

A SPECIAL MEETING REVIEW EDITION

Highlights in IBS-C From the American College of Gastroenterology 2025 Annual Scientific Meeting

A Review of Selected Presentations From the ACG 2025 Annual Scientific Meeting
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Special Reporting on:

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Tenapanor Improves Abdominal Bloating Symptoms in Patients With IBS-C Experiencing Moderate-to-Severe Bloating

Abdominal bloating is a key symptom of irritable bowel syndrome with constipation (IBS-C) that has a significant influence on patient-reported outcomes, but is not included in the Rome IV diagnostic criteria.^{1,2} In 3 randomized trials, including a phase 2b trial and the phase 3 T3MPO-1 and T3MPO-2 trials, tenapanor 50 mg twice daily demonstrated improvements in abdominal symptoms over placebo.³⁻⁵ However, the effects of tenapanor on bloating have not been well defined.

At the American College of Gastroenterology's 2025 Annual Scientific Meeting & Postgraduate Course (henceforth referred to as the ACG 2025 Annual Scientific Meeting), Staller and colleagues presented results of a post hoc analysis from these 3 trials evaluating the effects of 12 weeks of tenapanor on abdominal bloating in 1253 patients with moderate-to-severe bloating at baseline.⁶ Daily abdominal bloating was assessed via phone diaries, with symptoms rates on a scale of 0 to

10 and categorized as mild (0-3), moderate (4-7), or severe (8-10). Average weekly bloating scores were calculated for each week, with at least 4 days of abdominal bloating reported.

In the cohort of patients with moderate-to-severe bloating at baseline, the mean age was 45 years, 83% were female, 64% were White, and 31% were Black/African American, and the mean duration of IBS-C symptoms before randomization was 11.4 years.

The analysis found a consistent, significantly greater reduction in average weekly bloating score with tenapanor compared with placebo over the first 12 weeks (Figure 1). At week 12, the least-squares (LS) mean change in average weekly abdominal bloating score was -2.66 in the tenapanor arm and -2.10 in the placebo arm, for a LS mean difference of -0.57 ($P=.0003$).

The analysis also reported a faster improvement in bloating with tenapanor compared with placebo. By week 1, the cumulative probability of

achieving a 30% or greater reduction in weekly bloating score was 18.0% with tenapanor vs 8.1% with placebo. This increased to 51.3% and 41.3%, respectively, at week 5, and 61.1% and 51.3%, respectively, at week 8.

The median time to onset of achieving a 30% or greater reduction from baseline in average weekly bloating score was 5 weeks with tenapanor vs 8 weeks with placebo ($P<.0001$). At week 12, improvements in average weekly bloating score of 50% or greater were achieved by 49.3% of patients in the tenapanor arm and 40.8% of patients in the placebo arm ($P=.0007$).

In the safety analysis, the incidence of study drug-related treatment-emergent adverse events (TEAEs) was 19.7% with tenapanor and 8.6% with placebo, and the incidence of serious TEAEs was 1.3% and 1.1%, respectively. The most frequent study drug-related TEAE associated with tenapanor was diarrhea, reported in 13.1% of patients, compared with 1.6% of patients receiving placebo.

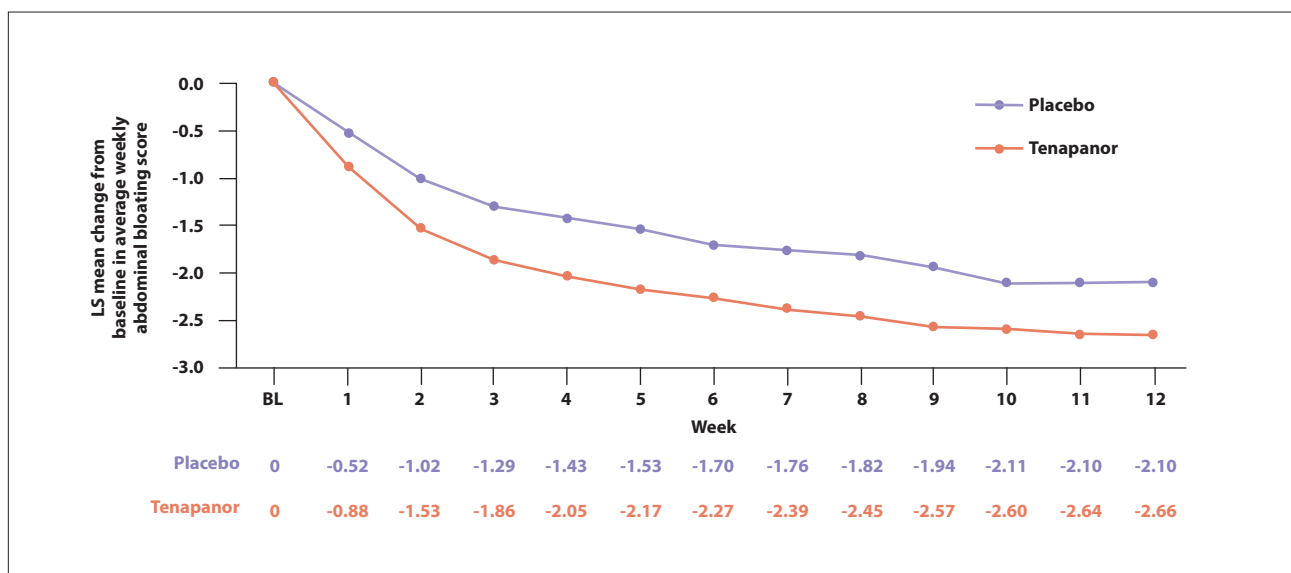


Figure 1. LS mean change from baseline in average weekly abdominal bloating score in patients with moderate-to-severe bloating at baseline (pooled analysis set).

