PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]IBSRELA®

Tenapanor tablets

Tenapanor (as Tenapanor hydrochloride) 50 mg, oral

sodium (Na+)/hydrogen (H+) exchanger 3 (NHE3) inhibitor

Knight Therapeutics Inc.

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Date of Initial Authorization:
APR 15, 2020

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, 7.1.2 Breast-feeding	[07/2025]

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Irritable Bowel Syndrome with Constipation (IBS-C)

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

1.1 Pediatrics

Pediatrics (< 18 years of age): IBSRELA is contraindicated in children up to 6 years of age and is not recommended in children between 6 and 18 years of age. In studies in juvenile rats, tenapanor resulted in decreased body weight and mortality due to dehydration [see 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7.1.3 Pediatrics, 16 NON-CLINICAL TOXICOLOGY, Juvenile].

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of IBSRELA in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): The safety profile of IBSRELA in patients > 65 years of age (8%) was consistent with the safety profile of overall IBS-C study population. Clinical studies of IBSRELA did not include sufficient numbers of patients > 65 years of age to determine whether they respond differently than patients < 65 years of age [see 7.1.4 Geriatrics].

2 CONTRAINDICATIONS

Tenapanor is contraindicated in:

- Pediatric patients under 6 years of age due to the risk of serious dehydration [see 1.1 Pediatrics, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7.1.3 Pediatrics, 16 NON-CLINICAL TOXICOLOGY, Juvenile].
- Patients who are hypersensitive to tenapanor or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Table 1 in the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with known or suspected mechanical gastrointestinal obstruction.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Tenapanor is contraindicated in patients less than 6 years of age.
- The use of Tenapanor in patients between 6 years and 18 years of age is not recommended.

[see 1.1 Pediatrics, 2 CONTRAINDICATIONS, 7.1.3 Pediatrics, 16 NON-CLINICAL TOXICOLOGY, Juvenile]

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

IBSRELA is a tablet containing 50 mg of tenapanor (53.2 mg of tenapanor hydrochloride).

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage in adults is 50 mg, oral twice daily.

Renal impairment: No dosage adjustment is required for patients with an eGFR >30 ml/min/1.73m^2. Patients with creatinine above 176 µmol/L, which includes all patients with severe or end stage renal impairment (eGFR <30 ml/min/1.73m^2), were excluded from the pivotal studies.

DDI: Monitor blood pressure and increase the dosage of enalapril (an OATP2B1 substrate), if needed, when IBSRELA is co-administered with enalapril [see 9.4 Drug-Drug Interactions].

Pediatrics: Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Take IBSRELA immediately prior to breakfast or the first meal of the day and immediately prior to dinner. Swallow IBSRELA tablets whole and do not crush or chew.

4.5 Missed Dose

In the event that a dose is missed, the patient should skip that dose. Do not take two tablets to account for the missed dose. Wait until it is time for the next dose and then take the usual dose.

5 OVERDOSAGE

There has been no overdosage experience with IBSRELA in patients with IBS-C.

Single oral doses as high as 900 mg of IBSRELA have been administered to healthy volunteers, with minimal systemic exposure. Based on nonclinical data, overdose of IBSRELA may result in local effects such as diarrhea as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	tablet 50 mg	colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid, and the coating agent OPADRY®, which consists of hypromellose, titanium dioxide and triacetin.

Tablets: 50 mg tenapanor supplied as an oval, white to off-white film-coated, biconvex tablet, debossed with "Δ50" on one side and "5791" on the other side.

The tablets are packaged in a 75 mL high-density polyethylene (HDPE) bottle, with silica gel desiccant, induction sealed, and capped with a polypropylene child-resistant closure. Each bottle contains 60 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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 has not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), oral administration of tenapanor resulted in decreased body weight and mortality due to dehydration. Although there are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years), given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, the use of IBSRELA in patients 6 years to less than 18 years of age is not recommended [See 1.1 Pediatrics, 2 CONTRAINDICATIONS, 7.1.3 Pediatrics, 16 NON-CLINICAL TOXICOLOGY, Juvenile].

Gastrointestinal

Diarrhea was the most common adverse reaction in IBSRELA-treated patients in the pooled IBS-C double-blind, placebo-controlled trials. The incidence of diarrhea was higher in IBSRELA-treated patients than placebo-treated patients. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. [see 8.1 Adverse Reaction Overview, 8.2 Clinical Trial Adverse Reactions].

If severe diarrhea occurs, suspend dosing and rehydrate patient.

Hepatic Impairment

The safety and efficacy of IBSRELA in IBS patients with hepatic dysfunction (ALT or AST > 2.5 times the upper limit of normal) has not been established. See Section 10.3 Pharmacokinetics, Special Populations and Conditions.

