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A SPECIAL MEETING REVIEW EDITION

Highlights in IBS-C From the American College of Gastroenterology 2024 Annual Scientific Meeting

A Review of Selected Presentations From the ACG 2024 Annual Scientific Meeting

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Special Reporting on:

- Irritable Bowel Syndrome With Constipation Poses a Substantial Burden to Patient Overall Health Status and Quality of Life: Results From the IBS in America 2024 Real-World Survey
- Reasons for Treatment Discontinuation in Patients With Irritable Bowel Syndrome With Constipation or Chronic Idiopathic Constipation
- Patients With Irritable Bowel Syndrome With Constipation From the IBS in America 2024 Real-World Survey Experience Burdensome Symptoms Beyond Constipation
- Efficacy and Safety of Plecanatide in Treatment of Irritable Bowel Syndrome With Constipation and Chronic Idiopathic Constipation
- Impact of Weight on the Efficacy, Time to Response, and Safety of Linaclotide in Adults With Chronic Idiopathic Constipation or Irritable Bowel Syndrome With Constipation: Post Hoc Descriptive Analysis by Body Mass Index
- An Association Between IBS Quality of Life Score and Symptoms of Abdominal Pain, Bloating, and Cramping in IBS-C: A Pooled Phase 3 Trial Correlation Analysis
- Plecanatide Is Efficacious in Patients With Irritable Bowel Syndrome With Constipation and Bloating: Evaluation Using Trisymptom Composite Endpoints

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Irritable Bowel Syndrome With Constipation Poses a Substantial Burden to Patient Overall Health Status and Quality of Life: Results From the IBS in America 2024 Real-World Survey

Shah and colleagues reported on overall health status and quality of life (QOL) findings from the IBS in America 2024 survey, an online, nationwide survey aimed to gain insight into the experience of patients with irritable bowel syndrome (IBS).[1] This 15-minute survey, conducted in partnership with Health Union between January and April 2024, included US residents aged 18 years and older.

The 284 patients who had IBS with constipation (IBS-C) included in this analysis had completed the IBS in America survey and met additional criteria to participate in an extension survey. These additional criteria included a diagnosis of IBS-C by a health care professional (HCP), currently seeing an HCP to treat their IBS-C, and prior or current use of an over-the-counter or prescription treatment for their IBS-C.

Among the 284 respondents, the mean age was 51.4 years (range, 18-86) and 92% were female. The majority were White (87%) and not Hispanic or Latino (96%). About one-third (32%) were employed full time; others were fully retired (26%), on disability (19%), employed part time (9%), unemployed (5%), a homemaker/stay-at-home parent (4%), self-employed (4%), or a student (2%). Most patients reported group insurance coverage (43%), Medicare (34%) or Medicaid (10%), private insurance (5%), a health insurance exchange (4%), or US military, Veterans Affairs, or TRICARE insurance (2%); 3 patients (1%) had no insurance.

More than one-third of respondents described their overall QOL as poor or fair (39%), which in many cases was attributed to having multiple health conditions. The remaining patients described their QOL as good (38%), very good (20%), or excellent (3%).

