

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211801Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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<b>Application Type</b>	NDA
<b>Application Number</b>	211801
<b>PDUFA Goal Date</b>	September 12, 2019
<b>OSE RCM #</b>	2018-1994
<b>Reviewer Name(s)</b>	Yasmeen Abou-Sayed, Pharm D.
<b>Team Leader</b>	Donella Fitzgerald, Pharm D.
<b>Deputy Division Director</b>	Jamie Wilkins, Pharm D., MPH
<b>Review Completion Date</b>	September 9, 2019
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Tenapanor
<b>Trade Name</b>	Ibsrela
<b>Name of Applicant</b>	Ardelyx Inc.
<b>Therapeutic Class</b>	NHE3 (sodium hydrogen antiporter) inhibitor
<b>Formulation(s)</b>	50 mg oral tablets
<b>Dosing Regimen</b>	50 mg twice daily

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## EXECUTIVE SUMMARY

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity llsrela (tenapanor) is necessary to ensure the benefits outweigh its risks. Ardelyx Inc. submitted a New Drug Application (NDA) 211801 for tenapanor with the proposed indication for the treatment of adult patients with irritable bowel syndrome with constipation (IBS-C). The risk associated with tenapanor is diarrhea. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK has determined that a REMS is not necessary to ensure the benefits of tenapanor outweigh its risks. The risk of diarrhea can be self-identified by patients and communicated via professional and patient labeling.

## 1 Introduction

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) llsrela (tenapanor) is necessary to ensure the benefits outweigh its risks. Ardelyx Inc. submitted a New Drug Application (NDA) 211801 for tenapanor with the proposed indication for the treatment of adult patients with irritable bowel syndrome with constipation (IBS-C). This application is under review in the Division of Gastroenterology and Inborn Errors Products (DGIEP). The applicant did not submit a proposed REMS or risk management plan with this application.

## 2 Background

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### 2.1 PRODUCT INFORMATION

llsrela (tenapanor), a new molecular entity (NME)<sup>a</sup>, is a sodium hydrogen exchange 3 (NHE3) inhibitor, proposed for the treatment of irritable bowel syndrome with constipation (IBS-C). NHE3 inhibits the import of sodium into cells, and blocks the export of hydrogen ions, thereby regulating sodium, overall pH, and water absorption in the intestine; blocking NHE3 results in intestinal secretion. Tenapanor is proposed as a 50 milligram (mg) oral tablet to be taken twice daily for chronic therapy.<sup>b</sup> Tenapanor is not currently approved in any jurisdiction.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211801 relevant to this review:

- 9/12/2018: NDA 211801 submission for the treatment of IBS-C received.
- 7/18/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tenapanor.<sup>1</sup>

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<sup>a</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

<sup>b</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

## 3 Therapeutic Context and Treatment Options

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### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder, manifesting as abdominal pain/discomfort and altered bowel function.<sup>2,c</sup> Additionally, clinical manifestations may include cramping, bloating, abdominal distension, flatulence, mucus in stool, urgency for bowel movements, and tenesmus. It is classified into four subtypes depending on the predominant change in bowel habits; IBS-constipation (IBS-C), IBS-diarrhea (IBS-D), IBS-mixed (IBS-M), or unclassified.<sup>3</sup>**Error!**

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**Bookmark not defined.** The worldwide prevalence of IBS is between 5% and 15%, with a prevalence of approximately 12% in the United States, with a higher prevalence in women than men. The prevalence of IBS-C among the IBS subtypes was 35%.<sup>4</sup>**Error! Bookmark not defined.**<sup>d</sup> Despite being a common disorder, a lack of understanding of etiopathogenesis and evaluation strategies results in diagnostic uncertainty, and in turn frustrate both the physician and the patient.<sup>2</sup> The pathophysiology of IBS is not definitively known; it is multifactorial and underlying causes may vary for different patients.