Renal Impairment

Safety and efficacy of patients with IBS-C and a creatinine above 176 µmol/L, which includes all patients with severe or end stage renal impairment (eGFR <30 ml/min/1.73m^2), have not been established.

In patients with IBS-C treated with IBSRELA, diarrhea, including severe diarrhea, is more common in those with renal impairment than in those with normal renal function [see 8 ADVERSE REACTIONS].

In patients with chronic kidney disease (eGFR 25-70 ml/min/1.73m^2) and Type 2 diabetes mellitus treated with IBSRELA in a clinical trial for an unapproved indication, serious adverse reactions of hyperkalemia were reported [see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data].

7.1 Special Populations

7.1.1 Pregnant Women

IBSRELA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

There are no adequate and well-controlled studies with IBSRELA in pregnant women.

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 and were 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 adverse effects on pre-and post-natal development with the exception of tenapanor-related lower mean body weight gains and mean body weight in pups throughout the pre-weaning periods at doses of 60 and 200 mg/kg/day.

7.1.2 Breast-feeding

Tenapanor and its major metabolite, M1, were not detected in the breast milk of lactating women. Maternal use of IBSRELA is not expected to result in exposure to tenapanor or its metabolite in breastfed infants. There is no information on the effects of IBSRELA on milk production. 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.

IBSRELA is not measurable in plasma following administration of the recommended clinical doses [see 10.3 Pharmacokinetics].

7.1.3 Pediatrics

Pediatrics (< 18 years of age): IBSRELA is contraindicated in children under 6 years of age and is not recommended for use in children between 6 and 18 years of age [see 1.1 Pediatrics, 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX].

In nonclinical studies, deaths occurred in young juvenile rats (< 1 to 3 week-old rats; approximately equivalent to human pediatric patients less than 2 years of age) following administration of single daily oral doses of IBSRELA [See 16 NON-CLINICAL TOXICOLOGY, Juvenile].

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of IBSRELA in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

The safety profile of IBSRELA in patients > 65 years of age (7%) was consistent with the safety profile of the overall IBS-C study population. Clinical studies of IBSRELA did not include sufficient numbers of patients > 65 years of age to determine whether they respond differently than patients < 65 years of age [see 1.2 Geriatrics].

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of IBSRELA for the treatment of irritable bowel syndrome with constipation (IBS-C) was evaluated in 1,073 patients exposed to IBSRELA 100 mg per day (either 100 mg QD or 50 mg BID) in the Phase 2 and 3 clinical studies and 738 patients exposed to placebo. The incidence of patients reporting a treatment-emergent adverse event (TEAE) was 44% in the IBSRELA 100 mg dose group and 33% in the placebo group. A TEAE was considered drug-related in 20% of the IBSRELA 100 mg dose group and 8.3% in the placebo group. A TEAE was considered severe in 2.2% and 0.3% of patients in the IBSRELA 100 mg dose group and placebo group, respectively. There were 1.2% and 1.1% patients with serious adverse events in the IBSRELA 100 mg dose group and placebo group, respectively.

Diarrhea was the most common TEAE reported by all patients who received IBSRELA (14.8% of those who received the proposed daily dose [100 mg] of tenapanor) and 2.3% of patients administered placebo, often occurring during the first week of treatment.

A total of 77 (7.2%) and 9 (1.2%) patients were discontinued due to adverse events in the IBSRELA 100 mg dose group and placebo group, respectively. Diarrhea was the most commonly observed adverse event leading to study discontinuation (5.9%) in the IBSRELA 100 mg dose group compared with placebo (0.5%). Most often, this diarrhea was mild to moderate in severity. Nonetheless, severe diarrhea leading to study discontinuation was experienced in 1.7% of patients receiving a daily dose of IBSRELA 100 mg (18 of 1073) compared to 0.14% (1 of 738) of patients receiving placebo.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The data described below reflect exposure to IBSRELA in two Phase 3 double-blind, placebo-controlled clinical trials (TEN-01-301 and TEN-01-302) involving 602 adult patients with IBS-C treated with tenapanor 100 mg per day. Demographic characteristics were comparable between treatment groups across all studies. Patients were randomized to receive placebo or IBSRELA at 100 mg daily. The double-blind treatment period lasted for 12 weeks in TEN-01-301 and 26 weeks in TEN-01-302 [see 14

CLINICAL TRIALS].

