DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Peter Honig, MD, MPH
Senior Vice President, Worldwide Safety and Regulatory
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

RE: NDA 020472
ESTRING® (estradiol vaginal ring)
MA 275

Dear Dr. Honig:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a direct-to-consumer video of an interview featuring paid and trained Pfizer Inc. (Pfizer) spokespersons regarding ESTRING® (estradiol vaginal ring) (Estring) posted on the website michiganmomliving.com, as well as the corresponding anchor lead in questions and answers provided to interview participants (PP-EST-USA-0235) submitted by Pfizer under cover of Form FDA 2253.[1] This video makes false or misleading claims and/or representations about the risks associated with and the efficacy of Estring. Thus, the video misbrands Estring within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(n); 321(n); 331(a). *See* 21 CFR 202.1(e)(3)(iii); (e)(5). This video is especially concerning from a public health perspective because it fails to include **any** risk information about Estring, which is a drug that bears a boxed warning due to several serious, life-threatening risks, including endometrial cancer, breast cancer, and cardiovascular disorders, as well as numerous contraindications and warnings. The video thus creates a misleading impression about the safety and efficacy of Estring.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Estring.[2] According to the FDA-approved product labeling (PI)[3]:

ESTRING is indicated for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause.

[1] This video is available on the internet at https://michiganmomliving.com/2017/05/09/womens-health-post-menopause-interview/ (last accessed June 18, 2018).
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.
[3] The version of the Estring PI referred to in this letter is dated September 2015.

This product is associated with a number of serious risks. The PI for the drug contains BOXED WARNINGS for endometrial cancer, cardiovascular disorders, breast cancer, and probable dementia. Estring 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 a 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 or hypersensitivity to Estring; 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 Estring includes Warnings regarding ovarian cancer, gallbladder disease, hypercalcemia, visual abnormalities, and hereditary angioedema. It also contains Precautions regarding addition of a progestin when a woman has not had a hysterectomy, elevated blood pressure, hypertriglyceridemia, past history of cholestatic jaundice, hypothyroidism, hypocalcemia, fluid retention, exacerbation of endometriosis, exacerbation of other conditions, location of Estring, vaginal irritation, and vaginal infection. In addition, the most common adverse reactions reported with Estring were headache, leukorrhea, back pain, upper respiratory tract infection, arthritis, insomnia, abdominal pain, sinusitis, vaginal hemorrhage, arthralgia, nausea, and flu-like symptoms.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The video, which features a physician and one of her patients, both of whom are spokespeople for Pfizer as acknowledged in the video,[4] contains claims and/or representations about the benefits of Estring. However, the video fails to communicate **any** risk information about the product. We acknowledge that in the video the Physician Spokesperson refers women to askforthering.com and to their healthcare provider for additional information. However, this does not mitigate the omission of the risk information from the video. By omitting the risks associated with Estring, the video fails to provide material information about the consequences that may result from the use of the drug and creates a misleading impression about the drug's safety. This misleading presentation is especially problematic from a public health perspective given the serious and potentially life-threatening risks associated with the drug.

Additionally, when the Patient Spokesperson is directly asked by the interviewer about "side effects," she replies, "I do not experience any side effects. I'm, for me, I, I was able to just feel relief." While the Patient Spokesperson's statements may be an accurate reflection of her own experience as an Estring-treated individual, these statements misleadingly suggest that patients using Estring will have similar results and will not experience side effects, further exacerbating the misleading impression created by the omission of risk information. The

[4] We note that the document titled, "**ESTRING® (estradiol vaginal ring) 2 mg SMT/RMT Q&A"** (emphasis original) submitted on Form FDA 2253 also states, "*Both spokespeople will be trained to say they are here on behalf of Pfizer in each interview"* (emphasis original).

personal experience of an Estring-treated individual such as this spokesperson does not constitute support for the suggestion that other patients will not experience adverse events after starting Estring therapy and does not obviate the requirement to present risk information.

Furthermore, towards the end of the interview, the Physician Spokesperson was asked by the interviewer, "Is there anything we didn't cover in this interview?" However, the Physician Spokesperson declined to take this opportunity to disclose any of the risks of Estring.

False or Misleading Claims about Efficacy

In the video, the Patient Spokesperson makes the following claim:

- "I have to say that it was…yeah once we came up with the plan and I began using the product it was pretty much an instant relief."

This claim misleadingly suggests that patients will experience similar results, i.e., instant relief of their symptoms, after initiating treatment with Estring. While the Patient Spokesperson's statement may be an accurate reflection of her own experience as an Estring-treated individual, the personal experience of an Estring-treated individual such as this spokesperson does not constitute support for the suggestion that patients will experience instant relief of their VVA symptoms after starting Estring therapy. Estrogens, including Estring, typically require an interval of time to improve the signs and symptoms of VVA, and FDA is not aware of data to support claims that Estring provides instant relief of moderate to severe symptoms of VVA due to menopause. In studies supporting the approval of Estring, endpoints including physician's global assessment of vaginal symptoms, patient's global assessment of vaginal symptoms, physician's assessment of improvement of vaginal mucosa, patient's assessment of improvement in vaginal dryness, symptoms of dysuria and urinary urgency, vaginal pH, and maturation index and/or maturation value, were evaluated after 12 weeks of treatment. If you have data to support the claim that patients using Estring experience instant relief of moderate to severe symptoms of VVA due to menopause, please submit such data to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the video misbrands Estring within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(n); 321(n); 331(a). *See* 21 CFR 202.1(e)(3)(iii); (e)(5).

OPDP requests that Pfizer immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before July 3, 2018, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Estring that contain violations 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 Ammendale Road, 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 275 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 Estring comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Lynn Panholzer, PharmD
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

Matthew J. Falter, PharmD
Team Leader
Division of Advertising & Promotion Review 2
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/s/

LYNN M PANHOLZER
06/19/2018

MATTHEW J FALTER
06/19/2018