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Traditionally, IBS was thought to be primarily due to visceral hypersensitivity and gastrointestinal motor disturbances. More recently, there is increasing evidence for the contributing factors of infection, immune activation, serotonin dysregulation, bacterial overgrowth, central dysregulation and brain-gut interaction, and genetics.<sup>5</sup> Studies also have shown that chronic stress is associated with the onset and exacerbation of symptoms of IBS.<sup>6</sup>

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment for IBS focuses on symptom relief which may involve dietary and lifestyle modification and/or pharmacologic agents. Depending on the severity of symptoms and response, patients often try a variety of treatments alone or in combination. In patients with mild and intermittent symptoms that do not impair quality of life, lifestyle and dietary modification alone are initially recommended, rather than specific pharmacologic agents. Nonpharmacologic treatment interventions include dietary modification to increase fiber intake, avoiding gluten, lactose, or gas-producing foods, or following a special eating plan called the low fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) diet.<sup>7,8</sup> Additional interventions include lifestyle modifications (e.g., stress relief, increased exercise and sleep) as well as biofeedback and acupuncture.<sup>9,10</sup>

In patients with mild to moderate symptoms who fail to respond to initial management and in patients with moderate to severe symptoms that affect quality of life, pharmacologic therapy is suggested as adjunctive treatment. Pharmacologic treatments are tailored to the subtype of IBS. For IBS-C, over-the-

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<sup>c</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

<sup>d</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

counter (OTC) fiber supplements, laxatives, or enemas may provide relief. Four treatments have been approved by FDA for IBS-C. Amitiza (lubiprostone), a chloride channel activator which increases intestinal fluid secretion, resulting in increased motility in the intestine, was approved for use in IBS-C in 2008.<sup>11</sup> Linzess (linaclotide) is a guanylate cyclase-C agonist which results in increased intestinal fluid and accelerated transit was approved for use in IBS-C in 2012.<sup>12</sup> Trulance (plecanatide) is also a guanylate cyclase-C agonist, and was recently approved for use in IBS-C in 2018.<sup>13</sup> Zelnorm (tegaserod), is a 5-hydroxytryptamine (serotonin) 4 receptor agonist that stimulates release of neurotransmitters and increases colonic motility. It was initially approved in 2002, then withdrawn from the market in 2007 when the Agency requested Novartis to suspend U.S. marketing and sales due to a retrospective analysis of pooled clinical trial data showing an imbalance in cardiovascular ischemic adverse events. The Agency approved a reintroduction to the market in March 2019, with revised labeling to limit the indication to treatment of adult women less than 65 years of age with irritable bowel syndrome with constipation (IBS-C).<sup>14</sup> Despite the availability of new therapies, there is still a need for treatment options for patients with IBS-C that are distinctly different than the currently available approved therapies.

## 4 Benefit Assessment

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The efficacy of tenapanor is supported by evidence from two pivotal phase 3 clinical trials, 606 patients in study TEN-01-301 (301; National Clinical Trial [NCT] 02621892) and 592 patients in study TEN-01-302 (302; NCT02686138).<sup>15</sup> Both trials were conducted as double blind, randomized, placebo-controlled, and multi-center studies (120-122 sites across the United States), evaluating the efficacy and safety of 50 mg of tenapanor administered twice daily. Subjects were ambulatory and met the definition of IBS-C using Rome III Criteria<sup>e,16</sup> for the diagnosis of IBS. The design of these 2 trials was identical through the first 12 weeks of treatment, and thereafter differed in that 301 included a 4-week randomized withdrawal (RW) period, and 302 continued for 14 additional weeks of double-blind treatment (total of 26 weeks) to evaluate long-term efficacy.

