

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211801Orig1s003

Trade Name: IBSRELA

Generic or Proper Name: (tenapanor)

Sponsor: Ardelyx INC

Approval Date: May 19, 2021

Indication: IBSRELA is a sodium/hydrogen exchanger 3 (NHE3) inhibitor indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

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RESEARCH**

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APPROVAL LETTER



NDA 211801/S-003

SUPPLEMENT APPROVAL

Ardelyx, Inc.
Attention: Robert C. Blanks
Chief Regulatory and Quality Officer
34175 Ardenwood Boulevard
Suite 100
Fremont, CA 94555

Dear Mr. Blanks:

Please refer to your supplemental new drug application (sNDA) dated March 26, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for lbsrela (tenapanor) tablets.

This Prior Approval sNDA provides for addition of pharmacokinetic results from a study conducted in subjects with hepatic impairment to the Clinical Pharmacology section of the Prescribing Information.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling with minor editorial revisions listed below and reflected in the enclosed labeling.

- Updated the revision date at the end of Highlights in the Prescribing Information and at the end of the Medication Guide to the approval date.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Andrew Dodson, PharmD, Regulatory Project Manager, at 301-796-8760.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, MD, MMSc
Director
Division of Gastroenterology
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
 - Prescribing Information
 - Medication Guide

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JESSICA J LEE
05/19/2021 11:33:35 AM

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IBSRELA® safely and effectively. See full prescribing information for IBSRELA.

IBSRELA (tenapanor) tablets, for oral use
Initial U.S. Approval: 2019

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

See full prescribing information for complete boxed warning.

- IBSRELA is contraindicated in patients less than 6 years of age; in young juvenile rats, tenapanor caused death presumed to be due to dehydration. (4, 8.4)
- Avoid use of IBSRELA in patients 6 years to less than 12 years of age. (5.1, 8.4)
- The safety and effectiveness of IBSRELA have not been established in pediatric patients less than 18 years of age. (8.4)

INDICATIONS AND USAGE

IBSRELA is a sodium/hydrogen exchanger 3 (NHE3) inhibitor indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage in adults is 50 mg, orally twice daily. (2)
- Take immediately prior to breakfast or the first meal of the day and immediately prior to dinner. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg tenapanor. (3)

CONTRAINDICATIONS

- Pediatric patients less than 6 years of age. (4, 5.1, 8.4)
- Patients with known or suspected mechanical gastrointestinal obstruction. (4)

WARNINGS AND PRECAUTIONS

Diarrhea: Patients may experience severe diarrhea. If severe diarrhea occurs, suspend dosing and rehydrate patient. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥2%) are diarrhea, abdominal distension, flatulence and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ardelyx at 1-844-427-7352 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING 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 Contraindications (4), Use in Specific Populations (8.4)].**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age [see Warnings and Precautions (5.1), Use in Specific Populations (8.4)].**
- **The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age [see Use in Specific Populations (8.4)].**

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

The recommended dosage of IBSRELA in adults is 50 mg orally twice daily.

Administration Instructions

- Take IBSRELA immediately prior to breakfast or the first meal of the day and immediately prior to dinner [see Clinical Pharmacology (12.2)].
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take 2 doses at the same time.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg tenapanor supplied as an oval, white to off-white tablet debossed with “**A50**” on one side and “5791” on the other side.

4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [see Warnings and Precautions (5.1), Use in Specific Populations (8.4)].
- Patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 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 [see *Contraindications (4)*, *Warnings and Precautions (5.2)*, *Use in Specific Populations (8.4)*].

5.2 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 [see *Adverse Reactions (6.1)*]. If severe diarrhea occurs, suspend dosing and rehydrate patient.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 1203 adult patients with IBS-C in two randomized, double-blind, placebo-controlled clinical trials (Trial 1 and Trial 2). Patients were randomized to receive placebo or IBSRELA 50 mg twice daily for up to 52 weeks. Demographic characteristics were comparable between treatment groups in the two trials [see *Clinical Studies (14)*].

Most Common Adverse Reactions

The most common adverse reactions reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo during the 26-week double-blind placebo-controlled treatment period of Trial 1 are shown in [Table 1](#).

