



Suzanne Strang, Ph.D.
Executive Director, Regulatory Affairs and Quality Assurance
ASCEND Therapeutics US, LLC
607 Herndon Parkway, Suite 110
Herndon, VA 20170

RE: NDA 021166
EstroGel® 0.06% (estradiol gel) for topical use
MA 430

Dear Dr. Strang:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional EstroGel Sell Sheet-PS (2017-EG-0022) (sell sheet) for EstroGel® 0.06% (estradiol gel) for topical use (EstroGel) submitted by ASCEND Therapeutics US, LLC (Ascend) under cover of Form FDA 2253. This sell sheet makes false or misleading claims and/or representations about the efficacy of EstroGel. As a result, the sell sheet misbrands EstroGel within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), and makes distribution of the product violative. 21 U.S.C. 352(a); 331(a). Cf. 21 CFR 202.1(e)(5); (e)(7)(i). This sell sheet is concerning because it falsely suggests that EstroGel contains the lowest effective dose of estrogen compared to other estrogen products when, in fact, there are other FDA-approved products that are available at doses lower than EstroGel.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of EstroGel.¹ According to its FDA-approved product labeling (PI), EstroGel is indicated for the following (emphasis original):

- 1.1 Treatment of Moderate to Severe Vasomotor Symptoms [VMS] due to Menopause.**
- 1.2 Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy [VVA] due to Menopause.**

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

Limitation of Use

When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, topical vaginal products should be considered.

EstroGel is associated with boxed warnings for endometrial cancer, cardiovascular disorders, breast cancer, and probable dementia. In addition, the BOXED WARNING section of the PI states, “Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.” EstroGel is contraindicated in women with undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active deep vein thrombosis, pulmonary embolism, or history of these conditions; active arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions; known anaphylactic reaction or angioedema to EstroGel; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders; and known or suspected pregnancy.

The PI for EstroGel includes warnings and precautions regarding malignant neoplasms, gallbladder disease, hypercalcemia, visual abnormalities, addition of a progestin when a woman has not had a hysterectomy, elevated blood pressure, hypertriglyceridemia, past history of cholestatic jaundice, hypothyroidism, fluid retention, hypocalcemia, exacerbation of endometriosis, hereditary angioedema, exacerbation of other conditions, flammability of alcohol-based products, moisturizer lotion application, laboratory tests, and drug-laboratory test interactions. The most common adverse reactions reported with the use of EstroGel include headache, flatulence, and breast pain.

False or Misleading Claims about Efficacy

The sell sheet includes the following representations and claims:

- “Provides the lowest, effective dose of transdermal estrogen therapy to help meet your patients’ treatment goals[.][²]”
- “In the 2017 North American Menopause Society (NAMS) Position Statement, NAMS recommends first-line treatment of VMS with the most appropriate, often lowest effective dose, of estrogen therapy consistent with treatment goals[.][³]”
- “The dose of estradiol in EstroGel has been proven to be the lowest effective dose for the treatment of symptomatic postmenopausal women[.][²]”

These claims, in the context of this sell sheet, are false or misleading because they suggest that EstroGel provides the lowest effective dose of estrogen for the treatment of moderate to

² Archer DF, Pickar JH, MacAllister DC, Warren MP. Transdermal estradiol gel for the treatment of symptomatic postmenopausal women. *Menopause*. 2012;19(6):622-629.

³ The North American Menopause Society. The 2017 hormone therapy position statement of The North American Menopause Society [published online June 22, 2017]. *Menopause*. 2017. doi: 10.1097/GME.0000000000000921.

severe VMS due to menopause and moderate to severe VVA due to menopause compared to other estrogen therapies, including transdermal estrogen therapies, when this is not the case. According to the EstroGel PI, the approved dose of EstroGel 0.06% for the treatment of moderate to severe VMS due to menopause and moderate to severe VVA due to menopause is 1.25 grams (g) of gel per day, which contains 0.75 milligrams (mg) of estradiol. However, there are other estrogen products, including other transdermal estrogen therapies, approved by the FDA for the treatment of moderate to severe VMS due to menopause and moderate to severe VVA due to menopause that have approved estrogen doses lower than EstroGel.

The sell sheet cites to an article by Archer et al. to support the above claims. The article describes the results of two studies, neither of which provide support. The first study is a phase 3 study comparing 1.5 mg estradiol (2.5 g estradiol gel 0.06%) and 0.75 mg estradiol (1.25 g estradiol gel 0.06%) to placebo. The second study is a phase 4 study comparing 0.375 mg estradiol (1.25 g estradiol gel 0.03%) and 0.27 mg estradiol (0.9 g estradiol gel 0.03%) to placebo. The authors conclude, in pertinent part, that, “[T]he currently available 0.75 mg estradiol in a transdermal gel is the lowest practical dose of *this estrogen therapy* in the treatment of moderate to severe vasomotor symptoms and vulvar and vaginal atrophy due to menopause.” (emphasis added). However, neither EstroGel nor estradiol gel 0.03% were compared in these studies to other FDA-approved formulations of estrogen (e.g., gels, transdermal patches, or other oral formulations) at any dose. Therefore, they are not sufficient to support claims suggesting that the dose of estradiol in EstroGel has been proven to be the lowest effective dose of estrogen for the treatment of symptomatic postmenopausal women. Similarly, these studies are not sufficient to support claims suggesting that approved doses below 0.75 mg of other estrogen products are not effective.

Conclusion and Requested Action

For the reasons discussed above, the sell sheet misbrands EstroGel within the meaning of the FD&C Act, and makes distribution of the product violative. 21 U.S.C. 352(a); 331(a). Cf. 21 CFR 202.1(e)(5); (e)(7)(i).

OPDP requests that Ascend immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before August 30, 2018, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for EstroGel that contain statements such as those described above, and explaining your plan for discontinuing use of such violative materials. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Amundson Avenue, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 430 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should

include a subject line that clearly identifies the submission as a Response to Untitled Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for EstroGel comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Lynn Panholzer, Pharm.D.
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

Matthew J. Falter, Pharm.D.
Team Leader
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

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/

LYNN M PANHOLZER
08/16/2018

MATTHEW J FALTER
08/16/2018