The primary efficacy endpoint was based on a subject being a weekly responder for at least 6 of the first 12 weeks of treatment (designated “6/12 weeks”). For the 6/12 week overall combined primary responder endpoint, a subject was required to achieve at least a 30% reduction from baseline in mean abdominal pain score and an increase of at least 1 complete spontaneous bowel movement (CSBM) from baseline, both in the same week, for at least 6 of the first 12 weeks of treatment. The responder rates for the two components of the primary endpoint (CSBMs and abdominal pain) were pre-specified key secondary endpoints. IBS symptoms were captured using a telephone diary (Interactive Voice Response System (IVRS) diary), and patients were asked nine items daily and four items weekly. The

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<sup>e</sup> The criteria for a diagnosis of irritable bowel syndrome (IBS) require that a person be experiencing chronic abdominal pain or discomfort at least three days over the course of the last three months, with an onset of symptoms at least six months prior.

recall period was “the past 24 hours” for the daily items and was “the past week” for the weekly items. Symptom severity based on the IBS Symptom eDiary/IVRS was assessed daily.

Both studies achieved statistically significant results on the primary endpoint (301,  $p = 0.02$ ; 302,  $p < 0.001$ ). On the first key secondary endpoint, overall CSBM responder rate was not statistically significant in study 301 ( $p = 0.299$ ) but was in study 302 ( $p < 0.001$ ). On the second key secondary endpoint of a reduction in abdominal pain, both studies achieved statistically significant result (301,  $p = 0.01$ ; 302,  $p = 0.003$ ).

Overall, the clinical reviewer has concluded, based on the collective evidence from studies 301 and 302, tenapanor demonstrated efficacy for the treatment of IBS-C in adults.<sup>17,f</sup>

## 5 Risk Assessment & Safe-Use Conditions

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The core safety analysis set for IBS-C consists of five phase 2 and 3 trials: 301, 302, TEN-01-303(303; NCT02727751), D5612C00001 (NCT01923428), and RDX5791-201 (NCT01340053), and contains data from 1343 subjects who received tenapanor.<sup>18</sup> Study 303 is a phase 3, open-label long-term safety study, designed to provide a total of 52 weeks of drug exposure to patients previously enrolled in studies 301 and 302. Studies RDX5791-201 and D5612C00001 were phase 2 studies designed to evaluate pharmacodynamic properties, efficacy, and safety of tenapanor.

There were no deaths in the IBS-C development program. Of patients enrolled in the core safety analysis set, 7.6% (99/1343) of tenapanor patients discontinued due to adverse events (AEs), compared to 0.8% of placebo treated patients. Most AEs leading to discontinuation were gastrointestinal in nature, with 6.5% of patients discontinuing tenapanor due to diarrhea, compared to 0.7% of patients on placebo. The most commonly reported AE with tenapanor was diarrhea, occurring in 13% of tenapanor patients versus 2.3% of placebo patients, followed by abdominal distention in 2% of tenapanor patients and 0.14% of placebo patients.

### 5.1 SEVERE ADVERSE EVENTS

Severe adverse events (SAEs) occurred rarely and in comparable proportion of patients on tenapanor or placebo. In the IBS-C clinical development program, 25 SAEs occurred in tenapanor patients (1.86%) and 11 on placebo (1.49%). The majority of SAEs that occurred in tenapanor patients were gastrointestinal in nature, most commonly diarrhea.

### 5.2 ADVERSE EVENTS OF SPECIAL INTEREST

#### 5.2.1 Diarrhea

Of the 25 severe AEs that occurred on tenapanor, 16 were attributed to severe diarrhea (1.19%). Diarrhea is expected given the mechanism of action of the drug, which acts locally in the intestine as a

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<sup>f</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

secretagogue.<sup>8</sup> The applicant proposes using labeling to communicate the risk of diarrhea in the Warnings and Precautions section of the label and in section 6, Adverse Reactions. To inform patients and increase the prominence of this information as well as to promote its mitigation, DGIEP has determined that this information will also be included in section 17, Patient Counseling Information, and in the Medication Guide.