Table 1: Most Common Adverse Reactions* in Patients with IBS-C in Trial 1 (26 Weeks)

Adverse Reactions	IBSRELA N=293 %	Placebo N=300 %
Diarrhea	16	4
Abdominal Distension	3	<1
Flatulence	3	1
Dizziness	2	<1

* Reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo

The adverse reaction profile was similar during the 12-week double-blind placebo-controlled treatment period of Trial 2 (610 patients: 309 IBSRELA-treated and 301 placebo-treated) with

diarrhea (15% with IBSRELA vs 2% with placebo) and abdominal distension (2% with IBSRELA vs 0% with placebo) as the most common adverse reactions.

Adverse Reaction of Special Interest – Severe Diarrhea

Severe diarrhea was reported in 2.5% of IBSRELA-treated patients compared to 0.2% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 [see *Warnings and Precautions (5.2)*].

Patients with Renal Impairment

In Trials 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m²). In patients with renal impairment, diarrhea, including severe diarrhea, was reported in 20% (39/194) of IBSRELA-treated patients and 0.6% (1/174) of placebo-treated patients. In patients with normal renal function at baseline, diarrhea, including severe diarrhea, was reported in 13% (53/407) of IBSRELA-treated patients and 3.5% (15/426) of placebo-treated patients. No other differences in the safety profile were reported in the renally impaired subgroup. The incidence of diarrhea and severe diarrhea in IBSRELA-treated patients did not correspond to the severity of renal impairment.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 7.6% of IBSRELA-treated patients and 0.8% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2. The most common adverse reaction leading to discontinuation was diarrhea: 6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of IBSRELA-treated patients and at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 were: rectal bleeding and abnormal gastrointestinal sounds.

Hyperkalemia

In a trial of another patient population with chronic kidney disease (defined by eGFR from 25 to 70 mL/min/1.73m²) and Type 2 diabetes mellitus, three serious adverse reactions of hyperkalemia resulting in hospitalization were reported in 3 patients (2 IBSRELA-treated patients and 1 placebo-treated patient).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [see *Clinical Pharmacology (12.3)*]. Therefore, maternal use is not expected to result in fetal exposure to the drug. The available data on IBSRELA exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were

observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.1 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 8.8 times the maximum recommended human dose, based on body surface area).

In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 9.7 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IBSRELA and any potential adverse effects on the breastfed infant from IBSRELA or from the underlying maternal condition.

8.4 Pediatric Use

IBSRELA is contraindicated in patients less than 6 years of age. Avoid IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.1)*].

The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred in young juvenile rats (less than 1 week-old-rats approximate human age equivalent of less than 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats (post-natal day (PND) 5) at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5 and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5 and 5 mg/kg/day dose groups [see *Contraindications (4), Warnings and Precautions (5.1)*].

8.5 Geriatric Use

Of the 1203 patients in placebo-controlled clinical trials of IBSRELA, 100 (8%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Based on nonclinical data, overdose of IBSRELA may result in gastrointestinal adverse effects such as diarrhea as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged [see *Warnings and Precautions (5.1)*].

11 DESCRIPTION

IBSRELA (tenapanor) tablets contain tenapanor hydrochloride as an active ingredient. Tenapanor hydrochloride is a sodium/hydrogen exchanger 3 (NHE3) inhibitor for oral use. The chemical name for tenapanor hydrochloride is 12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]-N-[2-[2-[2-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2). Tenapanor hydrochloride has the molecular formula of C₅₀H₆₈Cl₆N₈O₁₀S₂, the molecular weight of 1218 Daltons, and the chemical structure below:

12.3 Pharmacokinetics

Absorption

Tenapanor is minimally absorbed following repeated twice daily oral administration. Plasma concentrations of tenapanor were below the limit of quantitation (less than 0.5 ng/mL) in the majority of samples from healthy subjects following single and repeated oral administration of IBSRELA 50 mg twice daily. Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), maximum concentration (C_{\max}), and half-life ($t_{1/2}$) could not be determined.

Distribution

Plasma protein binding of tenapanor and its major metabolite, M1, is approximately 99% and 97%, respectively, in vitro.

Elimination

Metabolism

Tenapanor is metabolized primarily by CYP3A4/5 and low levels of its major metabolite, M1, are detected in plasma. The C_{\max} of M1 is approximately 13 ng/mL after single dose of IBSRELA 50 mg and 15 ng/mL at steady state following repeated dosing of IBSRELA 50 mg twice daily in healthy subjects.