LS, least-squares.

Adapted from Staller K et al. Presented at: American College of Gastroenterology 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona, USA. Abstract P0809.⁶

Investigators cautioned that there are limitations with their analysis, including a lack of standardization of bloating severity assessment and unclear generalizability of this clinical trial population to real-world practice. However, they concluded that tenapanor may provide clinically meaningful reductions in bloating in patients with IBS-C that can be observed as soon as 1 week after starting treatment.

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Individuals with IBS-C often suffer from abdominal sensory symptoms other than pain. Bloating is extremely common and a chief complaint of many individuals seeking care. This study validates that tenapanor efficiently and persistently reduces bloating in patients with IBS-C.

—Darren M. Brenner, MD

Plecanatide Is Efficacious in Women Aged 18 to 40 Years With IBS-C and Bloating: A Pooled Analysis of Two Phase 3, Randomized, Placebo-Controlled Trials

Plecanatide is a guanylate cyclase-C agonist that is approved by the US Food and Drug Administration (FDA) for use in adults with chronic idiopathic constipation (CIC) or IBS-C.¹ In 2 randomized, phase 3, placebo-controlled trials, plecanatide 3 mg (the FDA-approved dose) was associated with significant improvements in bowel movement frequency and other gastrointestinal symptoms in patients with IBS-C.^{1,2} In a post hoc analysis, the benefits of plecanatide also demonstrated benefit in patients with moderate-to-severe bloating at baseline.³

At the ACG 2025 Annual Scientific Meeting, Brenner and colleagues presented a post hoc analysis from these trials, reporting on the efficacy and safety of plecanatide in the subset of women aged 18 to 40 years with IBS-C and bloating, defined as a baseline bloating score of 1 or greater on a scale from 0 (no bloating) to 10 (worst possible bloating), and with a BMI of 18 to 40.⁴

The trials were identically designed,

enrolling a total of 2189 adults with IBS-C who were randomly assigned to plecanatide 3 mg, plecanatide 6 mg, or placebo once daily for 12 weeks.³

The current analysis included 651 female adults with IBS-C with a median age of 31 years and with bloating that was moderate or severe at baseline in 71.3% of patients.⁴ Plecanatide administered at either 3 mg or 6 mg was associated with a significant improvement over placebo

in the proportion of patients attaining a 3-variable composite response incorporating abdominal pain, bloating, and complete spontaneous bowel movements (CSBMs) per week.

The efficacy benefit with plecanatide over placebo was observed whether the threshold for improvement in pain and bloating was at least 2 points, at least 30%, or at least 40%, and whether the threshold for completeness of bowel movements was at least 1 or

Bloating is a common and distressing IBS-C symptom among women aged 18 to 40 years, and plecanatide significantly reduces it and abdominal pain while concurrently improving rates of complete spontaneous bowel movements. These findings support plecanatide's relevance as a highly effective therapeutic option for comprehensive symptom relief in younger female patients with IBS-C with bloating.

—Darren M. Brenner, MD

Table 1. IBS-C Trisymptom Composite Responders in Women 18-40 Years With Mild or Moderate/Severe Baseline Bloating Intensity

IBS-C trisymptom composite responders with mild baseline bloating intensity			
Criterion	Plecanatide 3 mg (n=65) ^a	Plecanatide 6 mg (n=71) ^a	Placebo (n=51)
≥2-point ↓ in pain + bloating + ≥1 CSBM/wk	15.4%	19.7%	3.9%
≥2-point ↓ in pain + bloating + ≥2 CSBM/wk	15.4%	19.7%	2.0%
≥30% ↓ in pain + bloating + ≥1 CSBM/wk	21.5%	26.8%	11.8%
≥30% ↓ in pain + bloating + ≥2 CSBM/wk	21.5%	25.4%	5.9%
≥40% ↓ in pain + bloating + ≥1 CSBM/wk	18.5%	22.5%	5.9%
≥40% ↓ in pain + bloating + ≥2 CSBM/wk	18.5%	22.5%	2.0%
IBS-C trisymptom composite responders with moderate/severe baseline bloating intensity			
Criterion	Plecanatide 3 mg (n=155) ^a	Plecanatide 6 mg (n=147) ^a	Placebo (n=162)
≥2-point ↓ in pain + bloating + ≥1 CSBM/wk	25.2%	22.4%	11.1%
≥2-point ↓ in pain + bloating + ≥2 CSBM/wk	21.9%	17.0%	6.8%
≥30% ↓ in pain + bloating + ≥1 CSBM/wk	25.8%	21.8%	12.3%
≥30% ↓ in pain + bloating + ≥2 CSBM/wk	21.9%	16.3%	8.0%
≥40% ↓ in pain + bloating + ≥1 CSBM/wk	18.7%	18.4%	10.5%
≥40% ↓ in pain + bloating + ≥2 CSBM/wk	16.8%	12.2%	6.8%

^a*P*<.05 vs placebo.