Table 2 - Treatment-Emergent Adverse Events Reported by ≥1% of Patients treated with IBSRELA 100 mg and at an Incidence Greater than in Placebo-Treated Patients in Two Phase 3 Placebo-Controlled Trials in IBS-C

System Organ Class Preferred Term	IBSRELA 100 mg (N=602) n (%)	Placebo (N=601) n (%)
Gastrointestinal Disorders		
Diarrhea	92 (15.3)	16 (2.7)
Flatulence	15 (2.5)	10 (1.7)
Abdominal Distension	15 (2.5)	1 (0.2)
Gastrointestinal Sounds Abnormal	7 (1.2)	1 (0.2)
Infections and Infestations		
Nasopharyngitis	18 (3.0)	16 (2.7)
Nervous System Disorders		
Dizziness	6 (1.0)	2 (0.3)

Diarrhea was the most common adverse reaction that occurred more frequently in IBSRELA-treated patients (15.3%) compared to placebo-treated patients (2.7%) as described in Table 2**.**

Diarrhea was the most common adverse event leading to discontinuation: 6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients. The majority of these events were of mild or moderate intensity (67.4%).

Patients with Renal Impairment

There were 368 patients (31%) with baseline renal impairment (eGFR between 30 and 90mL/min/1.73m^2) and 835 patients (69%) with normal renal function in studies TEN-01-301 and TEN-01-302. 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.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions Reported by <1% of Patients treated with IBSRELA 100 mg are listed below by system organ class.

Gastrointestinal disorders: abdominal tenderness, defecation urgency, fecal incontinence, gastroesophageal reflux disease, rectal hemorrhage, vomiting.

General Disorders and Administration Site Conditions: thirst.

Infections and Infestations: gastroenteritis viral.

Investigations: blood bicarbonate decreased, blood potassium increased.

Metabolism and Nutrition Disorders: dehydration, hyperkalemia.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Refer to 8.3 Less Common Clinical Trial Adverse Reactions, Investigations and Metabolism and Nutrition Disorders for information on abnormal hematologic and clinical chemistry findings.

Hyperkalemia
In a trial of another patient population with chronic kidney disease (defined by eGFR from 25 to 70 mL/min/1.73m^2) 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). In this trial, there were 7 (9%) IBSRELA-treated patients who experienced hyperkalemia or increase in blood potassium vs 1 (1%) placebo-treated patient.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of IBSRELA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: hypersensitivity (including anaphylactic reaction, angioedema, pruritus, rash, stomatitis, urticaria).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

CYP Metabolism Mediated Drug Interactions

IBSRELA and its major metabolite did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 *in vitro*. Although IBSRELA and its major metabolite inhibited CYP3A4 *in vitro*, there was no inhibition of CYP3A4 by IBSRELA in clinical studies.

IBSRELA and its major metabolite did not induce CYP1A2, CYP2B6, and CYP3A4 *in vitro*. IBSRELA did not induce CYP3A4 in clinical studies.

Membrane Transporter Mediated Drug Interactions

IBSRELA and its major metabolite did not inhibit P-gp, BCRP, OATP1B1, and OATP1B3. The major metabolite of IBSRELA did not inhibit OAT1, OAT3, OCT2, MATE1, and MATE2-K. IBSRELA is not a substrate of P-gp, BCRP, OATP1B1, and OATP1B3 *in vitro*. The major metabolite of IBSRELA is a weak substrate of P-gp, but not a substrate of BCRP, OAT1, OAT3, OCT2, MATE1, and MATE2K *in vitro.*

IBSRELA had no effect on PepT1 activity in clinical studies.

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1. Enalapril, an OATP2B1 substrate, may have reduced exposures when concomitantly taken with IBSRELA.

9.3 Drug-Behavioural Interactions

Interactions with individual behavioural risks have not been established.

9.4 Drug-Drug Interactions

In clinical studies, co-administration of omeprazole, a proton pump inhibitor, did not affect safety and tolerability of IBSRELA. Co-administration of sevelamer carbonate, a phosphate binder, did not affect the pharmacodynamic activity of IBSRELA.

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, which is not active against NHE3, was decreased 50% in healthy subjects. Plasma concentrations of tenapanor were mostly below the limit of quantitation (less than 0.5 ng/mL) after co-administration of itraconazole.

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

No significant effect on CYP2C9 activity using warfarin as a substrate was observed when tenapanor 30 mg was administered twice a day (a dosage 0.6 times the recommended dosage) for 12 days in healthy subjects.

No significant effect on P-gp activity using digoxin as a substrate was observed when tenapanor 30 mg was administered twice a day (a dosage 0.6 times the recommended dosage) for 12 days in healthy subjects.

Enalapril is a substrate of OATP2B1. Following administration of a single 20 mg dose of enalapril with tenapanor (30 mg twice daily for five days, a dosage 0.6 times the recommended dosage) at steady state in healthy subjects, the mean systemic exposure (AUC) and peak exposure (Cmax) of enalapril was decreased by 64% and 69%, respectively, compared to when enalapril was administered alone. Furthermore, the mean AUC and C_{max} of its active metabolite, enalaprilat, was decreased by 52% and 68%, respectively. Monitor blood pressure and increase the dosage of enalapril, if needed, when IBSRELA is co-administered with enalapril.

