Use of Very Low-Dose Vaginal Estrogens Among Postmenopausal Women in the United States

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DISCLOSURES

This study was funded by TherapeuticsMD. CWS, JAK, CBJ, BC, and AVM are employees of RTI Health Solutions. RTI Health Solutions is a unit of RTI International, an independent, nonprofit organization that conducts work for government, public, and private organizations, including pharmaceutical companies. DAD, CMW, and PS are employees of CVS Health. JP was an employee of CVS Health at the time of study conduct. LP and JF are employees of Optum and may own company stock. BB and SG were employees of TherapeuticsMD at the time of study conduct.

BACKGROUND

- Vulvar and vaginal atrophy is a common condition, reported in surveys by approximately half of postmenopausal women.[1,2] It results from estrogen deficiency, and symptoms include dyspareunia, vaginal dryness, and dysuria.
- Systemic and vaginal estrogen treatments, including but not limited to very low-dose vaginal estrogen therapy, defined as 10 µg or less estradiol or 0.30 mg or less conjugated estrogens daily, have proven successful in controlling vulvar and vaginal atrophy symptoms.
- The label for estrogens in the United States (US) indicates that women with a uterus who use unopposed estrogens have increased risk for endometrial cancer, but clinical evidence evaluated in a systematic review does not support an increased risk of endometrial cancer with low-dose, unopposed vaginal estrogen use.[3]

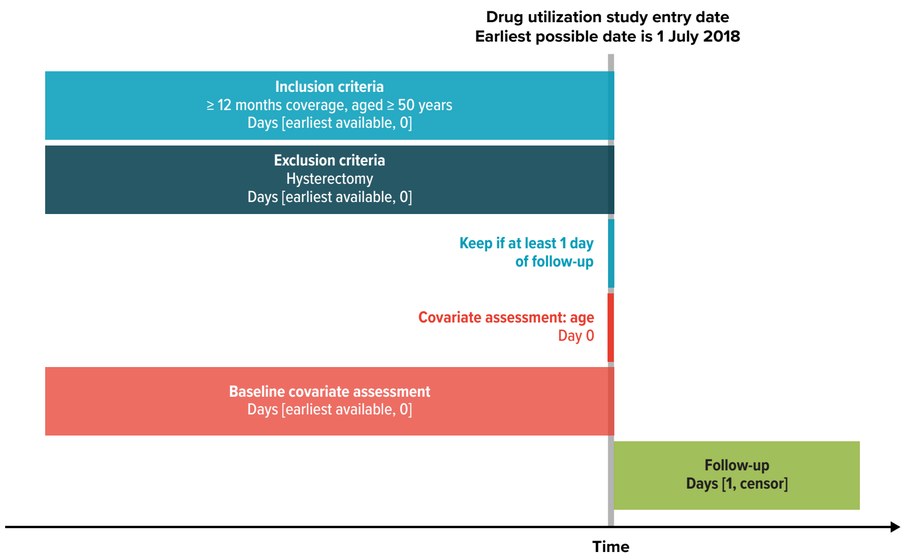
OBJECTIVE

- To describe the duration and patterns of use of very low-dose vaginal estrogen products as part of a postmarketing requirement from the US Food and Drug Administration (EUPAS41957) for the very low-dose vaginal estrogen product Imvexxy (estradiol vaginal inserts).