CSBM, complete spontaneous bowel movement; IBS-C, irritable bowel syndrome with constipation; wk, week.

Adapted from Brenner DM et al. Presented at: American College of Gastroenterology 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona, USA. Abstract P5097.⁴

at least 2 CSBMs per week, with all 3 symptoms improving in the same week for at least 6 of 12 weeks. In subgroup analyses, most composite endpoints remained significantly improved with plecanatide over placebo at both doses, regardless of baseline bloating intensity (Table 1).

The rate of AEs of any grade was 27.7% with plecanatide 3 mg, 22.5% with plecanatide 6 mg, and 18.3% with placebo. The most common AE was diarrhea, reported in 3.6% of patients receiving plecanatide 3 mg, 3.7% of patients receiving plecanatide

6 mg, and no patient receiving placebo. Diarrhea appeared to be more frequent in patients with moderate-to-severe bloating (5.2% with plecanatide 3 mg and 3.4% with plecanatide 6 mg) than in patients with mild bloating at baseline (0% and 4.2%, respectively).

Investigators concluded that plecanatide demonstrated simultaneous and significant improvements in abdominal pain, bloating, and CSBM frequency in women aged 18 to 40 years with IBS-C and bloating, and these differences were observed regardless of baseline bloating intensity.

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Efficacy and Safety of Tenapanor in IBS-C: A Systematic Review and Meta-Analysis

Tenapanor is a locally acting inhibitor of sodium/hydrogen exchanger isoform 3 (NHE3) that received FDA approval

in 2019 for the treatment of IBS-C.¹ By inhibiting sodium and phosphate absorption into the gastrointestinal tract, tenapanor causes fluid retention

and softening of stool. Tenapanor also reduces abdominal pain through its effects on visceral hypersensitivity and intestinal permeability.¹

Tenapanor was compared with placebo in 3 randomized trials in patients with IBS-C aged 18 to 75 years.²⁻⁴ In a phase 2 trial, 365 patients were randomly assigned to tenapanor at 5 mg, 20 mg, or 50 mg, or placebo twice daily for 12 weeks.² The randomized, phase 3 T3MPO-1 trial compared tenapanor 50 mg twice daily vs placebo for 12 weeks followed by a 4-week crossover period in 629 patients.³ The randomized, phase 3 T3MPO-2 trial compared tenapanor 50 mg vs placebo twice daily for 26 weeks.⁴ All 3 trials demonstrated a benefit in a composite primary endpoint incorporating abdominal pain and CSBM.²⁻⁴

At the ACG 2025 Annual Scientific Meeting, Aref and colleagues reported results of a meta-analysis evaluating the efficacy and safety of tenapanor across these 3 randomized trials that enrolled a total of 1378 patients.⁵ Tenapanor was associated with significant improvements over placebo in multiple symptoms, including abdominal bloating, cramping, discomfort, fullness, pain, and CSBM (Table 2).

In regard to safety, tenapanor was associated with a significant increase over placebo in the incidence of treatment-related adverse events (TRAEs) (risk ratio [RR], 2.3; 95% CI, 1.72-3.06; $P < .01$) and AEs lead-

Table 2. Efficacy Outcomes With Tenapanor vs Placebo in a Meta-Analysis of 3 Randomized Trials

Symptom	Risk ratio with tenapanor vs placebo (95% CI)	P value
Abdominal bloating	1.32 (1.15-1.51)	<.01
Cramping	1.27 (1.13-1.44)	<.01
Discomfort	1.37 (1.21-1.56)	<.01
Fullness	1.37 (1.20-1.58)	<.01
Pain	1.37 (1.17-1.49)	<.01
CSBM	1.54 (1.24-1.91)	<.01

CSBM, complete spontaneous bowel movement.

Adapted from Aref A et al. Presented at: American College of Gastroenterology 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona, USA. Abstract P2933.⁵

ing to treatment discontinuation (RR, 9.08; 95% CI, 3.63-22.71; $P < .01$). The most common AE with tenapanor was diarrhea, with a frequency significantly higher than placebo (RR, 5.75; 95% CI, 3.44-9.6; $P < .01$). There was no significant increase in the rate of serious AEs with tenapanor vs placebo. Tenapanor was also associated with a significant reduction in the use of rescue medications compared with placebo (RR, 0.77; 95% CI, 0.68-0.88; $P < .01$).

The investigators concluded that tenapanor was significantly

more effective than placebo across endpoints, particularly in regards to abdominal pain. They noted that, although all 3 trials were multicenter and included patients with similar baseline characteristics, the population was primarily White females. Moreover, the studies used the older Rome III criteria and relied on subjective patient-reported outcomes and diary entries. Additional research is warranted to compare tenapanor with other current therapies for IBS-C.

