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Dear Colleagues and Patients,

I have written this informal note to you to summarize my knowledge from my Gynecologic Oncology practice about use of vaginal estrogens in women with breast cancer. My impression is that it is not only compassionate but necessary, especially for sexually active women whose vaginal function will deteriorate significantly without estrogen. When the ovaries fail to function either due to age or after chemotherapy, vaginal estrogen can provide a lifeline of benefit to the vaginal<sup>1</sup> and urethral walls<sup>2</sup> without increasing the serum levels of estrogen over that of the menopausal women. This meets the needs of the Medical Oncologist to reduce estrogen delivery to the breast tissue, and helps the patient continue her normal relations with her spouse and avoid frequent urinary tract infections, urinary urgency, urinary leakage and bleeding.<sup>1-4</sup>

In summary, it is not simply compassionate, but essential that we oncologists provide women the opportunity to have their vaginal lining supported by local estrogen as needed, by safely using doses that have been proven to not increase serum levels.

Handa, V. L., K. E. Bachus, et al. (1994). "Vaginal administration of low-dose conjugated estrogens: systemic absorption and effects on the endometrium." Obstet Gynecol **84**(2): 215-8.

**OBJECTIVE:** To test the hypothesis that a very-low-dose regimen of vaginal estrogen would provide effective relief from atrophic vaginitis without endometrial proliferation. **METHODS:** Twenty postmenopausal women with symptoms, signs, and cytologic evidence of atrophic vaginitis were enrolled. Each subject was treated with 0.3 mg of conjugated estrogens, administered vaginally 3 nights per week for 6 months. We examined the following outcomes: symptoms, vaginal cellular (cytologic) maturity, endometrial histology, sonographic evaluation of endometrial thickness, Doppler measures of uterine artery blood flow, and serum levels of estrone and estradiol. Pre- and post-treatment data were compared for each subject. **RESULTS:** Satisfactory relief of symptoms occurred in 19 of 20 cases. Vaginal cellular maturation improved significantly with therapy ( $P < .01$ ). **There were no significant changes in endometrial thickness, uterine artery blood flow, or serum estrogen levels.** Endometrial proliferation was observed in one case. **CONCLUSIONS:** Relief from atrophic vaginitis can be achieved with 0.3 mg of conjugated estrogens administered vaginally two times per week. Endometrial proliferation may occur at this low dose, albeit rarely.

Notelovitz, M., S. Funk, et al. (2002). "Estradiol absorption from vaginal tablets in postmenopausal women." Obstet Gynecol **99**(4): 556-62.

**OBJECTIVE:** To evaluate absorption of estradiol (E2) and compare two low doses of 17 beta-E2 (25 microgram and 10 microgram) in postmenopausal women with atrophic vaginitis. **METHODS:** In a double-masked, randomized, parallel-group study, 58 postmenopausal women were treated with 25 microgram or 10 microgram of 17 beta-E2 for 12 weeks. We report data for 42 eligible subjects who had serum E2 concentrations below 20 pg/mL at baseline and complete data available at the baseline visit (30 minutes before tablet insertion) and weeks 2 and 12. Serum E2 and FSH concentrations were measured at specified intervals. The area under the curve, maximal concentration, and time to maximal concentration were measured for serum E2 concentrations. Maturation values of vaginal epithelial cells were assessed as indicators of change in vaginal epithelium condition in response to treatment. **RESULTS:** After 12 weeks of treatment, the area under the curve, maximal and average over 24-hour E2 concentration were higher in the 25-microgram (563 pg. hour/mL, 49 and 23 pg/mL) than in the 10-microgram (264 pg. hour/mL, 22 and 11 pg/mL) group. **Seventy-four percent in the 25-microgram and 96% in the 10-microgram groups had low systemic absorption of E2, that is, area under the curve (0-24 hour) less than 500 pg/mL.** All but three women who received 25 microgram had mean FSH levels below 35 mIU/mL. **CONCLUSION:** Treatment with 25 or 10 microgram of 17 beta-E2 vaginal tablets resulted in low absorption of estrogen without systemic effects often associated with hormone replacement therapy. **After 12 weeks of therapy for atrophic vaginitis, absorption patterns remained consistent, and women did not have accumulations of circulating E2.**

Rioux, J. E., C. Devlin, et al. (2000). "17beta-estradiol vaginal tablet versus conjugated equine estrogen vaginal cream to relieve menopausal atrophic vaginitis." Menopause 7(3): 156-61.