A number of comorbidities were

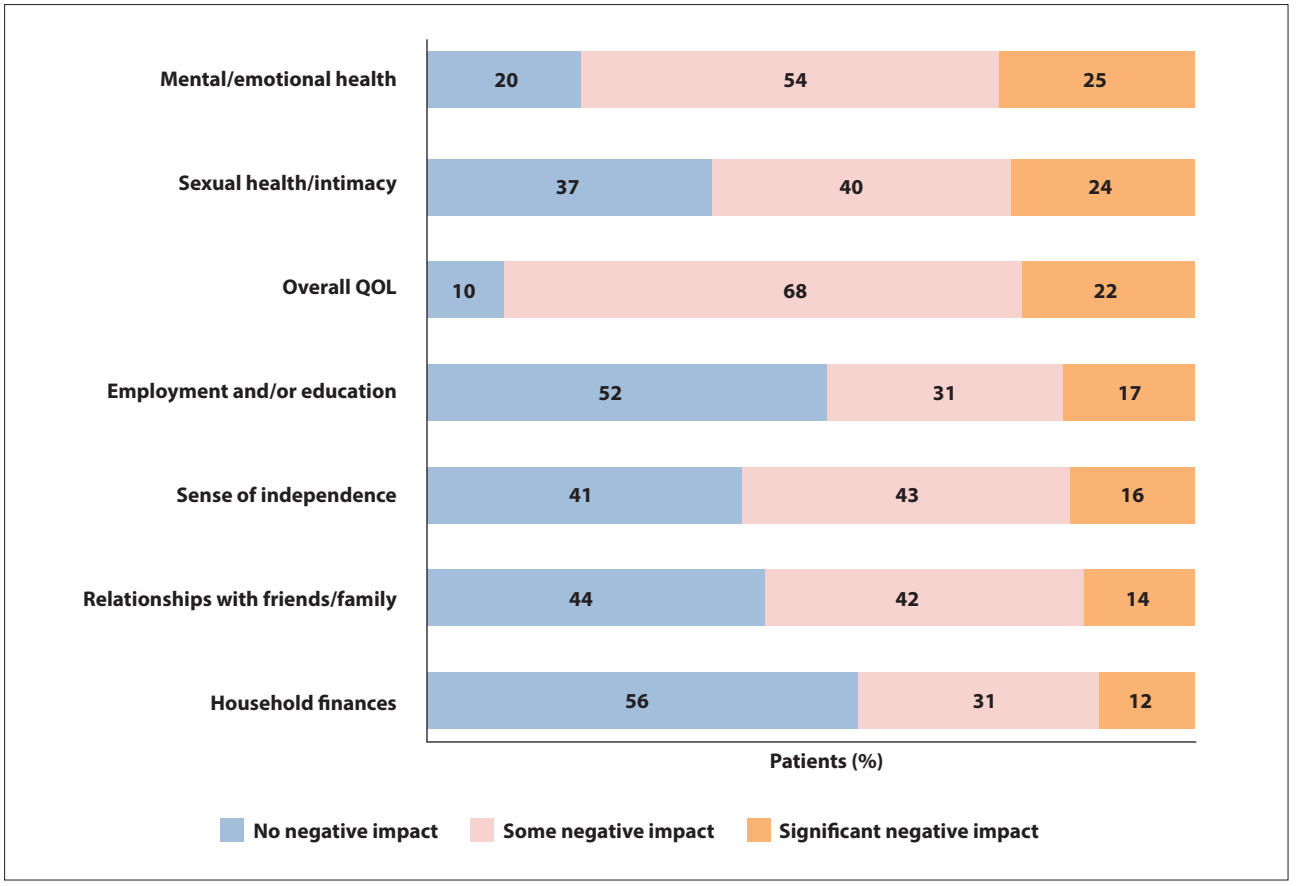

Figure 1. Impact of irritable bowel syndrome with constipation on the QOL of patient respondents in the IBS in America 2024 Real-World Survey. QOL, quality of life. Adapted from Shah E, et al. Abstract P0641. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[1]

In patients with IBS-C, various QOL impairments impact their financial, emotional, physical, and sexual well-being. Notably, 45% feel out of control with their financial situation. Moreover, a majority of patients feel some negative impact on sexual intimacy, their sense of independence, and family/friend relationships. This study provides a nice framework for identifying areas of QOL improvements still needed in IBS-C holistic care.

—Baharak Moshiree, MD, MSc

reported by patient respondents in the survey. The most common of these were allergies (58%), mental health conditions (anxiety [57%] or major depressive disorder/depression [42%]), chronic pain (42%), migraine (37%), chronic dry eye (34%), hyperlipidemia (32%), hypertension (29%), obesity (26%), hypothyroidism (26%), fibromyalgia (25%), and asthma (25%). In the prior 30 days, patients reported their physical health as not good for a mean of 15 days, and their mental health as not good for a mean of 11 days.

The impact of IBS-C on the different facets of QOL is shown in Figure 1. The vast majority of respondents (90%) reported at least some negative (68%) or significant negative (22%) impact to their overall QOL. The effects on mental health were also apparent, with 54% and 25% reporting at least some or significant negative impact, respectively, on their mental/emotional health. Other QOL impacts included those on sexual health/intimacy (40% some negative; 24% significant negative), employment and/or education (31% some negative; 17% significant negative), sense of independence (43% some negative; 16% significant negative), relationships with friends/family (42% some negative; 14% significant negative), and household finances (31% some negative; 12% significant negative).

Only 23% of respondents strongly agreed with the statement "IBS does not stop me from doing the things I enjoy"; the remaining respondents either strongly disagreed (26%) or were neutral (51%) to this statement. About 1 in 3 respondents (31%) reported having the support needed to help manage their IBS; most respondents strongly disagreed (27%) or were neutral (42%) to this. Few respondents (26%) reported that their loved ones understood what it is like to live with IBS, whereas 31% strongly disagreed with this and 42% were neutral regarding this statement.