Excretion

Following administration of a single 15 mg radiolabeled ^{14}C -tenapanor dose to healthy subjects, approximately 70% of the radioactivity was excreted in feces within 120 hours post-dose and 79% within 240 hours post-dose, mostly as the parent drug accounting for 65% of dose within 144 hours post-dose. Approximately 9% of the administered dose was recovered in urine, primarily as metabolites. M1 is excreted in urine unchanged accounting for 1.5% of dose within 144 hours post-dose.

Specific Populations

Patients with Hepatic Impairment

Following a single dose of tenapanor 100 mg in patients with moderate hepatic impairment (Child-Pugh B), plasma concentrations of tenapanor were mostly below the limit of quantitation (< 0.5 ng/mL) and the pharmacokinetic parameters for tenapanor could not be determined. The geometric mean AUC and C_{\max} of the major metabolite, M1, were approximately 33% and 27% lower, respectively, in patients with moderate hepatic impairment compared to those of healthy subjects. The decrease in M1 systemic exposure is not clinically relevant.

Patients with Renal Impairment

Based on a cross-study comparison, plasma concentrations of M1 in end-stage renal disease patients on hemodialysis (eGFR less than 15 mL/min/1.73m²) was not notably different from those of healthy subjects given comparable doses of IBSRELA.

Drug Interaction Studies

CYP Metabolism Mediated Drug Interactions

Tenapanor and M1 did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 in vitro.

Tenapanor and M1 did not induce CYP1A2 and CYP2B6 in vitro.

No significant inhibition or induction of CYP3A4 enzyme using midazolam as a substrate was observed when IBSRELA 50 mg was administered twice a day for 13 days in healthy subjects.

Following co-administration of a single dose of IBSRELA 50 mg with repeated doses of itraconazole 200 mg, a CYP3A4 inhibitor, the mean AUC and C_{max} of M1 was decreased 50% in healthy subjects. The decrease in M1 systemic exposure is not clinically relevant. Plasma concentrations of tenapanor were mostly below the limit of quantitation (less than 0.5 ng/mL) after co-administration of itraconazole.

Membrane Transporter Mediated Drug Interactions

Tenapanor and M1 did not inhibit P-gp, BCRP, OATP1B1, and OATP1B3. M1 did not inhibit OAT1, OAT3, OCT2, MATE1, and MATE2-K.

M1 is a substrate of P-gp. Tenapanor is not a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. M1 is not a substrate of BCRP, OAT1, OAT3, OCT2, MATE1 and MATE2-K.

No significant effect on PepT1 activity using cefadroxil as a substrate was observed when IBSRELA 50 mg was administered twice a day for 12 days in healthy subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

The carcinogenic potential of tenapanor was assessed in a 6-month carcinogenicity study in Tg rasH2 mice and in a 2-year carcinogenicity study in rats.

Tenapanor was not tumorigenic at oral doses up to 100 mg/kg/day (approximately 4.5 times the recommended human dose, based on the body surface area) in male mice and 800 mg/kg/day (approximately 39 times the maximum recommended human dose, based on the body surface area) for female mice. Tenapanor was not tumorigenic in male and female rats at oral doses up to 5 mg/kg/day (approximately 0.5 times the recommended human dose, based on the body surface area). The major metabolite of tenapanor, M1, was not tumorigenic in Tg rasH2 mice at oral doses up to 165 mg/kg/day (approximately 8 times the maximum recommended human dose, based on the body surface area)

Mutagenesis

Tenapanor was not genotoxic in the in vitro bacterial reverse mutation (Ames) assays, an in vitro chromosomal aberration assay in cultured human peripheral blood lymphocytes or the in vivo micronucleus assays in mice and rats.

Impairment of Fertility

Tenapanor had no effect on fertility or reproductive function in male rats at oral doses up to 10 mg/kg/day (approximately 0.97 times the recommended human dose, based on the body surface area) and in female mice at oral doses up to 50 mg/kg/day (approximately 2.4 times the recommended human dose, based on the body surface area).