Although tenapanor is not indicated in pediatric patients, nor has it been studied in patients under the age of 18, the label will include a boxed warning to indicate tenapanor is contraindicated for use in patients under 6 years of age, should be avoided in patients 6 to 12 years of age, and that safety and effectiveness of tenapanor has not been established in pediatric patients under 18 years of age, as pediatric patients are at increased risk for hypovolemia associated with diarrhea.<sup>19</sup> This labeling recommendation is based on nonclinical toxicity studies in juvenile rats, in which findings demonstrated premature mortality.<sup>20</sup> A similar boxed warning and contraindication is included in the PIs for linaclotide and plecanatide, based on similar findings.<sup>12,13</sup>

## **6 Expected Postmarket Use**

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Patients are likely to be treated by multiple prescriber types including general practitioners and gastroenterologists, who likely prescribe the existing approved treatments for IBS-C: lubiprostone, linaclotide, plecanatide, and tegaserod. Tenapanor will be prescribed primarily in outpatient settings.

## **7 Risk Management Activities Proposed by the Applicant**

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The Applicant did not propose any risk management activities for tenapanor beyond routine pharmacovigilance and labeling.

## **8 Discussion of Need for a REMS**

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The Clinical Reviewer recommends approval of tenapanor on the basis of the efficacy and safety information currently available.<sup>18</sup> Tenapanor was demonstrated to be effective for the treatment of adults with IBS-C in two adequate and well controlled trials (Study 301 and Study 302) that were submitted with this application. The safety profile of tenapanor supports approval, with AEs occurring primarily in the gastrointestinal tract. Diarrhea was the most common AE, which is expected given the mechanism of action of the drug, occurring in approximately 13% of treated patients in the development program (compared to 2.3% on placebo). Severe diarrhea occurred in 1.19 % of all tenapanor treated patients (compared to 0.2% on placebo) and diarrhea was the most common AE

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<sup>8</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

leading to discontinuation. Diarrhea is an adverse event that patients can self-identify and initiate treatment. The risk will be communicated in the Warnings and Precautions section of the label, section 6 Adverse Reactions, section 17 Patient Counseling Information, and in a Medication Guide to inform prescribers and patients. In addition, due to the risk of hypovolemia associated with diarrhea in pediatric patients, labeling will include a boxed warning to advise against use in pediatric patients, including a contraindication under the age of 6, this information is also included in boxed warnings for other treatments for IBS-C plecanatide and linaclotide.

Tenapanor represents a new treatment option with a novel mechanism of action as a NHE3 inhibitor, to complement currently approved therapies for patients with IBS-C. IBS-C affects a large population and there is a continued unmet medical need in select patients for who may not respond to currently approved therapies.

DRISK and the Division of Gastroenterology and Inborn Errors Products (DGIEP) agree that if approved, a REMS is not necessary to ensure the benefits of tegaserod outweigh its risks.

## 9 Conclusion & Recommendations

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Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for tenapanor to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should DGIEP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

## 10 Appendices

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### 10.1 REFERENCES

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<sup>2</sup> Sayuk GS, Gyawali CP. Irritable bowel syndrome: modern concepts and management options. *Am J Med.* 2015;128(8):817-827.

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- <sup>14</sup> Zelnorm. Prescribing Information (last updated 3/2019).
- <sup>15</sup> Ardelyx Inc. Summary of Clinical Efficacy for tenapanor, September 12, 2018.
- <sup>16</sup> Ford, A. et al. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gastroenterology*. 2013;145(6):1262.
- <sup>17</sup> Division of Gastroenterology and Inborn Errors Products. Draft Unireview for lbsrela (tenapanor), NDA 211801, August 22, 2019.
- <sup>18</sup> Ardelyx Inc. Summary of Clinical Safety for tenapanor, September 12, 2018.
- <sup>19</sup> Somers, MJ. Clinical assessment and diagnosis of hypovolemia (dehydration) in children. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on August 20, 2019.)
- <sup>20</sup> Ardelyx Inc. Draft Prescribing Information for tenapanor, September 12, 2018.

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