9.5 Drug-Food Interactions

IBSRELA was more effective at increasing the 24-hour stool sodium excreted when administered before a meal compared to after a meal or in fasting conditions in a crossover study with healthy volunteers. In clinical studies in IBS-C patients, IBSRELA was administered immediately prior to breakfast or the first meal of the day and immediately prior to dinner [see 10.3 Pharmacokinetics].

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

IBSRELA is a locally acting inhibitor of the sodium/hydrogen exchanger 3 (NHE3), an antiporter expressed on the apical surface of the small intestine and colon primarily responsible for the absorption of dietary sodium.

In vitro and animal studies indicate its major metabolite, M1, is not active against NHE3.

By inhibiting NHE3 on the apical surface of the enterocytes, IBSRELA reduces absorption of sodium from the small intestine and colon, resulting in an increase in water secretion into the intestinal lumen, which accelerates intestinal transit time and results in a softer stool consistency.

IBSRELA has also been shown to reduce abdominal pain by decreasing visceral hypersensitivity and by decreasing intestinal permeability in animal models. In rat model of colonic hypersensitivity, tenapanor reduced visceral hyperalgesia and normalized colonic sensory neuronal excitability.

10.2 Pharmacodynamics

Cardiac Electrophysiology

No formal thorough QT prolongation study was conducted. In a dose-ranging study with tenapanor, at 3 times the mean maximum exposure of M1 at the recommended dosage, there were no clinically relevant effects on the QTc interval.

Food effect

IBSRELA was more effective at increasing the 24-hour stool sodium excreted when administered 5 minutes before a meal, standardized for sodium content (1500 mg/meal) compared to 30 minutes after a meal or in fasting conditions (1 hour before breakfast or 3 hours after dinner and 1 hour before the next meal) in a crossover study with healthy volunteers. In clinical studies in IBS-C patients, IBSRELA was administered immediately prior to breakfast or the first meal of the day and immediately prior to dinner.

10.3 Pharmacokinetics

Absorption

IBSRELA is minimally absorbed with negligible systemic availability following repeat, twice daily oral administration. Greater than 91% of plasma of plasma concentrations of IBSRELA were below the limit of quantitation (< 0.5 ng/mL) in patients following repeated dosing 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

In vitro protein binding studies show IBSRELA is approximately 99% bound to human plasma proteins. The major metabolite of IBSRELA is approximately 97% plasma protein-bound. Due to the low systemic exposures of IBSRELA, the volume of distribution could not be determined for IBSRELA or its major metabolite. As IBSRELA is minimally absorbed, it is not expected to distribute to tissues in any clinically relevant extent.

Metabolism

IBSRELA is metabolized primarily by CYP3A4/5 and low levels of its major metabolite are detected in plasma. The C_{max} of its major metabolite is approximately 11 ng/mL at steady state in patients. In vitro and animal studies indicate its major metabolite is not active against NHE3.

Elimination

Following administration of a single 15 mg radiolabeled ^{14}C-IBSRELA dose to healthy volunteers, approximately 79% of the radioactivity was excreted in feces through 240 hours post-dose (70% through 120 hours post-dose), mostly as the parent molecule. Approximately 9% of the dose was recovered in the urine, primarily as metabolites while IBSRELA was not detected. The major metabolite is excreted in urine unchanged (1.5% of dose recovered 144 hours post-dose).

Special Populations and Conditions

- **Pediatrics:** IBSRELA is contraindicated in children up to 6 years of age and is not recommended in children between 6 and 18 years of age as safety and efficacy of IBSRELA in pediatric patients

have not been established [see 1.1 Pediatrics, 2 CONTRAINDICATIONS, 7.1.3 Pediatrics, and 16 NON-CLINICAL TOXICOLOGY, Juvenile].

Clinical studies to determine the impact of age on the clinical pharmacokinetics of tenapanor have not been conducted as tenapanor is rarely detectable in plasma.

In a nonclinical range-finding study, deaths occurred in young juvenile rats (< 1 to 3 week-old-rats following oral administration of approximately equivalent to human pediatric patients less than 2 years of age) following administration of a single oral dose of IBSRELA [see 16 NON-CLINICAL TOXICOLOGY, Juvenile].

