August 15, 2024

VIA ELECTRONIC SUBMISSION

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

SUITABILITY PETITION

Dear Sir or Madam:

The undersigned petitioner submits this petition, on behalf of a client, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), and in accordance with 21 C.F.R. § 10.20 and 21 C.F.R. § 10.30 requesting the Commissioner of the Food and Drug Administration ("FDA") to declare that the proposed drug product Estradiol Vaginal Inserts, 1 g and 2 g is suitable for consideration in an Abbreviated New Drug Application ("ANDA").

I. ACTION REQUESTED

The petitioner requests that the Commissioner of the FDA declare that the proposed drug products, Estradiol Vaginal Inserts, 1 g and 2 g are suitable for submission as an ANDA[1]. The listed reference drug product (RLD), upon which this petition is based, is Estrace® Vaginal Cream, 0.01% Allergan Sales, NDA #086069.[2]

The petitioner hereby seeks approval of a change in dosage form to vaginal inserts, 1 g and 2 g to the approved vaginal cream, 0.01% of the RLD.

II. STATEMENT OF GROUNDS

[1] Each vaginal insert will contain either 1 g or 2 g of semi-solid base where the strength of estradiol in the base is 0.01% and the total weight of the insert is approximately 1.3 g or 2.3 g.

[2] Petitioner notes that Estrace® Vaginal Cream was approved on January 31, 1984, and was assigned application number A 86069 which appears in FDA's publication "Approved Drug Products With Therapeutic Equivalence Ratings", also known as "The Orange Book." FDA opened Docket No. FDA-2020-N-1245 on August 13, 2021 which in part acknowledges FDA's policy that pre-Hatch-Waxman abbreviated new drug applications (PANDAs) are in fact NDAs and can serve as a reference listed drug for purposes of ANDA submission. Estrace® Vaginal Cream is considered a PANDA under FDA's criteria.

The FD&C Act § 505(j)(2)(C) provides for the submission of an ANDA for a drug product that differs in dosage form from that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

Estrace® Vaginal Cream, 0.01% is indicated for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

Dosing and administration recommendations for Estrace® Vaginal Cream include the following information in the DOSAGE AND ADMINISTRATION:

> Usual Dosage: The usual dosage range is 2 to 4 g (marked on the applicator) daily for one or two weeks, then gradually reduced to one half initial dosage for a similar period. A maintenance dosage of 1 g, one to three times a week, may be used after restoration of the vaginal mucosa has been achieved.

Estrace® Vaginal Cream is administered via a calibrated plastic applicator that is provided with the 42.5-gram tube of Estrace® Vaginal Cream. This method of administration requires the patient to prepare or measure the correct dose by following stepwise instructions that are provided with the product. These steps include:

- removing the cap from the Estrace® Vaginal Cream.
- orienting the applicator according to the handling instructions.
- screwing the threaded end of the applicator onto the nozzle of Estrace® Vaginal Cream until secure.
-Positioning the tube with applicator upright to view calibration marks on the applicator.
-Squeezing the tube from the bottom to push the prescribed amount of Estrace® Vaginal Cream into the applicator while watching the plunger rise to the prescribed dose.
-Unscrewing the applicator from the tube and replacing the caps on the Estrace® Vaginal Cream tube.
-Administration of the product according to further instructions.

FDA's approved labeling for Estrace® Vaginal Cream acknowledges the variability that is associated with these steps when using the current cream dosage form with the Note that appears just prior to the How Supplied section of the Package Insert which states:

> NOTE: The number of doses per tube will vary with dosage requirements and patient handling.

It is understandable that the number of doses per tube will vary with dosage requirements since dosages can vary from 1 to 4 grams of cream. However, FDA's statement that "patient handling" can also impact the number of doses per tube is an acknowledgment that patients self-administering Estrace® Vaginal Cream often encounter problems with this method that results in excess product waste. The proposed Estradiol Vaginal Inserts, 1 g and 2 g will obviate any potential waste or problems with "patient handling" by providing a premeasured 1 or 2 g dose of product which can be administered by inserting the necessary number of inserts to obtain the 1 g to 4 g dose that is clinically required.