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IBS-C is characterized by both abdominal and bowel symptoms, and patients often seek consultation when conservative/over-the-counter options have failed. This systematic review and meta-analysis confirmed that tenapanor is both safe and effective in the management of not only global but individual (abdominal bloating, cramping, discomfort, fullness, pain, and complete spontaneous bowel movements) symptoms in individuals with IBS-C.

—Darren M. Brenner, MD

Reduction in Gastrointestinal Visits and Portal Messaging Following Tenapanor Initiation in Patients in Community Gastrointestinal Practices

IBS-C is associated with greater health care resource utilization (HCRU).¹ This may increase the use of electronic health record (EHR) systems, including messaging portals, which can increase provider workload when used at high volumes.² At the ACG 2025 Annual Scientific Meeting, Fossa and colleagues presented results of an observational study analyzing the effects of tenapanor on HCRU in patients with IBS-C based on EHR data.³

The analysis included 712 adults with IBS-C receiving care from one of 350 gastroenterology providers practicing

in a larger medical group across 7 states. All patients had at least 1 visit within the past year before starting tenapanor and had initiated tenapanor at least 1 year prior to the EHR data cutoff. Researchers evaluated changes in clinical encounters, defined as the total number of visits and labs, and changes in portal message activity, defined as the total number of messages and patient words, before vs after initiating tenapanor. The portal messaging analysis was limited to patients with at least 1 portal message in the year before starting tenapanor. For both analyses, patients were grouped by tertile as

high, moderate, or low users of clinical encounters and portal messaging.

Before starting tenapanor, the number of regular visits per 12 months ranged from 1 to 2 in the low-utilization tertile to 4 to 15 in the high-utilization tertile, and the number of lab visits ranged from 0 in the low-utilization tertile to 4 to 34 in the high-utilization tertile. In the full analysis set, the median change in within-patient gastrointestinal visits after tenapanor initiation was -1 (interquartile range [IQR], -2 to 0) and the median change in labs was 0 (interquartile range, -3 to 1). How-