About 45% of respondents were very much (29%) or quite a bit (16%) frustrated that they could not work or contribute as much as they usually do; an additional 13% agreed with this somewhat, and 20% agreed with this a little bit. When asked if IBS-C was a financial hardship to them or their family, 15% agreed very much, 14% quite a bit, and 18% somewhat agreed. Out-of-pocket medical expenses were more than expected for 48% of respondents (13% very much, 16% quite a bit, and 19% somewhat).

Overall, the study authors concluded that the data in this survey pointed to IBS-C having a substantial burden on the overall health, QOL, and financial situation of patients.

Reference

1. Shah E, Ruddy J, Gist B, Stremke E, Williams L, Moshiree B. Irritable bowel syndrome with constipation poses a substantial burden to patient overall health status and quality of life: results from the IBS in America 2024 real-world survey. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P0641.

Reasons for Treatment Discontinuation in Patients With Irritable Bowel Syndrome With Constipation or Chronic Idiopathic Constipation

Given the chronic and incurable nature of both IBS-C and chronic idiopathic constipation (CIC), patients are frequently managed with long-term treatments including prescription and/or over-the-counter medications. Although it is known that treatment discontinuation is a common occurrence, both in clinical trials and real-world settings, the reasons for this are unclear.[1]

Shah and colleagues reported on results from an observational, cross-sectional study designed to evaluate the management of patients with IBS-C or CIC, particularly focusing on reasons for discontinuation.[2] Data were self-reported results collected from 2 online surveys of adults between August 2020 and December 2021. The first survey employed a random stratified sampling framework to ensure that the demographic composition of the respondents was representative of the US population. The second survey was administered to individuals prequalifying with IBS.

In this analysis, respondents were included if they were US residents aged 18 years and older, had selected IBS or constipation (chronic or more than occasional) in a checklist of comorbid conditions, met Rome IV

criteria for IBS-C or CIC, reported a physician diagnosis of IBS-C or CIC, and reported taking prescription linaclotide, prescription lubiprostone, or over-the-counter polyethylene glycol 3350 (PEG). Of the 29,359 survey participants, ultimately 1575 (5.4%) were included in the physician-diagnosed IBS-C or CIC cohort and thus in this analysis.

Among the included respondents, most were female (68.1%) and White (81.4%). Respondents were most frequently aged 18 to 44 years (60.6%); the remaining were 45 to 64 years of age (26.7%) or 65 years of age or older (12.6%). Either current or previous prescription medication for IBS-C or CIC was reported in 45.5% of respondents. These included linaclotide (41.4%), lubiprostone (22.3%), selective serotonin reuptake inhibitors (19.8%), lactulose (17.6%), plecanatide (8.6%), and prucalopride (4.9%). Current or previous usage of over-the-counter medications was reported by 67.7% of respondents. These included PEG (63.4%), bisacodyl laxatives (39.7%), sennosides and docusate (37.2%), psyllium husk (36.7%), wheat dextrin (29.9%), and other (7.4%).

Prescribed linaclotide demonstrated the highest rates of adherence to daily treatment compared with prescribed lubiprostone and over-the-counter PEG. Accordingly, prescribed linaclotide was also associated with a lower discontinuation rate (37.7%) compared with prescribed lubiprostone (47.5%) and over-the-counter PEG (45.4%). The most common reason reported for treatment discontinuation was an inadequate effect on bowel movement–related symptoms, which was 32.1% for prescribed linaclotide, 35.5% for prescribed lubiprostone, and 33.2% for over-the-counter PEG (Figure 2). Side effects (24.1% with linaclotide, 19.7% with lubiprostone, and 10.1% with PEG) and inadequate effect on abdominal symptoms (20.5% with linaclotide, 19.7% with lubiprostone, and 22.8% with PEG) were the next most common reasons for discontinuation. Cost was not in the top 3 reasons for discontinuing IBS-C/CIC treatment.

