/ml which FDA approved under NDA 021344 on April 25, 2002. There is no basis for FDA to deny this request. Accordingly, the assignment of a TE code is warranted.

## II. STATEMENT OF GROUNDS

### A. Factual and Regulatory Background

The Orange Book Preface explains that there are "two basic categories into which multisource drugs have been placed: (1) "A-rated drug products (i.e., "Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products": and (2) "B-rated" drug products (i.e., "Drug products that FDA at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products"). Orange Book Preface (39th ed., 2019), at xiii (emphasis in original).

FDA defines "therapeutic equivalents" to mean "approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." 21 C.F.R. § 314.3(b). FDA defines "pharmaceutical equivalents" to mean:

> drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug product, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir of overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.

Id. Drug products designated with an "A" TE Code fall under one of two main policies:

(1) for those active ingredients or dosage forms for which no in vivo bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions) or satisfied by a showing that an acceptable in vitro dissolution standard is met. A therapeutically equivalent rating is assigned such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated AA, AN, AO, AP or AT, depending on the dosage form, as described below); or

(2) for those Drug Efficacy Study Implementation (DESI) drug products containing active ingredients or dosage forms that have been identified by FDA as having actual

> or potential bioequivalence problems, and for post-1962 drug products in a dosage form presenting a potential bioequivalence problem, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through in vivo and/or in vitro studies, the bioequivalence of the product to a selected reference product (these products are designated as AB).

Orange Book Preface (39th ed., 2019) at xiii - xiv. The Orange Book also defines and explains FDA's policies for various "A" sub-codes. Specifically, the TE code "AO" is defined as "Injectable oil solutions." Orange Book Preface (39th ed., 2019) at xvi. The electronic Orange Book entry for AstraZeneca's FASLODEX® (fulvestrant) 50 mg/ml is shown below:

| | |
|---|---|
| **Active Ingredient:** | FULVESTRANT |
| **Proprietary Name:** | FASLODEX |
| **Dosage Form; Route of Administration:** | INJECTABLE; INTRAMUSCULAR |
| **Strength:** | 50MG/ML |
| **Reference Listed Drug:** | Yes |
| **Reference Standard:** | Yes |
| **TE Code:** | AO |
| **Application Number:** | N021344 |
| **Product Number:** | 001 |
| **Approval Date:** | Apr 25, 2002 |
| **Applicant Holder Full Name:** | ASTRAZENECA PHARMACEUTICALS LP |
| **Marketing Status:** | Prescription |

The FDA has approved other ANDAs for pharmaceutically equivalent versions of AstraZeneca's FASLODEX®. These ANDAs appear as follows in the electronic version of the Orange Book:

| | |
|---|---|
| **Active Ingredient:** | FULVESTRANT |
| **Proprietary Name:** | FULVESTRANT |
| **Dosage Form; Route of Administration:** | INJECTABLE; INTRAMUSCULAR |
| **Strength:** | 50MG/ML |
| **Reference Listed Drug:** | No |
| **Reference Standard:** | No |
| **TE Code:** | AO |
| **Application Number:** | A210044 |
| **Product Number:** | 001 |
| **Approval Date:** | Mar 4, 2019 |
| **Applicant Holder Full Name:** | AMNEAL PHARMACEUTICALS CO GMBH |
| **Marketing Status:** | Prescription |

| | |
|---|---|
| **Active Ingredient:** | FULVESTRANT |
| **Proprietary Name:** | FULVESTRANT |
| **Dosage Form; Route of Administration:** | INJECTABLE; INTRAMUSCULAR |
| **Strength:** | 50MG/ML |

| | |
|---|---|
| **Reference Listed Drug:** | No |
| **Reference Standard:** | No |
| **TE Code:** | AO |
| **Application Number:** | A208811 |
| **Product Number:** | 001 |
| **Approval Date:** | Jul 23, 2019 |
| **Applicant Holder Full Name:** | MYLAN INSTITUTIONAL LLC |
| **Marketing Status:** | Prescription |

| | |
|---|---|
| **Active Ingredient:** | FULVESTRANT |
| **Proprietary Name:** | FULVESTRANT |
| **Dosage Form; Route of Administration:** | INJECTABLE; INTRAMUSCULAR |
| **Strength:** | 50MG/ML |
| **Reference Listed Drug:** | No |
| **Reference Standard:** | No |
| **TE Code:** | AO |
| **Application Number:** | A205935 |
| **Product Number:** | 001 |
| **Approval Date:** | May 14, 2019 |
| **Applicant Holder Full Name:** | SANDOZ INC |
| **Marketing Status:** | Prescription |

**B. <u>Request for TE Code Assignment for Teva's Fulvestrant Injection 250 mg/5 ml (50 mg/ml)</u>**

According to FDA's website, FDA considers drug products which are classified as injectable oil solutions to be pharmaceutical equivalents if they meet these three criteria:

- they contain the identical active ingredient
- they are identical in concentration
- they use the identical type of oil as a vehicle

https://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm

As shown in Teva's NDA No. 210063, Teva's Fulvestrant Injection, 250 mg/5 ml (50 mg/ml) product has the identical: active ingredient (fulvestrant), strength (50 mg/ml), and type of oil as a vehicle (castor oil) as the RLD (FASLODEX®). As such, Teva's Fulvestrant Injection, 250 mg/5 ml (50 mg/ml) is a pharmaceutical equivalent.

Further, Teva's Fulvestrant Injection, 250 mg/5 ml (50 mg/ml) should be assigned a therapeutic equivalence code of "AO" because it has already been deemed bioequivalent to FASLODEX® by FDA as shown by the Approval of Teva's NDA No. 210063. Moreover, both Teva's Fulvestrant Injection, 250 mg/5 ml (50 mg/ml) and AstraZeneca's FASLODEX® "can be expected to have the same clinical effect and safety profile when administered to patients under

the conditions specified in the labelling." 21 C.F.R. § 314.3(b) (defining "therapeutic equivalents"). As such, Teva's Fulvestrant Injection, 250 mg/5 ml (50 mg/ml) and FASLODEX® are pharmaceutical and therapeutic equivalents and Teva's Fulvestrant Injection, 250 mg/5 ml (50 mg/ml) should be identified in the Orange Book with an "AO" TE Code

## III. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31

## IV. ECONOMIC IMPACT STATEMENT

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b)

## V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner that are unfavorable to the Petition.

Respectfully submitted,

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