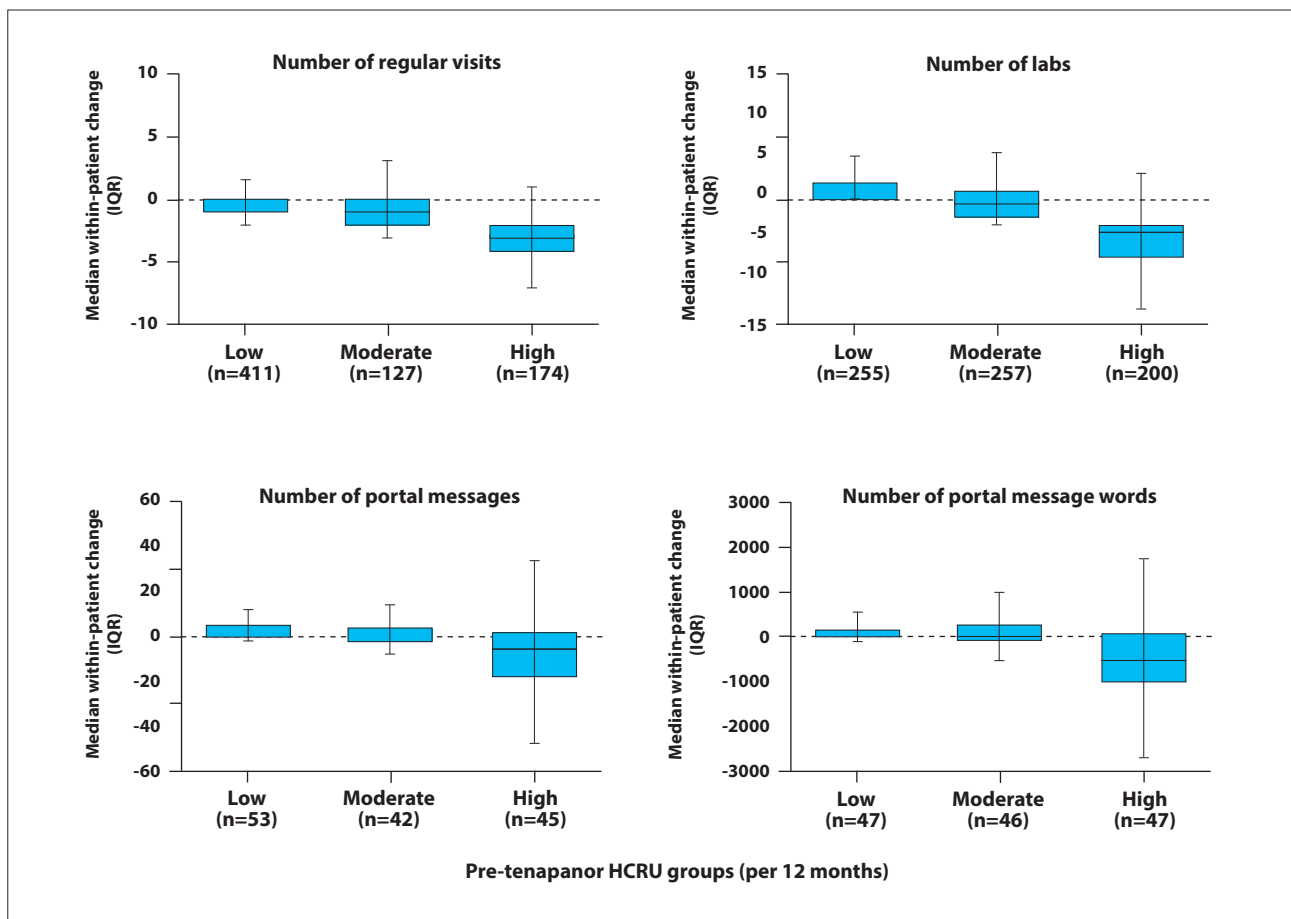


Figure 2. Within-patient change in clinical encounters and portal message activity after tenapanor initiation stratified by tertiles of pre-tenapanor HCRU.

HCRU, health care resource utilization; IQR, interquartile range.

Adapted from Fossa A et al. Presented at: American College of Gastroenterology 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona, USA. Abstract P0787.³

ever, in the high-utilization tertile, the median number of regular visits and labs changed by -3 (IQR, -4 to -2) and -4 (-7 to -3), respectively (Figure 2).

Changes in patient portal messaging after initiating tenapanor were assessed for 140 eligible patients. Before starting tenapanor, the number of messages per 12 months ranged from 1 to 2 in the low-utilization tertile to 10 to 61 in the high-utilization tertile, and the number of message words per 12 months ranged from 4 to 133 and from 606 to 5270, respectively.

In the full analysis set, the median change in the number of portal messages was -1 (IQR, -3 to 3) and the median number of patient message words changed by -38 (IQR, -257 to 227). In the high-message-utilization quartile, the median number of messages changed by -6 (IQR, -19 to 2) and the median number of patient message words changed by -531 (IQR, 1059 to 54) (Figure 2).

Investigators concluded that their preliminary findings indicate that in patients with IBS-C requiring

Healthcare resource utilization remains a concern in the management of IBS-C. Clinically, identifying therapies that can mitigate this burden is of considerable relevance. This study's findings of a reduction in gastrointestinal-related clinical encounters following initiation of tenapanor suggests that tenapanor, when effective, may reduce both financial strain on the healthcare system and the burden of care for both providers and patients.

—Darren M. Brenner, MD

high HCRU, gastrointestinal-related clinical encounters and patient portal message activity are both reduced after starting tenapanor. However, the investigators cautioned that they did not assess medication compliance, they lacked a comparator group, and the portal messaging cohort was small. However, if tenapanor does yield reductions in HCRU, this could benefit both patients and providers and may reduce costs.

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Improvement in Health-Related Quality of Life in Adults With IBS-C Not Achieving Bowel Movement Frequency Criterion: Analysis of Two Phase 3 Plecanatide Trials

Plecanatide demonstrated a significant benefit over placebo in 2 randomized, phase 3 trials in patients with IBS-C.¹ The trials used a composite efficacy endpoint that included changes in CSBMs during the treatment period. The threshold for stool frequency response included in the trial—an increase of at least 1 CSBM from baseline per week for at least one-half of the treatment—was recommended by the FDA.² However, even patients not meeting this threshold may derive other benefits from plecanatide. At the ACG 2025 Annual Scientific Meeting, Brenner and colleagues presented results of a post hoc analysis evaluating changes in health-related QOL (HRQOL) in patients with IBS-C enrolled in the 2 random-

ized phase 3 trials of plecanatide who did not meet the FDA-recommended threshold for a CSBM response.³

The analysis included 928

patients from the trials who were randomly assigned to plecanatide 3 mg (n=428) or placebo (n=500) who did not attain an increase from baseline of

It is a common misnomer that overall well-being in individuals with IBS is directly tied to improved defecation. The visceral mechanisms underlying this disorder are much more complex. This analysis reveals that plecanatide can significantly improve health-related quality of life independent of any changes in bowel habits. These findings suggest plecanatide may offer meaningful symptom relief and functional benefit even when bowel symptoms remain refractory.

—Darren M. Brenner, MD

at least 1 CSBM per week for at least 6 of 12 treatment weeks during the trials. HRQOL was assessed using the Irritable Bowel Syndrome Quality of Life (IBS-QOL) questionnaire, which was administered at baseline and at weeks 4, 8, 12, and 14. A change of at least 14 points from baseline was considered a minimal clinically important difference in IBS-QOL, as previously validated.⁴

Overall, the percentage of patients with a clinically meaningful improvement in IBS-QOL total score at week 12 was significantly higher in the plecanatide group than the placebo group (36.9% vs 28.8%; $P < .01$) (Figure 3). Nonsignificant numerical improvements were observed with plecanatide vs placebo for 7 of the 8 IBS-QOL subdomains, including dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, and relationship.

In the safety analysis, plecanatide was well tolerated and the most common AEs were diarrhea, reported in 4.9% of patients receiving plecanatide 3 mg and 1.0% of patients receiving

placebo, and headache, reported in 2.3% and 2.2% of patients, respectively. In summary, plecanatide was associated with clinically meaningful improvements in IBS-QOL even in patients not meeting the stringent FDA definition for CSBM response. Investigators commented that patients with IBS may experience QOL improvements independent from changes in bowel habits.