The study authors noted several limitations to this study. First, data

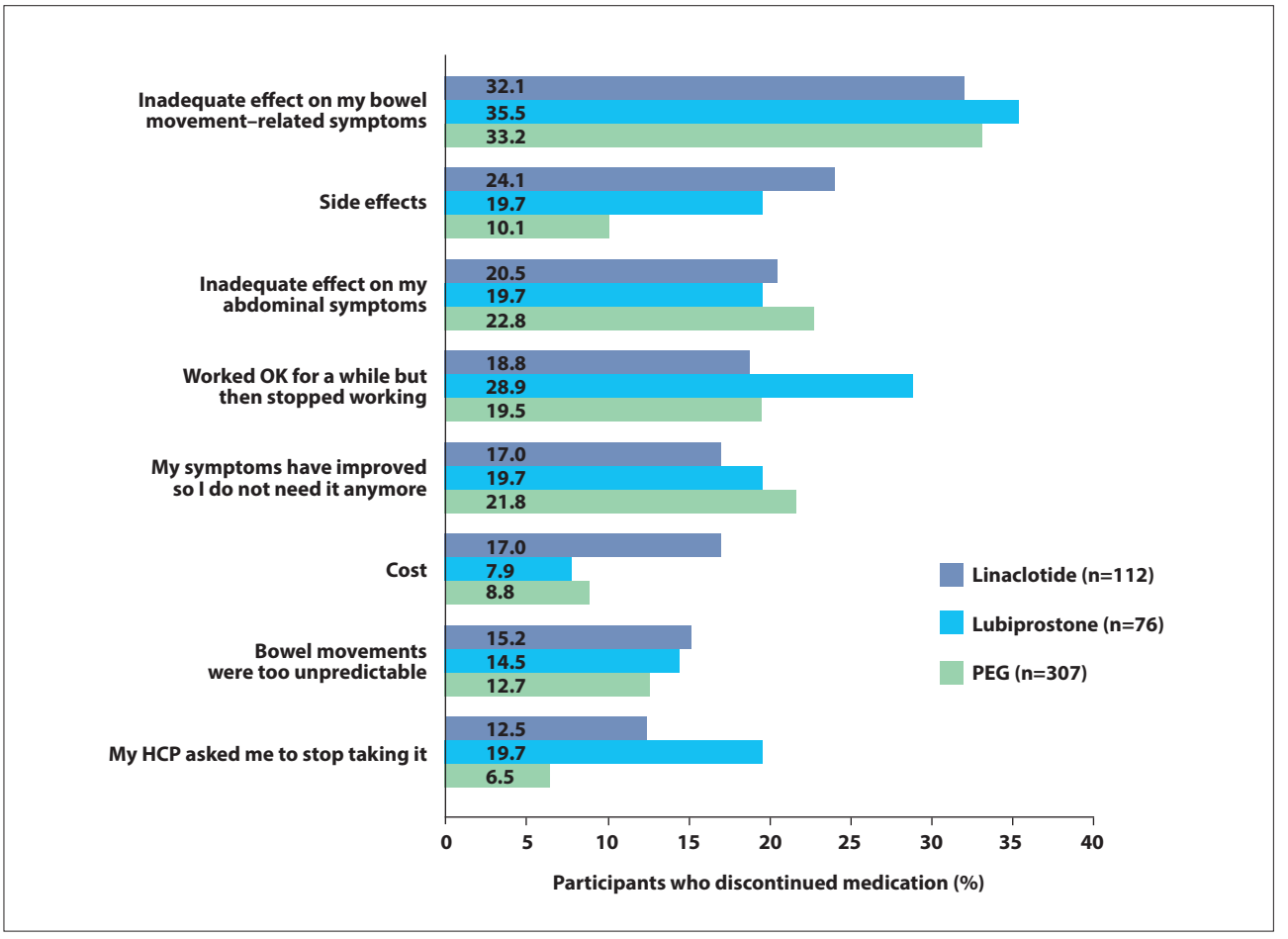

Figure 2. Most frequent reasons for treatment discontinuation in patients with irritable bowel syndrome with constipation or chronic idiopathic constipation. HCP, health care professional; PEG, polyethylene glycol 3350. Adapted from Shah ED, et al. Abstract P0617. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[2]

were self-reported, and only participants with online access were able to participate. Because the study was undertaken during the COVID-19 pandemic, this may have affected outcomes. Further, some data were unable to be adequately captured in these surveys, such as the length of time that medication was taken before discontinuation and reasons for nonadherence to daily treatment. As a result, additional evaluation is required to better understand whether the self-reported lack of abdominal and bowel symptom improvement was owing to premature discontinuation of treatment or lack of adherence. Finally, the authors noted that the frequency of prescribed medications is lower than the frequency of over-the-counter medications, which may limit the generalizability of the results.