- **Geriatrics:** No clinical studies to determine the impact of age on the pharmacokinetics of IBSRELA were conducted [See 7.1.4 Geriatrics].
- **Sex:** Clinical studies to determine the impact of sex on the pharmacokinetics of IBSRELA have not been conducted. Gender is not expected to affect the pharmacokinetics of IBSRELA.
- **Pregnancy and Breast-feeding:** Insufficient information is available to evaluate the use of IBSRELA in pregnant women with IBS-C. IBSRELA is minimally absorbed with low systemic availability following, repeat twice-daily oral administration [See 7.1.1 Pregnant Women].

  A clinical lactation study was conducted in seven healthy adult women who were between 22 to 37 years of age. Following oral administration of IBSRELA 50mg twice daily for 3 days, the concentrations of tenapanor and its major metabolite were below the limit quantitation (<1 ng/mL and 1 ng/mL) in all breast milk samples collected over 24 hours post-dosing [7.1.2 Breast-feeding].
- **Ethnic Origin:** Ethnic origin is not expected to affect the pharmacokinetics of IBSRELA.
- **Hepatic Insufficiency:** Following a single dose of tenapanor 100 mg in patients with moderate hepatic impairment (Child Pugh B), more PK profiles had quantifiable tenapanor concentrations (6 out 10 vs 3 out of 10 in subjects with moderate hepatic impairment and normal hepatic function, respectively) and geometric mean C_{max} was higher (approximately 53%) when compared to those of healthy subjects. However, it is notable that plasma concentrations of tenapanor for all subjects 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, which is not active against NHE3, were approximately 33% and 27% lower, respectively, in patients with moderate hepatic impairment compared to those of healthy subjects. [See 7 WARNINGS AND PRECAUTIONS, Hepatic Impairment].
- **Renal Insufficiency:** Patients with creatinine above 176 µmol/L, which includes all patients with severe or end stage renal impairment (eGFR <30 ml/min/1.73m^2), were excluded from the pivotal studies.

  The pharmacodynamic activity of IBSRELA in patients with renal disease is similar to IBS-C patients and healthy volunteers at comparable doses [See 7 WARNINGS AND PRECAUTIONS, Renal Impairment].

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 to 30°C).

Keep IBSRELA tablets in the original container. Protect from moisture. Do not remove desiccant from the container.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

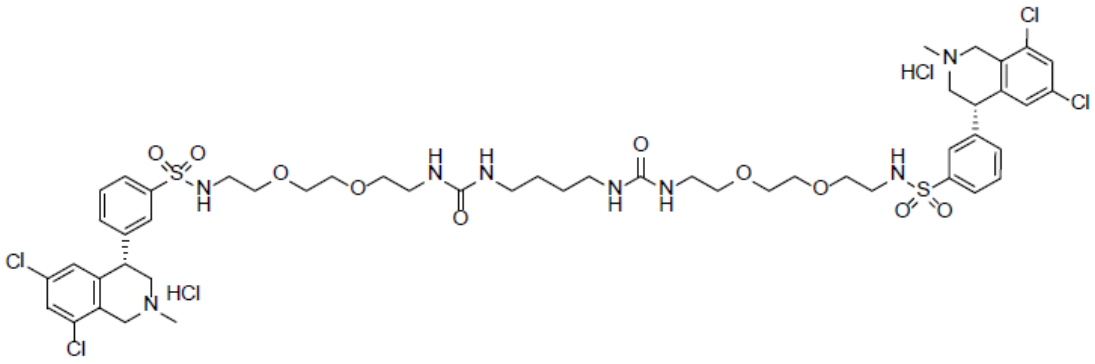
Drug Substance

Proper name: tenapanor hydrochloride

Chemical name: 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)

Molecular formula and molecular mass: $C_{50}H_{68}Cl_6N_8O_{10}S_2$, 1218 Daltons

Structural formula:



Physicochemical properties: Tenapanor is a white to off-white to light brown solid. It is a chiral molecule which contains 2 stereocenters, both of which are in the S configuration. Amorphous solid; Tg = 117°C; no known stable polymorphs. Has a high hygroscopicity. It is sparingly soluble in water, soluble in dilute hydrochloric acid, very slightly soluble in acetonitrile, sparingly soluble in ethanol and soluble in methanol.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Irritable Bowel Syndrome with Constipation (IBS-C)

Table 3 - Summary of Patient Demographics for Clinical Trials Supporting Efficacy of IBSRELA in the Treatment of IBS-C[a] (Intention-to-Treat [ITT] Population)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
TEN-01-301	Phase 3, multicenter, randomized, double-blind, placebo-controlled	Tenapanor 50 mg tablets or matching placebo; administered BID* PO** immediately prior to first meal of the day and dinner, for 12 weeks	606 patients	45.0 years (18-75)	Males: 113 Females: 493
TEN-01-302	Phase 3, multicenter, randomized, double-blind, placebo-controlled	Tenapanor tablets 50 mg tablets or matching placebo; administered BID* PO** immediately prior to first meal of the day and dinner, for 26 weeks	593 patients	45.4 years (18-75)	Males: 106 Females: 487