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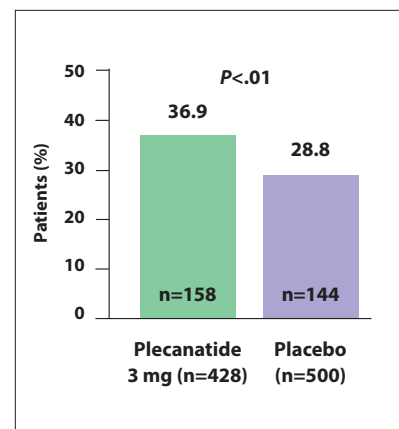


Figure 3. Percentage of CSBM nonresponders^a with a clinically meaningful improvement in IBS-QOL total score^b at week 12 with plecanatide.

^aPatients who did not achieve change from baseline of ≥ 1 CSBM per week during ≥ 6 of 12 weeks of treatment.

^bClinically meaningful defined as ≥ 14 -point improvement from baseline in IBS-QOL total score.

CSBM, complete spontaneous bowel movement; IBS-QOL, Irritable Bowel Syndrome Quality of Life.

Adapted from Brenner DM et al. Presented at: American College of Gastroenterology 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona, USA. Abstract P5098.³

Treatment Satisfaction With Tenapanor: Real-World Survey of Patients With IBS-C

Scott and colleagues presented results of a real-world survey assessing treatment satisfaction, changes in IBS-C symptoms, and changes in QOL in patients receiving tenapanor for IBS-C.¹ The analysis included 537 patients who had initiated tenapanor at least 6.5 weeks prior to the survey start and had a prescription dispensed within the past 90 days. The survey included both objective and open-ended questions. For the open-ended questions, responses were analyzed by researchers and categorized manually on a scale from -2 (negative sentiment) to +2 (positive sentiment), with scores of 1 or 2 considered a positive sentiment. They also manually identified and quantified themes that arose across patient entries. Patient characteristics were not collected as part of the survey.

Approximately 88% of respondents said that they were either somewhat satisfied (23.1%) or extremely satisfied (64.4%) with their treatment experience with tenapanor. Approximately 11% were somewhat dissatisfied (4.7%) or extremely dissatisfied (6.0%). Most patients reported at least some improvement in constipation (95.1%), bloating (75.1%), and

abdominal pain (83.9%) (Figure 4), and 69.1% of patients had improvement of all 3 symptoms.

The majority of respondents reported QOL improvements with tenapanor, indicating that the medication had significantly improved their ability to participate in work (74%) and social activities and exercise (74%). In a multivariate analysis, factors associated

Debilitating symptoms of IBS-C are often associated with compromised quality of life. In this real-world survey, tenapanor improved both classic IBS symptoms and quality of life underscoring tenapanor's potential to improve biopsychosocial functioning.

—Darren M. Brenner, MD

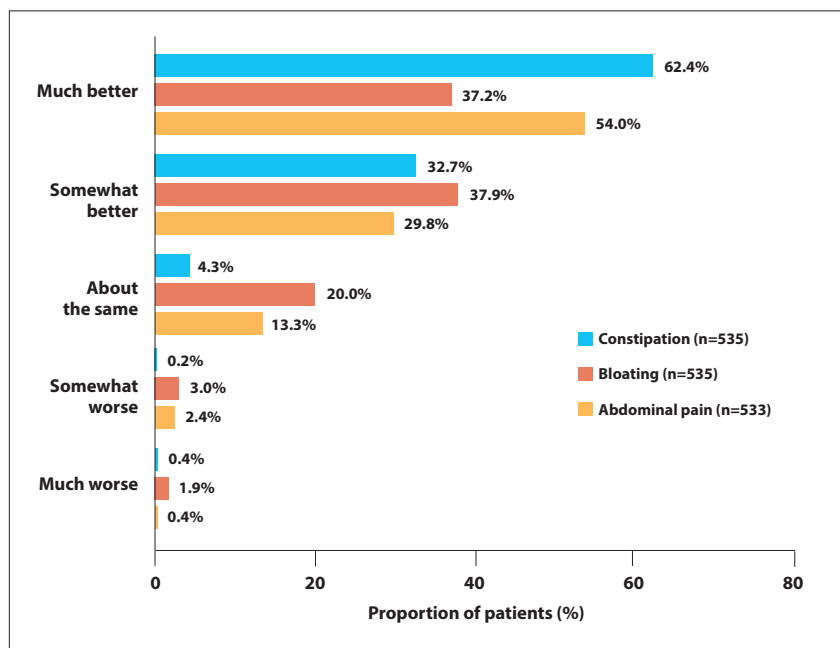


Figure 4. Improvement in IBS-C symptoms with tenapanor.

IBS-C, irritable bowel syndrome with constipation.

Adapted from Scott L et al. Presented at: American College of Gastroenterology 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona, USA. Abstract P5062.¹

with QOL improvement with tenapanor included improvements in constipation (odds ratio [OR], 2.80; 95% CI, 1.10-7.18; $P=.03$), bloating (OR, 3.05; 95% CI, 1.94-4.79; $P<.001$), and abdominal pain (OR, 4.02; 95% CI, 2.33-6.92; $P<.001$). Improvement in constipation was significantly associated with treatment satisfaction (OR, 3.19; 95% CI, 1.23-8.23; $P=.02$).

