Physical Characteristics of TX-004HR: An Ultra-Low-Dose (4- and 10-µg) Estradiol Softgel Capsule Vaginal Insert

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Background

- TX-004HR (IMVEXXY™, TherapeuticsMD) 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]
  - 4-, 10- and 25-µg doses of TX-004HR were evaluated clinically
- 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
  - Fast rupture and dissolution of the capsule are important, first for release of its contents and second to allow local absorption
- Contents of the capsule were developed to be viscous at body temperature to resist flow (to minimize messiness) and allow the inclusion of ingredients reported to be well tolerated by mucosal tissues

Objective

To describe the characteristics of the gelatin coat and the softgel capsule fill as optimized for vaginal delivery, and to discuss in vitro and in vivo evidence of the rapid release of E2

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
- Samples of the media were collected at 15, 30, 60, 90, and 120 minutes and analyzed for E2 by high performance liquid chromatography (HPLC)

Effects of Body Position on E2 Bioavailability

- Two phase 1 studies were conducted to assess the pharmacokinetics (PK) of E2 in healthy postmenopausal women following a single dose of 25-µg E2 vaginal insert
- Eligible postmenopausal women were 40 to 65 years of age and had a BMI between 18.5 and 30 kg/m^2; no VVA symptoms were required
- The first study was a randomized, open-label, two-way crossover study, which compared the bioavailability of a single dose of 25-µg TX-004HR with 25-µg Vagifem® (Novo Nordisk Inc);[3] only results for TX-004HR are reported here
  - Subjects were required to remain in a supine position for 4 hours after insertion
- 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 variables analyzed for E2 were C_{max}, $AUC_{0\text{-}24}$ and t_{max}
  - 13 blood samples for each subject 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

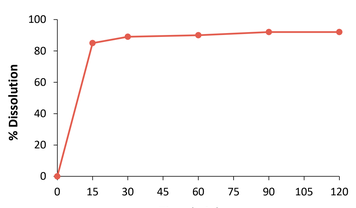
- This phase 2, randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of the E2 softgel vaginal insert in postmenopausal women (aged 40–75 years; BMI of ≤34 kg/m^2) with at least one moderate to severe symptom of VVA[4]
- Women were randomized to 10-µg E2 or matching placebo 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)

Results

In Vitro 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,** t_{max} in **Table 1)**

Figure 1. Dissolution Profile of the 25-µg Softgel Insert (n=6)



Effect of Body Position on E2 Bioavailability

- Women (n=36) enrolled in the first study had a mean age of 50 years, BMI of 26 kg/m^2 and were all Asian
  - 16 women from the first study were enrolled in the second study
- When comparing women who were in both studies, E2 plasma levels were similar between the supine versus ambulatory or seated positions (**Figure 2**)
  - PK parameters were also similar (**Table 1**)

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

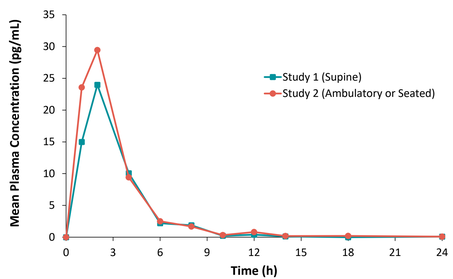


Table 1. Baseline-adjusted Estradiol PK Parameters for TX-004HR 25 µg

Estradiol Parameters	Study 1 (Supine)	Study 2 (Ambulatory or Seated)
N	16	16
C_{max}, pg/mL	24.1	34.3
$AUC_{0\text{-}24}$, h*pg/mL	77.6	93.7
t_{max}, h	2.1	1.9

Capsule Assessment Study

- 50 women were randomized to the softgel 10-µg E2 vaginal insert (n=24) or placebo (n=26); 2 women receiving placebo did not complete the study
- Participants had a mean age of 63 years and mean BMI of 27 kg/m^2; most were White (92%), followed by African American (6%) and Asian (2%)
- 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**)
- One woman (1/24; 4%) treated with TX-004HR had mild vaginal discharge

Table 2. Capsule Disintegration State in the Vagina on Days 1 and 15

	10 µg E2 (n=24)		Placebo (n=26)	
	Day 1	Day 15	Day 1	Day 15
No evidence of capsule present	23 (96)	24 (100)	26 (100)	24 (92)
Evidence of capsule present	0	0	0	0
Assessment not done	1 (4)	0	0	2 (8)

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 being observed in both supine and seated/ambulatory positions, 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),[1] suggest local adherence and dissolution of this softgel E2 vaginal insert

References

1. Constantine G, et al. *Menopause* 2017;24:409-416. **2.** Archer DF, et al. *Menopause* 2017;24:510-516.

3. Pickar JH, et al. *Climacteric* 2016;19:181-187. 4. Pickar JH, et al. *Menopause* 2016;23:506-510.

Disclosures

- Dr. Pickar is a consultant for Pfizer, Shionogi, and TherapeuticsMD and has stock options with TherapeuticsMD. Dr. Constantine consults for multiple pharmaceutical companies including but not limited to TherapeuticsMD and has stock options from TherapeuticsMD. Drs. Shadiack, Graham, Bernick, and Mirkin are employees of TherapeuticsMD with stock/stock options. Dr. Bernick is also a Board member of TherapeuticsMD. Mr. Warrier is an employee of TherapeuticsMD with stock/stock options.
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