* BID: twice daily

** PO: per os

[a] IBS-C: irritable bowel syndrome with constipation, defined by the Rome III Criteria for the Diagnosis of IBS

The efficacy of IBSRELA for the treatment of IBS-C was established in two double-blind, placebo-controlled, randomized, multicenter trials in adult patients (TEN-01-301 and TEN-01-302). A total of 606 patients in TEN-01-301 and 593 patients in TEN-01-302 in the ITT population were enrolled with a mean age of 45.7 years in the IBSRELA group and 45 years in the placebo group (range: 18 to 75 years). More than 80% of patients were females in both studies, the majority of patients were White (IBSRELA 66.1%, placebo 64.2%) or Black/African American (IBSRELA 28.5%, placebo 31.1%).

To enter the study, all patients who met Rome III criteria* for IBS-C 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

*ROME III criteria. Diagnosis required recurrent abdominal pain or discomfort at least 3 days/months in the last 3 months with 2 or more of the following:

- Improvement with defecation;

- Onset associated with a change in frequency of stool;
- Onset associated with a change in form of stool.

The trial designs of TEN-01-301 and TEN-01-302 were identical through the first 12 weeks of treatment, and thereafter differed in that TEN-01-301 included a 4-week randomized withdrawal (RW) period, and TEN-01-302 continued for 14 additional weeks (total of 26 weeks) of double-blind treatment. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take osmotic laxatives, bismuth, prokinetic agents, or other drugs to treat IBS-C or chronic constipation. Bisacodyl (5 mg tablet or 10 mg suppository) was allowed as rescue medication for severe constipation.

Study Results

Efficacy of IBSRELA was assessed using responder analyses based on abdominal pain intensity and stool frequency responder (CSBM) endpoint and change-from-baseline endpoints. Efficacy was assessed using information provided by patients on a daily basis in eDiaries.

A responder was defined as a patient who met both the abdominal pain intensity and stool frequency responder criteria in the same week for at least 6 of the first 12 weeks of treatment. The abdominal pain and stool frequency responder criteria assessed each week were defined as:

- Abdominal pain responder: a patient who experienced a decrease of at least 30% from baseline in abdominal pain score.
- Stool frequency responder: a patient who experienced an increase of at least 1 CSBM from baseline.

The responder rates for the components of the responder endpoint (abdominal pain or CSBM) were pre-specified key secondary endpoints (Table 4).

Durability of efficacy response in TEN-01-301 and TEN-01-302 studies was based on pre-specified key secondary endpoints. For the 9 of 12 weeks (designated as “9/12 weeks”) overall responder endpoint (CSBM and abdominal pain), a patient was required to have at least a 30% reduction from baseline in mean abdominal pain score, an increase of at least 1 CSBM from baseline, and at least 3 CSBMs, all in the same week, for at least 9 of the first 12 weeks of treatment. The responder rates for the component of the responder endpoint (i.e., CSBM or abdominal pain) were also pre-specified key secondary endpoints.

In addition, durability of efficacy was also assessed for a longer period in TEN-01-302 based on a patient being a weekly responder for at least 13 out of the 26 weeks of treatment. For the 13 out of 26 weeks (designated as “13/26 weeks”) overall responder endpoint (CSBM and abdominal pain), a patient had to have at least 30% reduction from baseline in mean abdominal pain score and an increase of at least 1 CSBM from baseline, all in the same week, for at least 13 out of the 26 weeks of continued treatment. The responder rates for the components of the responder endpoint (i.e., abdominal pain or CSBM) were also pre-specified key secondary endpoints.

Table 4 – Efficacy Responder Rates in Placebo-Controlled Trials (TEN-01-301 and TEN-01-302) in Adults with IBS-C: Responder for at least 6 of the 12 weeks of treatment

TEN-01-301				
Responder Rates	**IBSRELA 50 mg BID[a] (N=307)**	**Placebo (N=299)**	**Treatment Difference [95% CI[b]]**	**CMH p-value[d]**
Responder* (Abdominal Pain and CSBM[c] Responder in the same week)	27%	19%	8% [1.7%, 15.0%]	0.020
Abdominal Pain Responder** (≥ 30% Abdominal Pain Reduction from Baseline)	44%	33%	11% [3.2%, 18.6%]	0.008
CSBM[c] Responder** (Increase ≥ 1 CSBM from Baseline)	34%	29%	4% [-3.0%, 11.8%]	0.270
TEN-01-302				
Responder Rates	**IBSRELA 50 mg BID (N=293)**	**Placebo (N=300)**	**Treatment Difference [95% CI]**	**CMH p-value[d]**
Responder* (Abdominal Pain and CSBM Responder in the same week)	37%	24%	13% [5.5%, 20.2%]	<0.001
Abdominal Pain Responder** (≥ 30% Abdominal Pain Reduction from Baseline)	50%	38%	12% [3.6%, 19.4%]	0.004
CSBM[c] Responder** (Increase ≥ 1 CSBM from Baseline)	47%	33%	14% [6.3%, 21.9%]	<0.001

