PDL DRUG REVIEW

Proprietary Name: Ibsrela®
Common Name: tenapanor
PDL Category: GI- Irritable Bowel Syndrome Agents

Comparable Products	Preferred Drug List Status
Amitiza	Preferred with Conditions
Linzess	Preferred with Conditions

Summary

Pharmacology/Usage: Tenapanor, the active ingredient of 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 mainly 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, tenapanor 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.

Indication: For the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

There is no pregnancy category for this medication; however, the risk summary indicates that tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification following oral administration. Thus, maternal use is not expected to result in fetal exposure to the drug. The available data on exposure from a small number of pregnant women have not identified any drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Tablets: 50mg.

Recommended Dosage: Take 50mg PO BID, taken immediately prior to breakfast or the first meal of the day and immediately prior to 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.

There are no dosage adjustment requirements for those with renal or hepatic impairment.

Drug Interactions: Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with Ibsrela®. Monitor for signs related to loss of efficacy and adjust the dosage of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. Monitor blood pressure and increase the dosage of enalapril, if needed, when Ibsrela® is co-administered with enalapril.

Box Warning: Ibsrela® has a box warning regarding the risk of serious dehydration in pediatric patients. Ibsrela® is contraindicated in patients less than 6 years of age. In non-clinical studies in young juvenile rats, administration of tenapanor caused deaths presumed to be due to dehydration. Avoid use of Ibsrela® in patients 6 years to less than

12 years of age. The warning ends that the safety and effectiveness of Ibsrela® have not been established in patients less than 18 years of age.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Ibsrela®) minus reported % incidence for placebo in Trial 1 (26-week, double-blind, placebo-controlled treatment period). Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included diarrhea (12%), abdominal distension (>2%), flatulence (2%), and dizziness (>1%).

Diarrhea was the most common adverse reaction in the 2 phase 3 trials. Severe diarrhea was reported in 2.5% of Ibsrela®-treated patients compared to 0.2% of placebo-treated patients. If severe diarrhea occurs, suspend dosing, and rehydrate patient.

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.

Contraindications: In patients:

- Less than 6 years of age due to the risk of serious dehydration
- With known or suspected mechanical gastrointestinal obstruction.

Manufacturer: Ardelyx, Inc.

Analysis: The safety and efficacy of Ibsrela® were assessed in two double-blind, placebo-controlled, randomized, multicenter trials that included adult patients with IBS-C (Trial 1 and Trial 2). The intent-to-treat analysis population included 620 patients in Trial 1 and 606 patients in Trial 2. The mean age of the patients was 46 years (range 18 to 75), while 80% were female and 64% were white.

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 (NRS) where a score of 0 indicates no pain and 10 indicates very serve 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) and Trial 2 included a 4-week randomized withdrawal (RW) period.

The 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 the components of the primary endpoint (CSBM and abdominal pain), which were pre-specified key secondary endpoints, are presented in the table below, which was adapted from the prescribing information.

	Trial 1			Trial 2		
	Ibsrela® (N=293)	Placebo (N=300)	Treatment Difference	Ibsrela® (N=307)	Placebo (N=299)	Treatment Difference
Responder	37%	24%	13%	27%	19%	8%
NNT *calculated by CHC*	8			13		
Components of Responder Endpoint						
CSBM Responder	47%	33%		34%	29%	
Abdominal Pain Responder	50%	38%		44%	33%	

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.

Place in Therapy: Ibsrela® is a locally acting inhibitor of the sodium/hydrogen exchanger 3 (NHE3) indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults. It is the first product approved with this mechanism of action. This product does have a box warning regarding the risk of serious dehydration in pediatric patients. The warning adds that use is contraindicated in patients less than 6 years of age and should be avoided in patients 6 years to less than 12 years of age. Furthermore, the safety and efficacy of use have not been established in the pediatric population less than 18 years of age. In 2 double-blind, placebo-controlled, phase 3 studies, there were more CSBM responders and abdominal pain responders in those treated with Ibsrela® as compared with placebo. Per the full-text study by Chey et al[2] (Trial 1), a significantly greater proportion in the tenapanor treatment group were 6/12-week combined responders as compared with placebo ($p<0.001$). Per the full-text study by Chey et al[3] (Trial 2), a significantly greater proportion treated with tenapanor met the primary endpoint than placebo ($p=0.020$). Head-to-head comparator studies with other active agents with the same indication were not identified.

There is no evidence at this time to support that Ibsrela® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Ibsrela® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Ibsrela [package insert]. Waltham, MA: Ardelyx, Inc; 2022.
[2] Chey WD, Lembo AJ, Yang Y, et al. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: A 26-week, placebo-controlled phase 3 trial (T3MPO-2). *Am J Gastroenterol.* 2021; 116(6): 1294-1303.
[3] Chey WD, Lembo AJ, Rosenbaum DP, et al. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: A 12-week, placebo-controlled phase 3 trial (T3MPO-1). Am J Gastroenterol. 2020; 115(2): 281-293.