Society for Women's Health Research

October 15, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland, 20852

RE: Docket# FDA-2015-N-3275

To Whom it May Concern,

On behalf of the Society for Women's Health Research (SWHR), we would like to thank the Food and Drug Administration (FDA) for hosting and accepting public comments on the topic of the labeling for lower-drug estrogen products delivered vaginally, intended to treat moderate to severe symptoms of genitourinary syndrome, also known as vulvar and vaginal atrophy due to menopause. Additionally, we are pleased that the FDA is hosting this meeting to address advances in science that may facilitate a change to the product label, in a transparent fashion that allows for all stakeholder input.

SWHR, a national non-profit organization based in Washington D.C., is widely recognized as the thought leader in promoting research on sex and gender differences and is dedicated to improving women's health through advocacy, education, and research. We are greatly concerned with the issue of access to treatment of vulvar and vaginal atrophy due to menopause because of its significant impact on women. All menstruating women naturally undergo menopause as their ovaries stop producing estrogen and progesterone. Genitourinary signs and symptoms of menopause arise from decreasing levels of estrogens and other hormones. Symptoms include burning and irritation of reproductive organs and structures; dryness, discomfort, or pain with intercourse; and urinary urgency, dyspareunia, and recurrent infections. These symptoms affect up to 50 percent of midlife and older women[1] and are progressive in nature.

These symptoms dramatically impact the health and quality of life of post-menopausal women. Nearly 3 out of 4 women suffer from dyspareunia, or painful sexual

[11] MacBride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. Mayo Clin Proc 2010;85:87-94

intercourse, at some point during their lifetime[2]. Pain during sexual intercourse can have many different causes. In postmenopausal women, the most common cause of painful sexual intercourse is vulvovaginal atrophy, a condition caused by lower estrogen levels[3]. This condition affects the vagina by impacting its ability to secrete lubricant, expand and contract and grow new cells. Over time, blood flow diminishes, and the vagina and vulva shrink as cells die off and are not replaced, resulting in thinning, drying, and inflammation of the vaginal walls.

Importantly, these symptoms do not lessen without treatment. Treatment options may include lubricants, moisturizers, or low-dose vaginal estrogen treatment. Studies indicate that 80-90 percent of women show improvement on one or more of these treatments[4]; yet, many women suffer needlessly because they are not informed about, prescribed, or utilize these treatment options.

We know that women are often hesitant to discuss these aspects of menopausal changes with their healthcare providers. We also know that women want to discuss these issues with physicians and healthcare providers, but too often do not because of embarrassment[5] or because physicians do not have time[6]. These issues often impact sexual health, and many women wrongly assume that the issue is not a medical one[7]. Physicians are also hesitant to discuss these issues with their female patients, which we believe results from a lack of education, knowledge, and training regarding female sexual health across the lifespan and a lack of time[8].

Low-dose vaginal estrogen is the preferred mode of treatment when women report vaginal symptoms[9], yet this treatment option is often under-utilized. One reason that women do not use low-dose vaginal estrogen is because these medications have a boxed warning on the label. The current boxed warning on low-dose vaginal estrogen discusses risks of endometrial and breast cancer, cardiovascular disease, and probable dementia. These labels, also known as black box warnings, are the most serious action the FDA can take short of a product ban. Unfortunately, there is still significant confusion amongst patients and healthcare providers regarding the benefits and risks associated with hormone therapy generally. The addition of a black box warning adds a negative association and further impedes utilization of this treatment option.

SWHR supports the modified label proposal that was published as a commentary in the September 2014 issue of *Menopause*. SWHR has long noted that mitigation of risks associated with medicines is not a one size fits all approach. This commentary, echoed that call, and highlighted new research that demonstrates that the boxed warnings on low-dose

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[2] The American College of Obstetricians and Gynecologists. Frequently asked questions gynecologic problems. http://www.acog.org/~/media/For%20Patients/faq020.pdf. Accessed October 23, 2014.

[3] North American Menopause Society. Menopause and Aging. In: Menopause Practice: A Clinician's Guide. 3rd edition. 2007.

[4] North American Menopause Society. Menopause. 2007:14:357-369.

[5]Korenman SG. *AM J MED*. 1998;105:135-144

[6] Baum N, et al. Patient Care. Spring 1998 (suppl):17-21.

[77] Wyeth REVEAL: Revealing Vaginal Effects at Mid-Life: Surveys of Postmenopausal Women and Health Care Professionals who Treat Postmenopausal Women Madison, NJ: Wyeth; 2009. Available from: http://www.revealsurvey.com/pdf/reveal-survey-results.pdf.

[8] Broekman CPM, et al. International Journal of Impotence Research. 1994;6:67-72.

[9] Menopause. Vol. 21, No. 9, 2014. DOI. 10.1097/gme.0000000000000316.

estrogen products, does not accurately reflect the risk associated with the estrogen dosage for the product. In fact, the boxed warning reflects estrogen class labeling and is based on extrapolations of data from clinical trials of systemic hormone therapy that involves substantially higher level of estrogen exposure. The data presented in the commentary demonstrates the difference in blood levels of hormones achieved by low-dose vaginal estrogen verses conventional hormone therapy.

Instead of a boxed warning, the authors recommended bolding the cautions that women "**report any vaginal bleeding or spotting right away while using (the product),** and "**women with a history of cancer of the breast or uterus (womb) or other hormone-sensitive cancers are encouraged to consult their oncologists before using this product.[10]"**

Like the authors, SWHR believes that this change to the label will both improve patient safety by providing the relevant information, safety issues, and risks in a manner that is highly visible.

Thank you again for providing an opportunity to comment on this important meeting. If you have any questions, please contact Leslie Ritter, Vice President of Public Policy at SWHR at Leslie@swhr.org.

Sincerely,

Phyllis Greenberger, MSW
President & CEO
SWHR

[10] Menopause. Vol. 21, No. 9, 2014. DOI. 10.1097/gme.0000000000000316.