NEW DRUG APPROVAL

Brand Name	Ibsrela®
Generic Name	tenapanor
Drug Manufacturer	Ardelyx, Inc.

New Drug Approval

FDA approval date: September 12, 2019

Review designation: Standard

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 211801

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Irritable bowel syndrome is defined as abdominal discomfort or pain associated with altered bowel habits for at least three days per month in the previous three months, with the absence of organic disease. In North America, the prevalence of irritable bowel syndrome is 5 to 10 percent with peak prevalence from 20 to 39 years of age. Abdominal pain is the most common symptom and often is described as a cramping sensation. The absence of abdominal pain essentially excludes irritable bowel syndrome. Other common symptoms include diarrhea, constipation, or alternating diarrhea and constipation. The goals of treatment are symptom relief and improved quality of life. Exercise, antibiotics, antispasmodics, peppermint oil, and probiotics appear to improve symptoms. Over-the-counter laxatives and antidiarrheals may improve stool frequency but not pain. Treatment with antidepressants and psychological therapies are also effective for improving symptoms compared with usual care. Lubiprostone is effective for the treatment of constipation-predominant irritable bowel syndrome, and alosetron (restrictions for use apply in the United States) and tegaserod (available only for emergency use in the United States) are approved for patients with severe symptoms in whom conventional therapy has been ineffective.

Efficacy

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 1.

Table: 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*]
Responder†	37%	24%	13% [6%, 20%]
Components of Responder Endpoint:			
CSBM Responder‡	47%	33%	
Abdominal Pain Responder§	50%	38%	
Trial 2			
Responder Rates	**IBSRELA N=307**	**Placebo N=299**	**Treatment Difference [95% CI*]**
Responder†	27%	19%	8% [2%, 15%]
Components of Responder Endpoint:			
CSBM Responder‡	34%	29%	
Abdominal Pain Responder§	44%	33%	

* CI: Confidence Interval
† 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.
‡ 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.
§ 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.

Safety

ADVERSE EVENTS

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

WARNINGS & PRECAUTIONS

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

CONTRAINDICATIONS

- Pediatric patients less than 6 years of age.
- Patients with known or suspected mechanical gastrointestinal obstruction.

Clinical Pharmacology

MECHANISMS OF ACTION

Tenapanor 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, 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.

Tenapanor 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.

Dose & Administration

ADULTS

50 mg, orally twice daily.

PEDIATRICS

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

GERIATRICS

Refer to adult dosing, but greater sensitivity of some older individuals cannot be ruled out.

RENAL IMPAIRMENT

No dosage adjustments are needed.

HEPATIC IMPAIRMENT

No dosage adjustments are needed.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 50 mg tenapanor.