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Neither Tenapanor Nor Its Major Metabolite Were Detected in the Breast Milk of Healthy Lactating Females After 4 Days of Dosing: A Phase 1, Open-Label, Pharmacokinetic Study

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Background

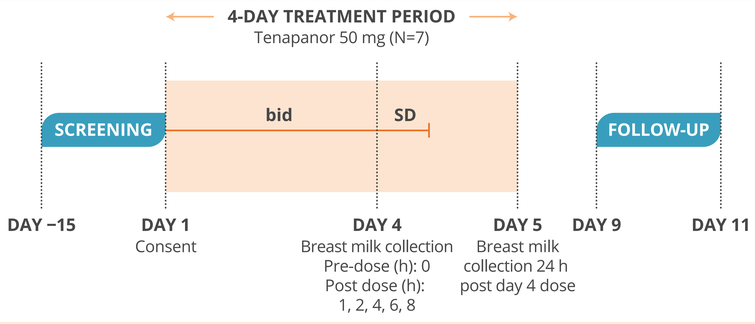
- Tenapanor, a first-in-class, small-molecule inhibitor of intestinal sodium/hydrogen exchanger isoform 3 (NHE3), is approved by the United States Food and Drug Administration (FDA) for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.[1-4]
- By inhibiting NHE3, tenapanor reduces absorption of sodium from the small intestine and colon, resulting in increased water retention within the intestinal lumen, leading to softer stools and faster transit.[1]
- Tenapanor is minimally absorbed following repeated twice-daily (bid) oral administration.[1,5]
  - In studies of repeated oral administration of tenapanor 50 mg bid, plasma concentrations were found to be below the limit of quantitation (<0.5 ng/mL) in the majority of samples from healthy subjects[1] and patients with IBS-C.[5]
  - Tenapanor is metabolized primarily by CYP3A4/5, and low levels of its primary metabolite, M1, are detected in plasma. M1 is not active and does not bind to NHE3. The maximum observed concentration (C_{max}) of M1 in plasma is approximately 15 ng/mL at steady state following repeated dosing of tenapanor 50 mg bid in healthy subjects.[1]
- The FDA provides recommendations for conducting clinical studies in lactating women so that patients and clinicians can make informed decisions about medication safety.[6] Despite this, there remains a paucity of clinical guidance on medication use in patients who are breastfeeding.[7]
- Therefore, this study (TEN-01-109; ClinicalTrials.gov: NCT06203444) was conducted with the following objectives:
  - **Primary objective: to determine the pharmacokinetics of tenapanor and M1 in breast milk.**
  - **Secondary objective: to assess the safety and tolerability of tenapanor in healthy lactating females.**

Methods

Study Design

- The total duration of study was up to 26 days (**Figure 1**).
- Females in good health aged ≥18 years were able to participate if they had a body mass index between 18.0 and 35.0 kg/m² and had been breastfeeding or actively pumping for ≥4 weeks.
- Participants received open-label tenapanor 50 mg bid on days 1 through 3 and once on day 4 (before breakfast).
  - The first and last doses were administered at the clinic; interim doses were taken at home.
- On day 4, breast milk was collected pre-dose (hour 0), then at 1, 2, 4, 6, 8, and 24 hours post dose. Some participants collected milk in between the defined timepoints, in which case the milk was analyzed separately.

Figure 1: Study Design



bid, twice daily; SD, single dose.

Study Endpoints

- To achieve the primary objective, the following pharmacokinetic parameters derived from the breast milk concentration–time profile were assessed:
  - For tenapanor and M1: area under the concentration (AUC)–time curve from 0 to 8 hours post dose, AUC for the dosing interval (12 hours), C_{max}, time of the maximum observed concentration, lowest observed concentration during the dosing interval, time of lowest observed concentration, average concentration at steady state, and estimated daily infant dose (DID).
  - For tenapanor only: maternal dose (µg/kg/d) and relative daily infant dose (RID; adjusted for weight and expressed as a percentage).
- Samples were analyzed using a validated high-performance liquid chromatography–tandem mass spectrometry method to evaluate concentrations of tenapanor and M1.
  - Participants were asked to discard all milk beginning on day 1 until 72 hours after the last dose, including any milk that was left over from the collection for pharmacokinetic analysis.
- To achieve the secondary objective, the following safety measures were assessed:
  - Adverse events, physical examination, vital signs (blood pressure, respiratory rate, heart rate, and temperature), a 12-lead electrocardiogram, and clinical laboratory tests.
- All pharmacokinetic and safety analyses were descriptive and exploratory, and no inferential analyses were performed.