In the open-ended questions, 93% of patients ($n=298$) expressed positive sentiments about their experience with tenapanor; 87% provided positive statements, including improvements in QOL and symptoms, superiority over other medications, and/or gratitude for the medication. A total of 30% expressed challenges, including side effects and incomplete symptom

resolution. Fewer than 3% stated that potential side effects had negatively affected their QOL.

Comparing tenapanor with their experience with other IBS-C medications ($n=328$), 89% expressed positive sentiments about tenapanor and 76% said that tenapanor was better than other medications they had used, primarily because it worked better and/or had fewer side effects.

The investigators noted that the survey was limited to patients who had received tenapanor for at least 6.5 weeks and thus the findings do not reflect the experiences of patients who discontinue tenapanor earlier. The investigators added that there was a lack of placebo control. Moreover, patients were receiving free product at the time of the survey, which could introduce bias. With those caveats, the researchers concluded that the survey highlights the effectiveness of tenapanor in patients with IBS-C, with most patients reporting treatment satisfaction, improvements in symptoms and QOL, and superiority of tenapanor over other IBS-C medications.

Reference

1. Scott L, Ruddy J, Sibelli A, Gist B, Williams L, Gray TD, Chakraborty S. Treatment satisfaction with tenapanor: real-world survey of patients with IBS-C. Presented at: American College of Gastroenterology 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona, USA. Abstract P5062.

Real-World Safety Analysis of the Constipation-Predominant IBS Treatment Options Linaclotide, Lubiprostone, Plecanatide, and Tenapanor

At the ACG 2025 Annual Scientific Meeting, Andrews and Adler presented results of a real-world analysis of the safety of the 4 medications FDA-approved for IBS-C: linaclotide, lubiprostone, plecanatide, and tenapanor.¹ The researchers obtained safety data from the FDA Adverse Event Reporting System (FAERS) database, an open, public-access database that allows submissions from any individual, including anonymous patients and providers. The database was queried for each

drug from its date of FDA approval through the last available update on June 30, 2024. Reports with other suspected drugs and reports with reasons for use of the medication other than IBS and/or constipation were excluded from the analysis.

Among the 5787 reports for linaclotide, 65.4% of patients were female (median age, 66 years) and 30.8% were male (median age, 73 years). Most events (86.6%) were nonserious; 3.0% of patients were hospitalized, 0.8% were disabled, 0.2% had life-

threatening events, and 0.8% died.

Among the 670 reports for lubiprostone, 73.6% of patients were female (median age, 51 years) and 18.4% were male (median age, 72 years). Approximately one-half of events (48.5%) were nonserious; 18.7% of patients were hospitalized, 2.2% had life-threatening events, 1.9% were disabled, and 1.9% died. Another 32.1% of events had outcomes classified as “other.”

Among the 368 reports for plecanatide, 60.3% of patients were female (median age, 66 years) and

This study aligns with clinical trial data for the currently available FDA-approved IBS-C therapies—linaclotide, lubiprostone, plecanatide, and tenapanor. Most adverse events reported to the FDA are nonserious and predominantly gastrointestinal (eg, nausea, vomiting, abdominal pain, diarrhea) in nature. These results reinforce the established safety profiles of these agents in real-world settings.

—Darren M. Brenner, MD

19.3% were male (median age, 69 years). Most events (85.1%) were nonserious; 3.3% of patients were hospitalized, 1.6% died, and 0.5% had life-threatening events.

Among the 122 reports for tenapanor, 70.5% of patients were female (median age, 70 years) and 16.4%

were male (median age, 60.5 years). Most events (76.2%) were nonserious; 12.3% of patients were hospitalized, and 3.3% died. Another 11.5% reported outcomes classified as “other.”

Across the 4 medications, the most frequent AEs reported were gastrointestinal, most frequently diarrhea,

followed by abdominal pain, bloating, and nausea/vomiting. Several distinct, serious AEs were reported that Dr Andrews noted warrant further investigation, including clinically significant dehydration with linaclotide, and dyspnea and chest pain with lubiprostone.

Dr Andrews cautioned that the FAERS database cannot be used to determine causation or AE incidence rates and that results should be interpreted with caution. He added that prospective trials are needed to further evaluate AEs associated with these agents.

Reference

1. Andrews MB, Adler DG. Real-world safety analysis of the constipation-predominant irritable bowel syndrome treatment options linaclotide, lubiprostone, plecanatide, and tenapanor. Presented at: American College of Gastroenterology 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona, USA. Abstract P5083.