By virtue of being formulated in a ready to use vaginal insert, the proposed product will offer several advantages over the existing Estrace® Vaginal Cream. Availability in both 1 g and 2 g inserts will permit patients to obtain all labeled doses via insertion of either 1 or 2 insert(s).

Patients will no longer need to undertake the tedious process of attaching an applicator to a tube of cream, wondering if that attachment is secure, measuring out the required dose into an applicator, administering the dose, and then cleaning an applicator after use. This process of manipulating the applicator and tube of cream while subsequently withdrawing the required dosage requires manual dexterity and visual acuity which are both traits that deteriorate with age. Furthermore, patients that experience problems withdrawing the correct dosage may choose to simply administer whatever amount they are able to squeeze into the applicator. These issues can lead to therapeutic failures associated with underdosing or skipping doses. Availability of pre-measured dose of estradiol in a dosage form that is easy to administer will obviate issues related to measuring of doses and administration of a complete dose.

Petitioner notes that the change requested in this petition is limited solely to a change in dosage form and will not also represent a change in strength. The proposed soft gelatin vaginal insert will contain a semi-solid base formulated with excipients, including the soft gelatin shell, previously utilized in products approved by FDA for vaginal administration where the strength of estradiol within the semi-solid base will be 0.01%. The physical characterization of the semi-solid contained within the soft gelatin shell of the proposed vaginal insert should not be viewed by FDA as a second difference in dosage form (e.g. if the semi-solid base contained within the soft gelatin shell were most aptly characterized as an ointment) due to FDA's long standing policy governing determination of dosage forms. Since at least the mid 1990's, FDA has based dosage forms determinations on the concept of "gross recognition" and stated that a dosage form is "generally determined based on the physical form of the product prior to dispensing to the patient."[3] Indeed, FDA has previously determined that a compressed tablet inside a gelatin capsule shell is considered a capsule by FDA where FDA's decision was challenged by Warner-Lambert, with FDA's decision upheld by the United States Court for the District of Columbia, and affirmed on Appeal.[4]

Bioequivalence studies for the proposed Estradiol Vaginal Insert, 1 g and 2 g will be conducted consistent with FDA's Product Specific Guidance Estradiol Vaginal Cream NDA 86069 last revised in September 2014.

III. Pediatric Research Equity Act ("PREA") Applicability

PREA, which is codified at FD&C Act§ 505B, applies to the change proposed in the context of this suitability petition, a change in dosage form. The Act specifically requires changes of dosage form ares subject to pediatric evaluation. The Act also provides for a waiver from such requirement if the drug:

1. does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and
2. is not likely to be used in a substantial number of pediatric patients.

The sole indication for Estrace® Vaginal Cream is for women that are experiencing symptoms due to menopause. In May 2024, FDA published a list of conditions titled "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics". FDA's list includes menopause and perimenopausal disorders. Petitioner respectfully requests that FDA grant a full waiver of the requirements to conduct any pediatric studies as the only approved indication for the product that is the subject of this petition appears on FDA's May

[3] See response to FDA Docket Nos. 95P-0262 and 96P-0317 dated December 1, 2000
[4] See Warner-Lambert v. Donna E. Shalala, 202 F.3d 326 (D.C. Cir. 2000), Feb 11, 2000.

2024 list. Furthermore, the list stipulates that products approved for such conditions identified on the list "qualify for waiver because studies would be impossible or highly impractical."

IV. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

V. Economic Impact

The petitioner will submit information on economic impact upon request by the agency if applicable.

VI. 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, which are unfavorable to the petition.

Sincerely,

Martin Shimer Digitally signed by Martin Shimer Date: 2024.08.15 10:09:57 -04'00'

Martin Shimer
Executive Director, Regulatory Services
Lachman Consulting Services, Inc.

Please contact me at m.shimer@lachmanconsultants.com if you have any questions related to this petition.

Attachments accompanying this petition:

- Attachment 1: Copy of the relevant excerpt from the current electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) –
- Attachment 2: Current Package Insert for ESTRACE® VAGINAL CREAM, 0.01%, NDA #086069 Revision 11/2022; source: Drugs@FDA
- Attachment 3: Draft Package Insert Proposed for Estradiol Vaginal Inserts, 1 g and 2 g
- Attachment 4: FDA Automatic Full Waiver List May 2024