14 CLINICAL STUDIES

The efficacy of IBSRELA for the treatment of IBS-C was established in two double-blind, placebo-controlled, randomized, multicenter trials in adult patients: Trial 1 (TEN-01-302; NCT02686138) and Trial 2 (TEN-01-301; NCT02621892). The intent-to-treat (ITT) analysis population included 620 patients in Trial 1 and 606 patients in Trial 2 with mean age of 46 years (range 18 to 75 years), 80% females, 64% White and 31% Black/African American. In these clinical trials, IBSRELA was administered immediately prior to breakfast or the first meal of the day and immediately prior to dinner.

To enter the trials, all patients met Rome III criteria for IBS-C and were required to meet the following clinical criteria during the 2-week baseline run-in period:

- a mean abdominal pain score of at least 3 on a 0-to-10-point numeric rating scale where a score of 0 indicates no pain and 10 indicates very severe pain
- less than 3 complete spontaneous bowel movements (CSBMs) per week, where a CSBM is defined as a spontaneous bowel movement (SBM) that is associated with a sense of complete evacuation (an SBM is a bowel movement occurring in the absence of laxative use)
- less than or equal to 5 SBMs per week

The trial designs were identical through the first 12 weeks of treatment, and thereafter differed in that Trial 1 continued for an additional 14 weeks of treatment (26 weeks double-blind treatment), whereas Trial 2 included a 4-week randomized withdrawal (RW) period.

Efficacy of IBSRELA was assessed using responder analyses based on daily diary entries.

In both trials, the primary endpoint was the proportion of responders, where a responder was defined as a patient achieving both the stool frequency and abdominal pain intensity responder criteria in the same week for at least 6 of the first 12 weeks of treatment. The stool frequency (CSBM) and abdominal pain responder criteria assessed each week were defined as:

- CSBM responder: a patient who experienced an increase of at least 1 CSBM in weekly average from baseline.
- Abdominal pain responder: a patient who experienced at least a 30% reduction in the weekly average of abdominal pain score compared with baseline.

The responder rates for the primary endpoint and components of the primary endpoint (CSBM and abdominal pain), which were pre-specified key secondary endpoints, are shown in [Table 2](#).

Table 2: Efficacy Responder Rates in Placebo-Controlled Trials (Trial 1 and Trial 2) in Adults with IBS-C: Responder for at least 6 of the First 12 Weeks of Treatment

Trial 1			
	IBSRELA N=293	Placebo N=300	Treatment Difference [95% CI^a]
Responder^b	37%	24%	13% [6%, 20%]
<u>Components of Responder Endpoint:</u>			
CSBM Responder ^c	47%	33%	
Abdominal Pain Responder ^d	50%	38%	
Trial 2			
Responder Rates	IBSRELA N=307	Placebo N=299	Treatment Difference [95% CI^a]
Responder^b	27%	19%	8% [2%, 15%]
<u>Components of Responder Endpoint:</u>			
CSBM Responder ^c	34%	29%	
Abdominal Pain Responder ^d	44%	33%	

^a CI: Confidence Interval

^b A responder for these trials was defined as a patient who met both the abdominal pain and CSBM weekly responder criteria for at least 6 of the first 12 weeks.

^c A CSBM responder was defined as a patient who achieved an increase in at least 1 CSBM per week, from baseline, for a least 6 of at least 12 weeks.

^d An abdominal pain responder was defined as a patient who met the criteria of at least 30% reduction from baseline in weekly average of the worst daily abdominal pain, for at least 6 of the first 12 weeks.

In Trials 1 and 2, the proportion of responders for 9 out of the first 12 weeks, including at least 3 of the last 4 weeks, was greater in IBSRELA-treated patients compared to placebo-treated patients. In addition, in Trial 1, the proportion of responders for 13 out of 26 weeks was greater in IBSRELA-treated patients compared to placebo-treated patients.

In both trials, improvements from baseline in average weekly CSBMs and abdominal pain were observed by Week 1, with improvement maintained through the end of treatment.

In IBSRELA-treated patients re-randomized to placebo in Trial 2, CSBM frequency and abdominal pain severity worsened on average over the 4-week period but remained improved compared to baseline. Patients who continued on IBSRELA maintained their response to therapy on average over the additional 4 weeks. Patients on placebo who were re-randomized to IBSRELA had an average increase in CSBM frequency and a decrease in abdominal pain.