Exploring the Efficacy and Safety of Linaclotide in Pediatric Patients of Functional Constipation and IBS-C: A Meta-Analysis of Randomized Control Trials

The guanylate cyclase-C agonist linaclotide was the first drug to receive FDA approval for the treatment of children aged 6 to 17 years with functional constipation.¹ However, the optimal role of linaclotide in pediatric populations has not been well defined. At the ACG 2025

Annual Scientific Meeting, Khan and colleagues presented results of a meta-analysis evaluating clinical responses, dose-response patterns, and AEs associated with linaclotide in children with functional constipation and IBS-C.²

The analysis included 3 randomized clinical trials of linaclotide in 309

pediatric patients with functional constipation and IBS-C. Across these trials, linaclotide was associated with significant improvements over placebo in stool consistency and straining severity but not in CSBMs, abdominal pain, or bloating. The benefits observed with linaclotide were particularly evident at higher doses. Rates of TEAEs and TRAEs were not significantly different between groups.

With these findings, investigators concluded that linaclotide may have a benefit in improving stool consistency but has minimal effects on other symptoms.

References

1. U.S. Food & Drug Administration. FDA approves first treatment for pediatric functional constipation. <https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-treatment-pediatric-functional-constipation>. Accessed November 3, 2025.
2. Khan MS, Khalid M, Siddiqui E, et al. Exploring the efficacy and safety of linaclotide in pediatric patients of functional constipation and IBS-C: a meta-analysis of randomized control trials. Presented at: American College of Gastroenterology 2025 Annual Scientific Meeting; October 24-29, 2025; Phoenix, Arizona, USA. Abstract P1891.

Children commonly experience FC/IBS-C symptoms; yet there is little data supporting pharmaceutical use. This meta-analysis of 3 studies (2 FC [1 in 2-5 years; 1 in 6-17 years] and 1 IBS-C [7-17 years]) supports using linaclotide for reducing straining and improving stool consistency. There were no significant improvements in CSBMs, abdominal pain, or bloating; however, these results should be interpreted cautiously, given the small sample sizes, differences in populations (age ranges), and the fact that these studies were primarily powered to detect changes in spontaneous bowel movements, not CSBMs.

—Darren M. Brenner, MD

IBSRELA (tenapanor) tablets, for oral use Brief Summary of 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.

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).

6.2 Postmarketing Experience

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.

Hypersensitivity reactions: pruritis, rash, and urticaria

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 [see *Clinical Pharmacology (12.3)*]. 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. When enalapril was coadministered with tenapanor (30 mg twice daily for five days, a dosage 0.6 times the recommended dosage), the peak exposure (C_{max}) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by approximately 50% to 65% compared to when enalapril was administered alone [see *Clinical Pharmacology (12.3)*].

Monitor blood pressure and increase the dosage of enalapril, if needed, when IBSRELA is coadministered with enalapril.

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).

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/day 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

Tenapanor and its major metabolite, M1, were not detected in the breast milk of lactating women (see *Data*). In adults, concentrations of tenapanor were below the limit of quantification in plasma following multiple doses of IBSRELA [see *Clinical Pharmacology (12.3)*]. Maternal use of IBSRELA is not expected to result in exposure to tenapanor or its major metabolite in breastfed infants. There is no information on the effects of tenapanor or its major metabolite 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.

Data

A clinical lactation study was conducted in seven healthy adult women who were 22 to 37 years of age. Following oral administration of IBSRELA 50 mg twice daily for 3 days, the concentrations of tenapanor and its major metabolite were below the limit of quantification (<1 ng/mL and <1 ng/mL) in all breast milk samples collected over 24 hours post-dosing.

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)*].

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)*].



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FLIP THE SCRIPT ON IBS-C

In a survey of adults with IBS-C, only 25% were very satisfied with their prescription treatment.^{1*}

Treatment for IBS-C is not one size fits all.² When your patients aren't getting adequate relief, try a therapy with a different mechanism of action,[†] in a different class.³

IBSRELA
(tenapanor) tablets

IBSRELA WORKS DIFFERENTLY TO IMPROVE THE CONSTIPATION AND ABDOMINAL PAIN OF IBS-C.

INDICATION

IBSRELA (tenapanor) is indicated for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults.

IMPORTANT SAFETY 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. Avoid use of IBSRELA in patients 6 years to less than 12 years of age. The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age.

CONTRAINDICATIONS

- IBSRELA is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
- IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

WARNINGS AND PRECAUTIONS

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).

Please see Brief Summary of full Prescribing Information on the following page.

- 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.

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. If severe diarrhea occurs, suspend dosing and rehydrate patient.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in IBSRELA-treated patients (incidence $\geq 2\%$ and greater than placebo) were: diarrhea (16% vs 4% placebo), abdominal distension (3% vs $<1\%$), flatulence (3% vs 1%) and dizziness (2% vs $<1\%$).

References: 1. Rangan V et al. *Gastroenterology*. 2020;158(3):786-788.e1. 2. Saha L. *World J Gastroenterol*. 2014;20(22):6759-6773. 3. IBSRELA [prescribing information]. Waltham, MA: Ardelyx, Inc.;2022.

*Based on data from a 2015 online survey of 1,667 patients with IBS-C, 311 of the 1,667 patients were prescription-treated and responded to a 5-point scale where 1 is very dissatisfied and 5 is very satisfied.¹

[†]Mechanism of action=sodium/hydrogen exchanger isoform 3 (NHE3) inhibitor.



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IBSRELA
(tenapanor) tablets
50 mg BID



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