Results

Participants

- In total, 7 participants completed this study (**Table 1**).
  - Up to 7 participants were planned to be enrolled in order to have at least 6 participants complete the study. The sample size was based on precedent set by other pharmacokinetic studies of a similar nature instead of statistical considerations.[8,9]

Pharmacokinetics

- Concentrations of tenapanor and M1 were below the limit of quantitation of 1.00 ng/mL (assigned as zero) at all timepoints in all samples (**Table 2**). Therefore, AUC- and time-related parameters could not be calculated.

Safety

- No unexpected treatment-emergent adverse events (TEAEs) were reported (**Table 3**).
- In total, 3 of 7 (42.9%) participants experienced 6 TEAEs: diarrhea (3 of 7 participants), flatulence (2 of 7), and nausea (1 of 7). All of these events were mild in severity and had resolved by the end of the study.

Table 1: Baseline Demographics

	Total (N=7)
Mean (SD) age at informed consent, y	30.0 (5.1)
Race, n (%)	
American Indian or Alaska Native	1 (14.3)
Asian	0
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	5 (71.4)
Other	0
Multiple	1 (14.3)
Ethnicity, n (%)	
Non-Hispanic/Latino	6 (85.7)
Hispanic/Latino	1 (14.3)
Mean (SD) weight, kg	80.2 (12.6)
Mean (SD) height, cm	161.8 (7.7)
Mean (SD) BMI, kg/m²	30.9 (6.2)
Mean (SD) gestational age at delivery, wk	39.0 (1.9)

BMI, body mass index.

Table 2: Summary of Breast Milk Pharmacokinetic Parameters Through 24 Hours Post Dose

Mean (SD)	Tenapanor 50 mg bid (N=7)
Tenapanor	
C_{max}, ng/mL	0.000 (0.0000)
C_{trough}, ng/mL	0.000 (0.0000)
DID, µg/kg/d	0.000 (0.0000)
Maternal dose, µg/kg/d	1275 (211.37)
RID, %	0.000 (0.0000)
M1	
C_{max}, ng/mL	0.000 (0.0000)
C_{trough}, ng/mL	0.000 (0.0000)
DID, µg/kg/d	0.000 (0.0000)

Pharmacokinetic parameters were calculated following the last dose on day 4. Participants received tenapanor 50 mg bid on day 1 through day 3 and once before breakfast on day 4. bid, twice daily; C_{max}, maximum observed concentration; C_{trough}, lowest observed concentration during a dosing interval; DID, daily infant dose; RID, relative infant dose.

Table 3: Overall Summary of TEAEs

n (%)	Tenapanor 50 mg bid (N=7)
TEAE	3 (42.9)
Gastrointestinal disorders	3 (42.9)
SAR	3 (42.9)
Serious TEAE	0
TEAE leading to tenapanor discontinuation	0

bid, twice daily; SAR, suspected adverse reaction; TEAE, treatment-emergent adverse event.

Limitation

- Although safety data could vary between healthy individuals and patients with IBS-C, we do not anticipate tenapanor nor M1 to be present at detectable levels in the breast milk of patients with IBS-C.

Conclusions

Tenapanor and its primary metabolite, M1, were not present at detectable levels in the breast milk of healthy lactating females after repeated oral administration of tenapanor 50 mg bid (the prescribed dose for patients with IBS-C).

The safety profile of tenapanor (ie, gastrointestinal adverse events) in this study was similar to that seen in previous clinical studies of tenapanor in healthy volunteers.[10-13]

References

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Disclosures

Darren Brenner is a consultant, advisor, and speaker for Ardelyx, Inc. Karishma Raju, Kenji Kozuka, Yang Yang, Suling Zhao, and Susan Edelstein are full-time employees of Ardelyx, Inc.

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Digestive Disease Week (DDW) 2025; May 3-6, 2025; San Diego, CA, USA.

IBSRELA® (tenapanor) is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults

Important Safety Information

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats, administration of tenapanor caused deaths presumed to be due to dehydration.** ***[see PI Contraindications (4), Use in Specific Populations (8.4)]*****.**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age.** ***[see PI Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*****.**
- **The safety and effectiveness of IBSRELA have not been established in pediatric patients less than 18 years of age.** ***[see PI Use in Specific Populations (8.4)]*****.**

CONTRAINDICATIONS

IBSRELA is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.

IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

WARNINGS AND PRECAUTIONS

Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age.

Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. If severe diarrhea occurs, suspend dosing and rehydrate patient.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in IBSRELA-treated patients (incidence ≥2% and greater than placebo) were: diarrhea (16% vs 4% placebo), abdominal distension (3% vs <1%), flatulence (3% vs 1%) and dizziness (2% vs <1%).

For additional safety information, including the Boxed Warning, please see full Prescribing Information: click here.

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IBS-C, irritable bowel syndrome with constipation.

IBSRELA (tenapanor hydrochloride). Prescribing information. Ardelyx, Inc; 2025.
Available at: https://www.ibsrela-hcp.com/PI