16 HOW SUPPLIED/STORAGE AND HANDLING

IBSRELA tablets contain 50 mg tenapanor and are oval, white to off-white, debossed with “A50” on one side and “5791” on the other side.

IBSRELA is supplied in a white, opaque, high-density polyethylene bottle containing 60 tablets with a silica gel canister (as the desiccant) and screw-top polypropylene child-resistant cap lined and induction-activated aluminum foil liner (NDC 73154-050-60).

Storage

Store at room temperature, between 68°F and 77°F (20°C and 25°C).

Keep in original container and protect from moisture. Keep the container of IBSRELA tightly closed and in a dry place.

Do not remove desiccant from the bottle. Do not subdivide or repackage.

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling ([Medication Guide](#)).

Diarrhea

Instruct patients to stop IBSRELA and contact their healthcare provider if they experience severe diarrhea [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of IBSRELA in children, especially children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to store IBSRELA securely and out of reach of children [*see Contraindications (4), Warnings and Precautions (5.1)*].

Administration and Handling Instructions

Instruct Patients:

- To take IBSRELA immediately prior to breakfast or the first meal of the day and immediately before dinner [*see Dosage and Administration (2)*].
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take 2 doses at the same time [*see Dosage and Administration (2)*].
- To keep IBSRELA in a dry place. Protect from moisture. Keep in the original bottle. Do not remove desiccant from the bottle. Do not subdivide or repackage. Keep bottles tightly closed [*see How Supplied/Storage and Handling (16)*].

Manufactured for and distributed by Ardelyx, Inc.
Waltham, MA 02451 USA

IBSRELA[®] is a registered trademark of Ardelyx, Inc.

Patent: www.IBSRELA-patents.com

Medication Guide
IBSRELA® (ibs rel`a)
(tenapanor)
tablets, for oral use

What is the most important information I should know about IBSRELA?

- Do not give IBSRELA to children who are less than 6 years of age. It may harm them.
 - You should not give IBSRELA to patients 6 years to less than 18 years of age. It may harm them.
- IBSRELA can cause severe diarrhea and your child could get severe dehydration (loss of a large amount of body water and salt).

See “**What are the possible side effects of IBSRELA?**” for more information about side effects.

What is IBSRELA?

IBSRELA is a prescription medicine used in adults to treat:

- Irritable bowel syndrome with constipation (IBS-C).

It is not known if IBSRELA is safe and effective in children less than 18 years of age.

Who should not take IBSRELA?

- **Do not give IBSRELA to children who are less than 6 years of age.** IBSRELA can cause severe diarrhea and your child could get severe dehydration (loss of a large amount of body water and salt).
- Do not take IBSRELA if a doctor has told you that you have a bowel blockage (intestinal obstruction).

Before you take IBSRELA, tell your doctor about all your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if IBSRELA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if IBSRELA passes into your breast milk. Talk with your doctor about the best way to feed your baby if you take IBSRELA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

How should I take IBSRELA?

- Take IBSRELA exactly as your doctor tells you to take it.
- Take 1 IBSRELA tablet by mouth, 2 times each day.
- Take IBSRELA immediately before breakfast or the first meal of the day and immediately before dinner.
- If a dose is missed, skip the missed dose and take the next dose at the regular time. **Do not** take 2 doses at the same time.

What are the possible side effects of IBSRELA?

IBSRELA can cause serious side effects, including:

- See “**What is the most important information I should know about IBSRELA?**”
- **Diarrhea is the most common side effect of IBSRELA, and it can sometimes be severe. Stop taking IBSRELA and call your doctor if you develop severe diarrhea.**

The other most common side effects of IBSRELA include:

- swelling, or a feeling of fullness or pressure in your abdomen (distension).
- gas (flatulence).
- dizziness.

These are not all the possible side effects of IBSRELA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to www.fda.gov/medwatch.

How should I store IBSRELA?

- Store IBSRELA at room temperature, between 68°F and 77°F (20°C and 25°C).
- Keep IBSRELA in the original container and protect from moisture. Keep the container of IBSRELA tightly closed and in a dry place.
- Do not put IBSRELA in another container (repackage).
- The IBSRELA bottle contains a desiccant canister to help keep your medicine dry (protect it from moisture). Do not remove the desiccant from the bottle.

