Background

The TX-004HR (IMVEYO®) therapy is an ultra-low-dose (4- and 10-µg) 17β-estradiol (E2) softgel vaginal insert FDA-approved (May 2018) for the local treatment of moderate to severe dyspareunia associated with menopausal vulvar and vaginal atrophy (VVA), with negligible to very low systemic absorption.1,2

The softgel vaginal insert was designed to have mucoadhesive properties to facilitate the active ingredient being available in the body in a site-specific manner. Gelatin was selected as the capsule shell based on its mucoadhesive (due to its polymeric structure) and fast-dissolving properties.

Methods

In Vitro Study

In vitro testing for dissolution of the softgel capsule was performed using a USP Dissolution Apparatus Type 3 at 30 dips per minute with the media at 37°C.

Effect of Body Position on E2 Bioavailability

In both studies, PK parameters were analyzed for E2 were Cmax, AUC0-24 and tmax.13 The second study was a randomized, open-label, two-way crossover study, which assigned healthy postmenopausal women following a single dose of 25-µg E2 vaginal insert to group A or B for day 1 and day 15, respectively. The PK parameters were also similar (Table 2).

Results

In both studies,

The second study included a subset of subjects from the first study but women remained ambulatory or seated for 4 hours after insertion (they could not lie down).

- In both studies,
  - PK parameters analyzed for E2 were Cmax, AUC0-24 and tmax.
  - 13 baseline samples for each study were collected at specified timepoints.

- E2 in human plasma was determined using a validated HPLC-tandem mass spectrometry method (concentration range, 2–703 pg/mL).

Capsule Assessment Study

- This phase 2, randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of the E2 softgel vaginal insert in postmenopausal women (aged 40–75 years; BMI of ≤34 kg/m2) with at least one moderate to severe symptom of VVA4

- Women were randomized to 10-µg E2 or matching placebo vaginal insert, which were self-administered daily in the morning for 14 days; there were no restrictions on movement.

- A vaginal examination was performed to assess for remnants of the softgel capsule on day 1 (6 hours after insertion) and day 15 (24 hours after insertion).

- In the first study, 16 women from the first study were enrolled in the second study.

- In vitro dissolution testing of the softgel capsule resulted in >80% of E2 in the dissolution media by the first time point, demonstrating that the soft gelatin capsule shell ruptured and began to dissolve within 15 minutes, making the solubilized E2 in the capsule available for absorption (Figure 1).

- Mean plasma estradiol concentrations with the 25-µg softgel insert and placebo are shown in Figure 2. Table 1 provides a summary of pharmacokinetic parameters analyzed for E2 in response to 25-µg and 10-µg E2 in two phase 1 studies conducted to assess the safety and efficacy of the E2 softgel vaginal insert in postmenopausal women (aged 40–75 years; BMI of ≤34 kg/m2), followed by 4- and 10-µg dose (4- and 10-µg) E2 by high performance liquid chromatography (HPLC).

- Gelatin polymers in the coat together with the high viscosity of the fill material have aided in similar PK behavior observed in both supine and seated/ambulatory environments, allowing for flexibility in positions for administration.

- Furthermore, dissolution of the vaginal capsule within 6 hours of vaginal insertion was confirmed visually.

- These data, in conjunction with data showing significant improvements in dyspareunia, vaginal dryness, and objective measures of vaginal atrophy (vaginal pH, percentage of superficial and parabasal cells), suggest local adherence and dissolution of this softgel E2 vaginal insert.

Conclusions

- TX-004HR was specifically designed to be mucoadhesive and rapidly dissolving to release the drug quickly.

- The inclusion of gelatin polymers in the coat together with the high viscosity of the fill material have aided in similar PK behavior observed in both supine and seated/ambulatory environments, allowing for flexibility in positions for administration.

- Furthermore, dissolution of the vaginal capsule within 6 hours of vaginal insertion was confirmed visually.

- These data, in conjunction with data showing significant improvements in dyspareunia, vaginal dryness, and objective measures of vaginal atrophy (vaginal pH, percentage of superficial and parabasal cells), suggest local adherence and dissolution of this softgel E2 vaginal insert.

References


Disclosures

- Dr. Pickar is a consultant for Men's Health and TherapeuticsMD and has stock options with TherapeuticsMD. Content is reflective of independent investigative research and not influenced by TherapeuticsMD and has stock options from TherapeuticsMD. Drs. Shadiack, Graham, Bernick, and Mirkin are employees of TherapeuticsMD with stock options. Dr. Bernick is also a board member of TherapeuticsMD.
- Dr. Warnier is an employee of TherapeuticsMD with stock options.
- TherapeuticsMD sponsored the study and provided support for the medical writing assistance of Dominique Verlaan, PhD, CMPP (Precise Publications, LLC).

Table 1. Baseline-Adjusted Estradiol PK Parameters for TX-004HR 25 µg

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<tr>
<th>Parameter</th>
<th>25 µg</th>
<th>10 µg</th>
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<tr>
<td>Cmax (pg/mL)</td>
<td>24.1  (4- and 10-µg) E2 by high performance liquid chromatography (HPLC).</td>
<td>34.3  (4- and 10-µg) E2 by high performance liquid chromatography (HPLC).</td>
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<tr>
<td>AUC0-24 (h*pg/mL)</td>
<td>77.6  (4- and 10-µg) E2 by high performance liquid chromatography (HPLC).</td>
<td>93.7  (4- and 10-µg) E2 by high performance liquid chromatography (HPLC).</td>
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<tr>
<td>tmax (h)</td>
<td>2.1  (4- and 10-µg) E2 by high performance liquid chromatography (HPLC).</td>
<td>1.9  (4- and 10-µg) E2 by high performance liquid chromatography (HPLC).</td>
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Table 2. Capsule Disintegration State in the Vagina on Days 1 and 15

<table>
<thead>
<tr>
<th>Disintegration State</th>
<th>25 µg</th>
<th>10 µg</th>
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<tbody>
<tr>
<td>Evidence of capsule present</td>
<td>24 (92%)</td>
<td>24 (92%)</td>
</tr>
<tr>
<td>Visual examination of the vaginal vault on day 1 (6 hours after insertion) and on day 15 did not detect remnants of the softgel capsule (Table 2).</td>
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- One woman (1/24; 4%) treated with TX-004HR had mild vaginal discharge.

Figure 1. Dissolution Profile of the 25-µg Softgel Insert

Figure 2. Baseline-adjusted Mean Plasma Estradiol Concentration with the 25-µg Softgel Insert