**OBJECTIVES:** The efficacy and safety of 25-microg 17beta-estradiol vaginal tablets (Vagifem) were assessed and compared with 1.25-mg conjugated equine estrogen vaginal cream (Premarin Vaginal Cream) for the relief of menopausal-derived atrophic vaginitis, resulting from estrogen deficiency. **DESIGN:** In a multicenter, open-label, randomized, parallel-group study, 159 menopausal women were treated for 24 weeks with either vaginal tablets or vaginal cream. Efficacy was evaluated by relief of vaginal symptoms and concentrations of serum estradiol and follicle-stimulating hormone. Safety was monitored by the incidence of adverse events, evaluation of endometrial biopsies, and clinical laboratory results. Patients also assessed the acceptability of the study medications. **RESULTS:** Composite scores of vaginal symptoms (dryness, soreness, and irritation) demonstrated that both treatments provided equivalent relief of the symptoms of atrophic vaginitis. At weeks 2, 12, and 24, increases in serum estradiol concentrations and suppression of follicle-stimulating hormone were observed in significantly more patients who were using the vaginal cream than in those who were using the vaginal tablets ( $p < 0.001$ ). Fewer patients who were using the vaginal tablets experienced endometrial proliferation or hyperplasia compared with patients who were using the vaginal cream. Significantly more patients who were using the vaginal tablets rated their medication favorably than did patients who were using the vaginal cream ( $p < \text{or} = 0.001$ ). Patients who were receiving the vaginal tablets also had a lower incidence of patient withdrawal (10% versus 32%). **CONCLUSIONS:** Treatment regimens with 25-microg 17beta-estradiol vaginal tablets and with 1.25-mg conjugated equine estrogen vaginal cream were equivalent in relieving symptoms of atrophic vaginitis. **The vaginal**

**tablets demonstrated a localized effect without appreciable systemic estradiol increases or estrogenic side effects.** Vaginal tablet therapy resulted in greater patient acceptance and lower withdrawal rates compared with vaginal cream therapy.

Simunic, V., I. Banovic, et al. (2003). "Local estrogen treatment in patients with urogenital symptoms." *Int J Gynaecol Obstet* **82**(2): 187-97.

**OBJECTIVES:** Determination of the efficacy and safety of vaginally administered low dose (25 microg) micronized 17beta-estradiol in the management of patients with urogenital symptoms. **METHODS:** A total of 1612 patients with urogenital complaints were randomized to receive 25 microg of micronized 17beta-estradiol (n=828) or placebo (n=784) in a multicenter double-blind placebo-controlled study running for 12 months. Female patients were treated once a day over a period of 2 weeks, and then twice a week for the remaining of the 12 months with an active or placebo tablet. The assessment included full history-questionnaire, micturition diary, gynecologic and cystometric examination, transvaginal ultrasound, and serum 17beta-estradiol level determination. It was carried out at the beginning, and after 4 and 12 months of treatment. **RESULTS:** The overall success rate of micronized 17beta-estradiol and placebo on subjective and objective symptoms of postmenopausal women with vaginal atrophy was 85.5%, and 41.4%, respectively. A significant improvement of urinary atrophy symptoms was determined in vaginal ERT group as compared with the beginning of the study (51.9% vs. 15.5%, P=0.001). The maximal cystometric capacity (290 ml vs. 200 ml, P=0.023), the volume of the urinary bladder at which patients first felt urgency (180 vs. 140, P=0.048), and strong desire to void (170 ml vs. 130 ml, P=0.045) were significantly increased subsequent to the micronized 17beta-estradiol treatment. The number of patients with uninhibited bladder contractions significantly decreased following micronized 17beta-estradiol as compared with pretreatment values (17/30, P=0.013). Side effects were observed in 61 (7.8%) patients treated with low dose micronized 17beta-estradiol. **Therapy with 25 microg of micronized 17beta-estradiol did not raise serum estrogen level nor stimulated endometrial growth.** **CONCLUSIONS:** Local administration of 25 microg of micronized 17beta-estradiol is an effective and a safe treatment option in the management of women with urogenital complaints.