* Primary Endpoint

** Key Secondary Endpoint

[a] BID = twice daily

[b] CI- Confidence Interval

[c] CSBM = complete spontaneous bowel movement

[d] CMH p-value based on 1-degree of freedom test for association between treatment stratified by pooled investigator sites

In both clinical trials, the proportion of responders for the 9/12 weeks was greater in IBSRELA-treated patients compared to placebo-treated patients. In addition, in study TEN-01-302, the proportion of responders for the 13/26 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.

In study TEN-01-301, IBSRELA-treated patients re-randomized to placebo demonstrated a worsening on average of CSBM frequency and abdominal pain severity 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology (Repeat-dose toxicity): Repeat-dose oral toxicology studies with tenapanor were conducted at doses up to 10 mg/kg/day in Sprague Dawley rats for 6 months, 200 mg/kg/day in CD-1 mice for 28 days and 1000 mg/kg/day in Beagle dogs for 9 months. Clinical signs and toxic effects in rats and mice increased in severity and incidence with dose level and duration of dosing and were reflective of gastrointestinal pharmacological action of tenapanor. Clinical signs in rodents included diarrhea, softening of feces and/or decreased defecation. Secondary effects of tenapanor in rodents included: decreased body weight, food consumption, and altered water consumption; changes in activity levels (mice); lower heart and spleen weights (mice); decreased goblet cell numbers sometimes accompanied by inflammatory infiltrates in the cecum, colon, and/or rectum; transient changes in red cell indices, white blood cells and serum protein, potassium, and phosphorus. At higher dose levels, the exaggerated pharmacology led to dehydration, marked changes in body weight, hemoconcentration, debilitation and death. In studies that included a non-dosing period following treatment, signs of recovery or reversibility were noted in surviving animals. The lowest NOAEL in rats was 3 and 10 mg/kg/day (0.29 and 0.97 times the maximum recommended human dose based on body surface area in males and females respectively) in a 6 month study and 50 mg/kg/day (2.4 times the maximum recommended human dose based on body surface area) in a one month study in CD-1 mice.

In dogs, tenapanor was generally well tolerated and clinical signs related to the expected pharmacology of tenapanor were limited to sporadic abnormal excreta at most dose levels. The NOAEL in all dog studies was 1000 mg/kg/day (>100 times the maximum recommended human dose based on body surface area) and was independent of study duration from 28 days to 9 months.

Carcinogenicity: The carcinogenic potential of tenapanor was assessed in a 6-month carcinogenicity study in TgrasH2 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 TgrasH2 mice at oral doses up to 165 mg/kg/day (approximately 8 times the maximum recommended human dose, based on the body surface area).

Genotoxicity: IBSRELA was not mutagenic or clastogenic or genotoxic in the following tests with and without metabolic activation: *in vitro* bacterial reverse mutation (Ames) assays or *in vitro* chromosomal aberration assay in cultured human peripheral blood lymphocytes or *in vivo* micronucleus assays in mice and rats.

Reproductive and Developmental Toxicology: 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).

Juvenile Toxicity: 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.

In an 8-week definitive juvenile toxicology study followed by a 4-week recovery period, tenapanor administered to juvenile rats from PND 5 through PND 61 at dose levels of 0.03, 0.1 and 0.3 mg/kg/day resulted in tenapanor-related deaths, reduced mean absolute body weights (up to 15.8% and 16.8% in males and females, respectively) and shortened mean tibial lengths (starting on PND 22 and 19 in males and females, respectively) in the 0.3 mg/kg/day dose group [See 1.1 Pediatrics, 2 CONTRAINDICATIONS, 7.1.3 Pediatrics, 4.2 Recommended Dose and Dosage Adjustment].

