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Symptomatic vulvar and vaginal atrophy (VVA) relief was achieved with TX-004HR, an investigational vaginal estradiol softgel capsule, with negligible to very low systemic absorption of estradiol: PK comparison with systemic and a vaginal estradiol

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Context: Greater than 60% of postmenopausal breast cancer (BC) patients report dyspareunia and vaginal dryness, some of the most poorly addressed side effects of adjuvant endocrine therapy such as aromatase inhibitors (AIs), which may result in poor compliance. Local estrogen therapy is proven safe and effective for treating VVA in postmenopausal women; however, a major concern of prescribing local estrogens to BC patients is the potential risk of systemic absorption and that it will limit the effect of AIs, and it is contraindicated in this population in prescribing information. TX-004HR is a vaginal estradiol (E2) softgel capsule designed to minimize systemic absorption of E2 while treating symptomatic VVA.
Objective: To compare the pharmacokinetic (PK) profile of investigational TX-004HR with oral and vaginal E2 products currently available for treating postmenopausal VVA.
Methods: Medline searches identified PK studies of available estrogenic oral and vaginal products to contextualize the PK profile of TX-004HR. PK was evaluated in 2 single-dose, bioavailability trials that compared TX-004HR with a commercially available E2 vaginal tablet, and in a subset of subjects who participated in a phase 3 double-blind, placebo-controlled trial.
Patients: Postmenopausal women with VVA and moderate-to-severe dyspareunia.
Interventions: 4-, 10-, 25-?g TX-004HR, or 10-, 25-?g vaginal E2 tablets.
Main Outcome Measure: PK of TX-004HR versus other estrogen-based VVA treatments.
Results: TX-004HR 4 µg showed no statistical differences from placebo in E2 PK parameters. TX-004HR 10 µg was not different than placebo, with the exception of Cmax being higher than placebo on day 1. Estrone and estrone conjugate PK parameters with TX-004HR were similar to placebo with all doses. TX-004HR E2 concentrations on day 84 were similar to baseline and placebo. TX-004HR resulted in statistically significant lower E2 absorption than vaginal E2 tablets at identical doses; TX-004HR demonstrated an AUC less than 1/3 that of the vaginal tablet and up to 75-fold lower E2 levels than oral E2 products.
Conclusions: TX-004HR showed lower systemic absorption compared with oral E2 products and a commercially vaginal E2 tablet. TX-004HR resulted in negligible systemic absorption of E2. While TX-004HR has not been studied in women with a history of breast cancer, its PK profile suggests that further study in this patient population, especially those taking AIs, should be considered.

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