Keep IBSRELA and all medicines out of the reach of children.

General information about the safe and effective use of IBSRELA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use IBSRELA for a condition for which it was not prescribed. Do not give IBSRELA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about IBSRELA that is written for health professionals.

What are the ingredients in IBSRELA?

Active ingredient: tenapanor hydrochloride

Inactive ingredients: colloidal silicon dioxide, hypromellose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid, titanium dioxide, and triacetin.

Manufactured for and distributed by Ardelyx, Inc. Waltham, MA 02451 USA

IBSRELA® is a registered trademark of Ardelyx, Inc.

Patent: www.IBSRELA-patents.com

For more information, go to www.ardelyx.com or call 1-844-427-7352

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: May 2021

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/s/

JESSICA J LEE
05/19/2021 11:33:35 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211801Orig1s003

CLINICAL REVIEW(S)

Medical Officer Brief Memo

Regarding: NDA 211801/IND 108732 Isbrela (tenapanor); Prior Approval Supplement: Section 12.3 Patients with Hepatic Impairment

From: Suruchi Batra, MD, Medical Officer, DG / Suna Seo, MD, MSc, Clinical Team Leader, DG

Through: Jessica Lee, MD, MMSC, Director, DG

Date finalized: 5/19/21

Prior Approval Supplement: Section 12.3 Patients with Hepatic Impairment

NDA 211801/IND 108732 Isbrela (Tenapanor)

Tenapanor was approved for use in adults with irritable bowel syndrome constipation subtype (IBS-C) on 9/12/19 under NDA 211801. At the pre-NDA meeting on 5/1/18, the Agency requested the Sponsor to study the effects of hepatic impairment on the pharmacokinetics (PK) of tenapanor and its major metabolite, AZ13792925 (also referred to as M1), which is not pharmacologically active. Accordingly, the Sponsor submitted the protocol TEN-01-107 entitled "A Phase 1, Open-label, Single-dose Study to Investigate the Pharmacokinetics of Tenapanor in Subjects with Hepatic Impairment Compared to Subjects with Normal Hepatic Function" on 2/23/19. The study was initiated on 4/2/19 and completed on 6/18/19. The Final Study Report was received by the Agency on 2/21/20 and was previously reviewed by the clinical and clinical pharmacology teams. For full details, refer to the memo filed by Dr. Suruchi Batra under IND 108732 on 1/19/21.

In brief, tenapanor showed minimal systemic bioavailability following administration of a single 100 mg dose of tenapanor in subjects with moderate hepatic impairment and subjects with normal hepatic function. However, due to minimal systemic exposure to tenapanor, insufficient quantitative plasma concentrations were available to estimate the PK parameters in most subjects. Regarding the inactive major metabolite, AZ13792925, the geometric mean AUC and C_{max} of AZ13792925 were approximately 33% and 27%, respectively, lower in the patients with hepatic impairment compared to those of healthy subjects. Overall, the differences are considered clinically insignificant because AZ13792925 is not pharmacologically active and there were overall minimal systemic exposures of tenapanor and AZ13792925 in both groups. No significant adverse events were identified. On review of this data, tenapanor appears safe for short term use in patients with mild and moderate hepatic impairment.

Following this review, the Division requested a prior approval supplement (PAS) for labeling change regarding tenapanor use in patients with hepatic impairment under section 12.3 of the approved label. Notification of the PAS request and the recommended language to be included in section 12.3 were sent to the Sponsor on 1/26/21. The Sponsor response was received on 3/26/21, in which the Sponsor concurred with the recommendation for labeling change. After review, the following language was recommended by the Division to be included under Section 12.3 of Supplement Label 3:

Specific Populations

Patients with Hepatic Impairment

Following a single dose of tenapanor 100 mg in patients with moderate hepatic impairment (Child-Pugh B), plasma concentrations of tenapanor were mostly below the limit of quantitation (< 0.5 ng/mL) and the pharmacokinetic parameters for tenapanor could not be determined. The geometric mean AUC and C_{\max} of the major metabolite, M1, were approximately 33% and 27% lower, respectively, in patients with moderate hepatic impairment compared to those of healthy subjects. The decrease in M1 systemic exposure is not clinically relevant.

