DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Suzanne Strang, Ph.D.
Senior Director, Regulatory Affairs & Quality Assurance
ASCEND Therapeutics US, LLC
607 Herndon Parkway, Suite110
Herndon, VA 20170

RE: NDA #021166
EstroGel® 0.06% (estradiol gel) for topical use
MA #359

Dear Dr. Strang:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a professional EstroGel Zazzle Card A-IS (2015-EG-0021) (Zazzle card) for EstroGel® 0.06% (estradiol gel) for topical use (EstroGel) submitted by ASCEND Therapeutics US, LLC (Ascend) under cover of Form FDA 2253. The Zazzle card is false or misleading because it omits important risk information associated with the use of EstroGel. Thus, the Zazzle card misbrands EstroGel within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i), (iii).

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:

- Treatment of moderate to severe vasomotor symptoms due to menopause.
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

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.

[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.

EstroGel is associated with a number of serious risks. The PI includes boxed warnings regarding endometrial cancer, cardiovascular disorders, breast cancer, and probable dementia. 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.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The Zazzle card is misleading because it includes efficacy claims for EstroGel, but fails to include important risk information associated with the drug. For example, the Zazzle card fails to include information from the boxed warning that EstroGel, alone or with progestin, should not be used for the prevention of cardiovascular disease or dementia. Additionally, the Zazzle card includes a statement about the risks of Estrogel, “Estrogen therapies increase the risk of certain cancers, cardiovascular disorders, and probable dementia,” but fails to disclose material information about the specific risks related to cancers and cardiovascular disorders discussed in the BOXED WARNING section of the PI, which includes endometrial cancer, invasive breast cancer, deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction. Furthermore, the Zazzle card fails to include any of the conditions for which EstroGel is contraindicated. We note that the Zazzle card includes the statements, “Please visit www.estrogel.com for additional information” and “See enclosed full Prescribing Information and boxed warning.” However, this does not mitigate the omission of these important risks. By omitting serious risks associated with EstroGel, the Zazzle card misleadingly suggests that EstroGel is safer than has been demonstrated.

Conclusion and Requested Action

For the reasons discussed above, the Zazzle card misbrands EstroGel within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i), (iii).

OPDP requests that Ascend immediately cease violating the FD&C Act, as described above. Please submit a written response to this letter on or before July 8, 2015, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for EstroGel that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

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 Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (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 #359 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
Office of Prescription Drug Promotion

{See appended electronic signature page}

Twyla Thompson, Pharm.D., RAC
Acting Deputy Division Director
Office of Prescription Drug Promotion

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

/s/

LYNN M PANHOLZER
06/23/2015

TWYLA N THOMPSON
06/23/2015