METHODS

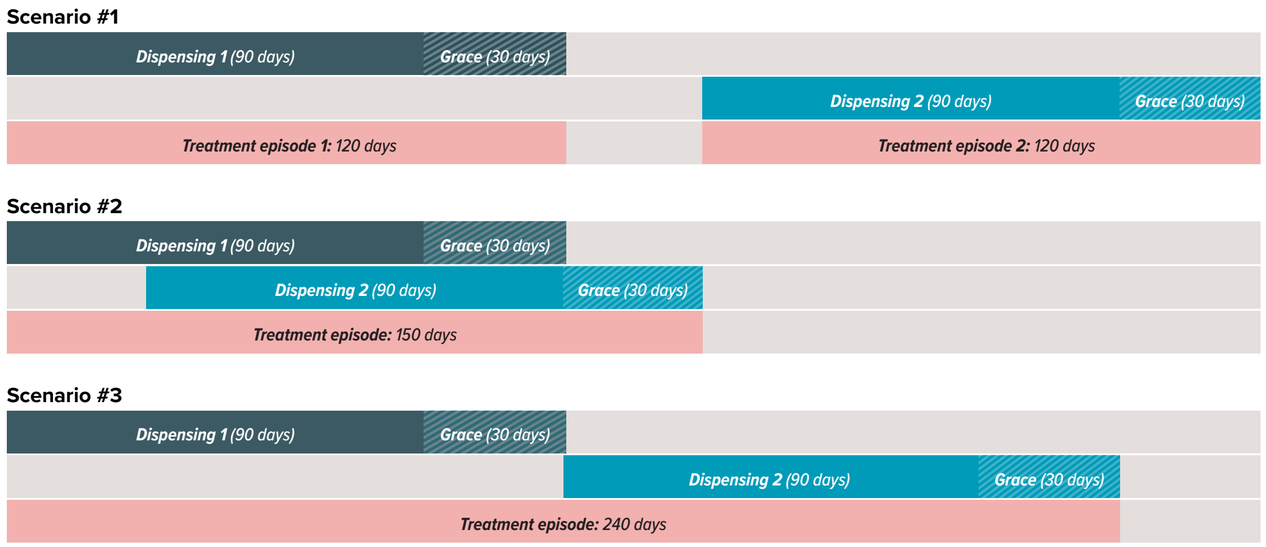
- Data sources from the US were Aetna claims data from July 2018 through June 2022 and the Optum Research Database from July 2018 through December 2021. All results presented are from both data sources combined.
- This was a cohort study of women aged 50 years or older with at least 12 months of continuous enrollment and no documented hysterectomy (Figure 1).
- Follow-up (Figure 1) ended at the earliest of endometrial cancer diagnosis, hysterectomy, death, disenrollment, or end of the study period.
- Among these women, we quantified treatment duration, prior use of systemic estrogens, concomitant use of very low-dose vaginal estrogens and systemic estrogens, and number of very low-dose vaginal estrogen treatment episodes (Figure 2).

Figure 1. Timing of Ascertainment of Study Elements



Note: Figure is based on templates for cohort studies in Schneeweiss S, Rassen JA, Brown JS, et al. Graphical depiction of longitudinal study designs in healthcare databases. Ann Intern Med. 2019 Mar 19;170(6):398-406.

Figure 2. Examples of Construction of Therapy Episodes From Dispensings

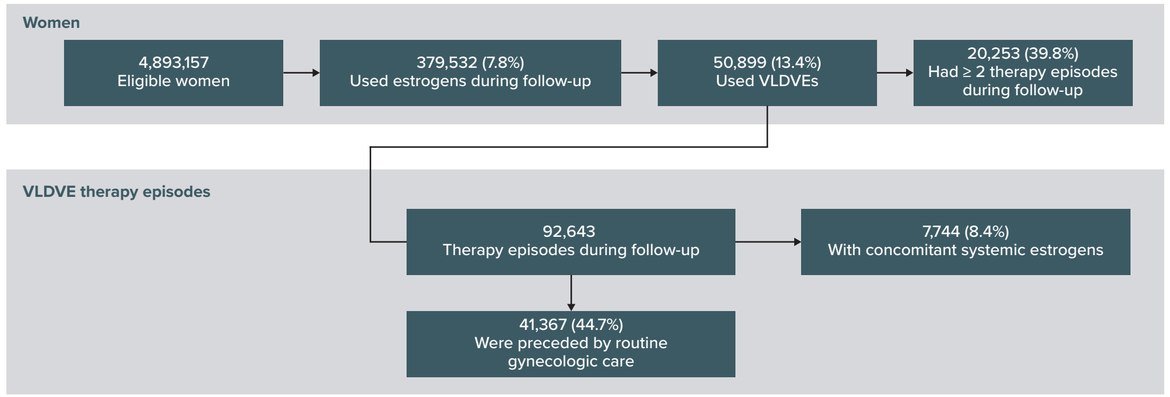


Note: The grace period was 30 days. Each dispensing could be for any low-dose vaginal estrogen product. Dispensing for different products could be combined in 1 therapy episode as long as the dispensings were for very low-dose vaginal estrogen products.