Patients with Renal Impairment

Based on a cross-study comparison, plasma concentrations of M1 in end-stage renal disease patients on hemodialysis (eGFR less than 15 mL/min/1.73m²) was not notably different from those of healthy subjects given comparable doses of IBSRELA.

Drug Interaction Studies

CYP Metabolism Mediated Drug Interactions

Tenapanor and M1 did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 in vitro.

Tenapanor and M1 did not induce CYP1A2 and CYP2B6 in vitro.

No significant inhibition or induction of CYP3A4 enzyme using midazolam as a substrate was observed when IBSRELA 50 mg was administered twice a day for 13 days in healthy subjects.

Following co-administration of a single dose of IBSRELA 50 mg with repeated doses of itraconazole 200 mg, a CYP3A4 inhibitor, the mean AUC and C_{\max} of M1 was decreased 50% in healthy subjects. The decrease in M1 systemic exposure is not clinically relevant. Plasma concentrations of tenapanor were mostly below the limit of quantitation (less than 0.5 ng/mL) after co-administration of itraconazole.

Recommendations for prior approval supplement (PAS) labeling change was communicated to the Sponsor on 4/13/21. The Sponsor response to PAS labeling change request was received on 4/23/21, in which the Sponsor agreed to all recommended changes.

The label was reviewed and is recommended for Division approval.

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/s/

SURUCHI K BATRA
05/19/2021 09:51:03 AM

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05/19/2021 09:52:13 AM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211801Orig1s003

ADMINISTRATIVE AND CORRESPONDENCE
DOCUMENTS

From: [Dodson, Andrew](#)
To: [Rob Blanks](#)
Subject: NDA 211801/S-003 Labeling Comments to Sponsor
Date: Tuesday, April 13, 2021 3:04:00 PM
Attachments: [draft-labeling-text-redline.pdf](#)
[draft-labeling-medication-guide-clean.docx](#)
[draft-labeling-medication-guide-redline.docx](#)
[draft-labeling-medication-guide-redline.pdf](#)
[draft-labeling-text-clean.docx](#)
[draft-labeling-text-redline.docx](#)
[image001.png](#)

Hi Rob,

Please refer to your supplemental new drug application (sNDA) submitted on March 26, 2021, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for lbsrela (tenapanor).

On March 26, 2021, we received your proposed labeling submission to this application, and have proposed revisions that are included as an attachment. We request that you resubmit labeling that addresses these issues by **April 26, 2021**. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) - a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

When resubmitting labeling, please use the "clean" version for changes. Please do not merge the documents. If, after reviewing the proposed revisions, you accept all of the changes and consider this "final" labeling, please include a statement to that effect in your cover letter.

Please confirm receipt and don't hesitate to contact me with any questions.

Best,
Andrew

Andrew Dodson, PharmD

Regulatory Project Manager

Division of Gastroenterology
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Tel: 301-796-8760

Andrew.Dodson@fda.hhs.gov



13 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANDREW M DODSON
04/13/2021 03:10:14 PM



NDA 211801/S-003

**ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT**

Ardelyx, Inc.
Attention: Robert C. Blanks
Chief Regulatory and Quality Officer
34175 Ardenwood Boulevard
Suite 100
Fremont, CA 94555

Dear Mr. Blanks:

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 211801
SUPPLEMENT NUMBER: 003
PRODUCT NAME: lbsrela (tenapanor hydrochloride) tablets
DATE OF SUBMISSION: March 26, 2021
DATE OF RECEIPT: March 26, 2021

This supplemental application proposes the following change for lbsrela:

- Update *Patients with Hepatic Impairment* in Section 12.3 Pharmacokinetics of the Prescribing Information (PI) with the results of clinical study TEN-01-107, titled "A Phase 1, Open-label, Single-dose Study to Investigate the Pharmacokinetics of Tenapanor in Subjects with Hepatic Impairment Compared to Subjects with Normal Hepatic Function."

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 25, 2021, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be September 26, 2021.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

FDA.gov.¹ Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

If you have questions, please call me at 301-796-8760.

Sincerely,

{See appended electronic signature page}

Andrew Dodson, PharmD
Regulatory Project Manager
Division of Regulatory Operations for Immunology
and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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/s/

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