A 60-day juvenile toxicity study was performed to determine the tolerability of tenapanor when given via oral gavage to juvenile Crl:CD(SD) Sprague-Dawley rats on PND 21 through 80 at dose levels of 0.1, 0.3, 0.7 (male) and 1.0 (female) mg/kg/day. Persistence or progression of any effects following a 14-day recovery period were also evaluated. No tenapanor-related mortality occurred on study. Abnormal consistency of the feces, and reductions in body weight and food consumption were observed in male and female rats at doses above 0.1 mg/kg/day. In the male rats at 0.3 and 0.7 mg/kg/day, there were decreases in tibia length recorded during the in-life phase of the study and a reduction in urine pH at the end of the dose. Therefore, the no-observed adverse-effect level (NOAEL) was considered to be 0.1 mg/kg/day in both sexes.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrIBSRELA®

Tenapanor tablet

Read this carefully before you start taking **IBSRELA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IBSRELA**.

Serious Warnings and Precautions

- **Do not give IBSRELA to children who are less than 6 years of age.** IBSRELA can cause severe diarrhea in children. This can lead to severe dehydration (loss of large amounts of water and salt in the body). This can seriously harm a child who is less than 6 years of age.

- **IBSRELA is not recommended for use in children between 6 years and 18 years of age.** It is not known if IBSRELA is safe in children and adolescents between 6 years and 18 years of age. It may harm them.

What is IBSRELA used for?

- IBSRELA is used in adults (18 years of age and older) to treat a condition called irritable bowel syndrome with constipation (IBS-C).

How does IBSRELA work?

IBSRELA is a medication in a class called an inhibitor of the sodium / hydrogen exchanger 3 (NHE3). It reduces the amount of sodium that your bowels absorb. This increases the release of fluid into the bowels. IBSRELA eases abdominal pain and increases the number of bowel movements. You should notice improvement within the first week of taking IBSRELA.

What are the ingredients in IBSRELA?

Medicinal ingredients: tenapanor (as tenapanor hydrochloride).

Non-medicinal ingredients: colloidal silicon dioxide, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid, and the coating agent OPADRY®, which consists of hypromellose, titanium dioxide and triacetin.

IBSRELA comes in the following dosage forms:

As tablets that contain 50 mg of tenapanor.

Do not use IBSRELA if:

- you are allergic to tenapanor hydrochloride or any of the other ingredients in IBSRELA;
- you are allergic to a component of the IBSRELA container;
- you are less than 6 years of age;
- a doctor has told you that you have or you might have a bowel blockage, called a gastrointestinal obstruction.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IBSRELA. Talk about any health conditions or problems you may have, including if you:

- Are pregnant, think you may be pregnant, or plan to become pregnant. It is not known if IBSRELA will harm your unborn baby.
- Are breast-feeding or planning to breastfeed, although IBSRELA is not expected to pass into your breast milk and harm your baby. Talk with your doctor about the best way to feed your baby.

Other warnings you should know about:

Diarrhea: IBSRELA can cause diarrhea. It can sometimes be severe. Severe diarrhea can cause dehydration. Stop taking IBSRELA and get immediate medical help if you get severe diarrhea (persistent watery stools).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

When IBSRELA is co-administered with enalapril you should monitor blood pressure and, if needed, your healthcare professional could ask you to increase the dosage of enalapril.

The following may interact with IBSRELA:

- Enalapril

How to take IBSRELA:

- Take IBSRELA exactly as your doctor tells you to take it.
- Take IBSRELA immediately before breakfast or your first meal of the day. Then, take your next tablet immediately before dinner.
- Swallow the IBSRELA tablet whole.
- Do not crush or chew the tablet.

Usual dose:

Take 1 tablet twice a day.

Overdose:

If you think you, or a person you are caring for, have taken too much IBSRELA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of IBSRELA, skip the missed dose. Take your next dose at the usual time. Never take two doses at the same time to make up for a missed dose.

What are possible side effects from using IBSRELA?
These are not all the possible side effects you may have when taking IBSRELA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:
- Diarrhea (loose, watery stool and passing stools more often)
- An urgent need to pass stool
- Flatulence (passing gas)
- Abdominal bloating or pain
- Abnormal sounds coming from your abdomen
- Inflammation of your nasal passages and throat such as with the common cold
- Dizziness

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Severe diarrhea			√
UNKNOWN			
Allergic reaction: skin rash, hives, itching, swelling including of the face, tongue, throat, mouth or lips, difficulty breathing or swallowing, wheezing, chest tightness.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store IBSRELA at room temperature between 15°C and 30°C.

Keep IBSRELA in the bottle that it comes in.

Protect from moisture.

The IBSRELA bottle contains a desiccant canister to help keep your medicine dry. Do not remove the desiccant canister from the bottle.

Keep out of reach and sight of children.

If you want more information about IBSRELA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://health-products.canada.ca/dpd-bdpp/); the manufacturer's website (https://www.knighttx.com/), by emailing medinfo@knighttx.com or by calling 1-844-483-5636.

This leaflet was prepared by Knight Therapeutics Inc.

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