RESULTS

- Among 4,893,157 eligible women, the mean age was 66 years; more than one-third of the study population was aged 70 years or older.
- The median duration of follow-up was approximately 2 years.
- Of these women, 379,532 (7.8%) used estrogen products during follow-up.
- Among the nearly 5 million eligible women, 50,899 (1%) used very low-dose vaginal estrogen products, with a total of 92,643 treatment episodes. Almost half of these episodes were preceded by a visit to a primary care provider for routine gynecologic care (Figure 3).
- Among very low-dose vaginal estrogen product users, 30,646 (60.2%) had 1 treatment episode during follow-up. Time between treatment episodes was 30 days or less for 42% of users and more than 60 days for 37% of users. More than half of users received between 1 and 3 dispensings; 16% received more than 10 dispensings in treatment episode or across the treatment episodes (Table 1).
- The median treatment duration was approximately 4 months (data not shown), and 7,744 treatment episodes (8.4%) had concomitant use of a systemic estrogen (Figure 3).
- Among very low-dose vaginal estrogen product users, 8,657 (17%) had previously used opposed systemic estrogens, and 4,755 (9.3%) had used unopposed systemic estrogens (Table 2).

Figure 3. Use of Very Low-dose Vaginal Estrogens Among Women Aged 50 Years or Older



VLDVE = very low-dose vaginal estrogen (10 µg or less estradiol or 0.30 mg or less conjugated estrogens daily).

Note: Estrogens used during follow-up included systemic estrogens, vaginal estrogen products, or combined vaginal contraceptives.

Table 1. Very Low-Dose Vaginal Estrogen Dispensings and Treatment Episodes

	n (%)
Users during follow-up	50,899 (100)
Number of dispensings per woman	
1-3	27,015 (53.1)
> 10	8,189 (16.1)
Number of treatment episodes per woman	
1	30,646 (60.2)
> 4	2,866 (5.6)
Time between treatment episodes[a, b]	
≤ 30 days	15,642 (41.9)
> 60 days	13,961 (37.4)

[a] Women with only 1 treatment episode were omitted from this analysis. This is the time between very low-dose vaginal estrogen episodes of the same type of treatment.

[b] Women may appear in more than 1 category.

Table 2. Use of Estrogens Before First Very Low-Dose Vaginal Estrogen Dispensing

	n (%)
Use of estrogen products before first very low-dose vaginal estrogen product dispensing[a,b]	50,899 (100)
Opposed systemic estrogens	8,657 (17.0)
Unopposed systemic estrogens	4,755 (9.3)
Vaginal estrogen products	33,289 (65.4)
Combined vaginal contraceptives	280 (0.6)
None	13,353 (26.2)

Notes: Vaginal estrogen products included 17β-estradiol (Estracea, Estring), conjugated estrogens (Premarin Vaginal Cream), and estradiol hemihydrate (Vagifem 10 µg, Yuvafem 10 µg).

[a] Percentages may add to more than 100 because an individual may have belonged to more than 1 category.

[b] Use of estrogens was ascertained any time before current dispensing, including time before cohort entry.

DISCUSSION AND CONCLUSIONS

- Among nearly 5 million women aged 50 years or older without documented hysterectomy, very low-dose vaginal estrogen product use was rare (1% over a median 2-year follow-up).
- Treatment episodes were generally short; the vast majority did not have concomitant systemic estrogen use.
- Although vulvar and vaginal atrophy is commonly reported in surveys,[1,2] current treatment with hormonal therapy is reported in less than 10% of women. Our study also found very little use of treatments for symptoms of vulvar and vaginal atrophy, including very low-dose vaginal estrogens in women of postmenopausal age, suggesting there may be barriers to the management of the condition.

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