Surprisingly, cost is a less common reason for discontinuing medications than lack of adequate effects on bowel movement–related symptoms, side effects, and lack of abdominal symptom improvement. The specific side effects leading to treatment discontinuation are not reported (ie, bloating with PEG), and treatment duration is unknown. PEG was the most commonly taken medication on an as-needed basis. Interestingly, more patients were told by their HCP to stop taking lubiprostone as compared to linaclotide and PEG, and almost 30% of patients suggested tachyphylaxis exists on lubiprostone. This side effect was reported less commonly with linaclotide and PEG. Because symptom severity of those surveyed is unknown and IBS-C and CIC results are combined, it is hard to know which abdominal symptom effect led to discontinuation. This is important to decipher because many nonprescription medications do not improve abdominal symptoms of IBS-C. In this study, all current IBS-C drugs are included except for tenapanor.

—Baharak Moshiree, MD, MSc

References

1. Shah ED, Suresh S, Jou J, Chey WD, Stidham RW. Evaluating when and why patients discontinue chronic therapy for irritable bowel syndrome with constipation and chronic idiopathic constipation. *Am J Gastroenterol*. 2020;115(4):596-602.
2. Shah ED, Lacy BE, Chey WD, et al. Reasons for treatment discontinuation in patients with irritable bowel syndrome with constipation or chronic idiopathic constipation. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P0617.

Patients With Irritable Bowel Syndrome With Constipation From the IBS in America 2024 Real-World Survey Experience Burdensome Symptoms Beyond Constipation

Moshiree and colleagues described a second analysis of data collected from the IBS in America 2024 real-world survey.[1] The same 284 patients with IBS-C were included in this analysis, having completed the IBS in America survey and meeting the additional criteria of the extension survey (a diagnosis of IBS-C by an HCP, currently seeing an HCP to treat their IBS-C, and prior or current use of an over-the-counter or prescription treatment for their IBS-C).

In this group of 284 respondents with IBS-C, the mean age was 51.4 years (range, 18-86) and 92% were female. Among these 262 females, 48% were postmenopausal (self-described) and 31% were currently having menstrual cycles, 9% were perimenopausal, and 12% were menopausal. There was a wide range of reported durations since IBS-C diagnosis, with individuals reporting as few as 2 to 5 years (23%), 5 to 10 years (21%), 10 to 15 years (15%), and 15 or more years (31%). In terms of frequency of IBS episodes, 44% of respondents reported weekly episodes over the past year, and 36% of respondents reported daily episodes.

Respondents were asked about their IBS-C symptoms over the previous 7 days. A total of 86% of patients with IBS-C experienced hard or lumpy stools at least once, with 50% experiencing them for 2 to 6 days over the 7 days, 5% experiencing them once daily, and 5% experiencing them more than once daily (Figure 3). These hard or lumpy stools were very much (21%) or quite a bit (30%) bothersome to

respondents. Straining was also a frequent symptom, with 95% of respondents reporting needing to strain while trying to have a bowel movement over the previous 7 days (23% reported straining always, 32% reported straining often, 31% reported straining sometimes, and 10% reported straining rarely). When asked how much strain was required while trying to have a bowel movement, 19% reported having to strain very much, 30% reported having to strain quite a bit, and 31% reported having to somewhat strain. Rectal or anus pain while trying to have bowel movements was also a frequent symptom among individual respondents. Over the previous 7 days, rectal or anus pain was reported as occurring always by 11%, occurring often by 21%, occurring sometimes by 32%, and occurring rarely by 20%. This pain was rated as very bad in 5%, quite bad in 22%, somewhat bad in 33%, and a little bad in 33%.

Respondents also frequently reported sensations of an incomplete bowel movement over the previous 7 days (tenesmus): 24% reported this occurring always, 32% often, 32% somewhat, and 10% rarely. Having to manually extract stool in the previous 7 days was also a frequent occurrence, reported to occur always (2%), often (12%), sometimes (21%), and rarely (12%).

In addition to constipation (94%), several other symptoms were reported among respondents. The most frequent of these were bloating (86%), abdominal cramps and pain (85%), abdominal fullness (73%), excessive gas/flatulence (68%), fatigue (64%), tenesmus (57%), and heartburn/gastroesophageal reflux disease (51%). Of the 95% of patients who experienced abdominal pain within the past 7 days, 33% described the pain as quite bad

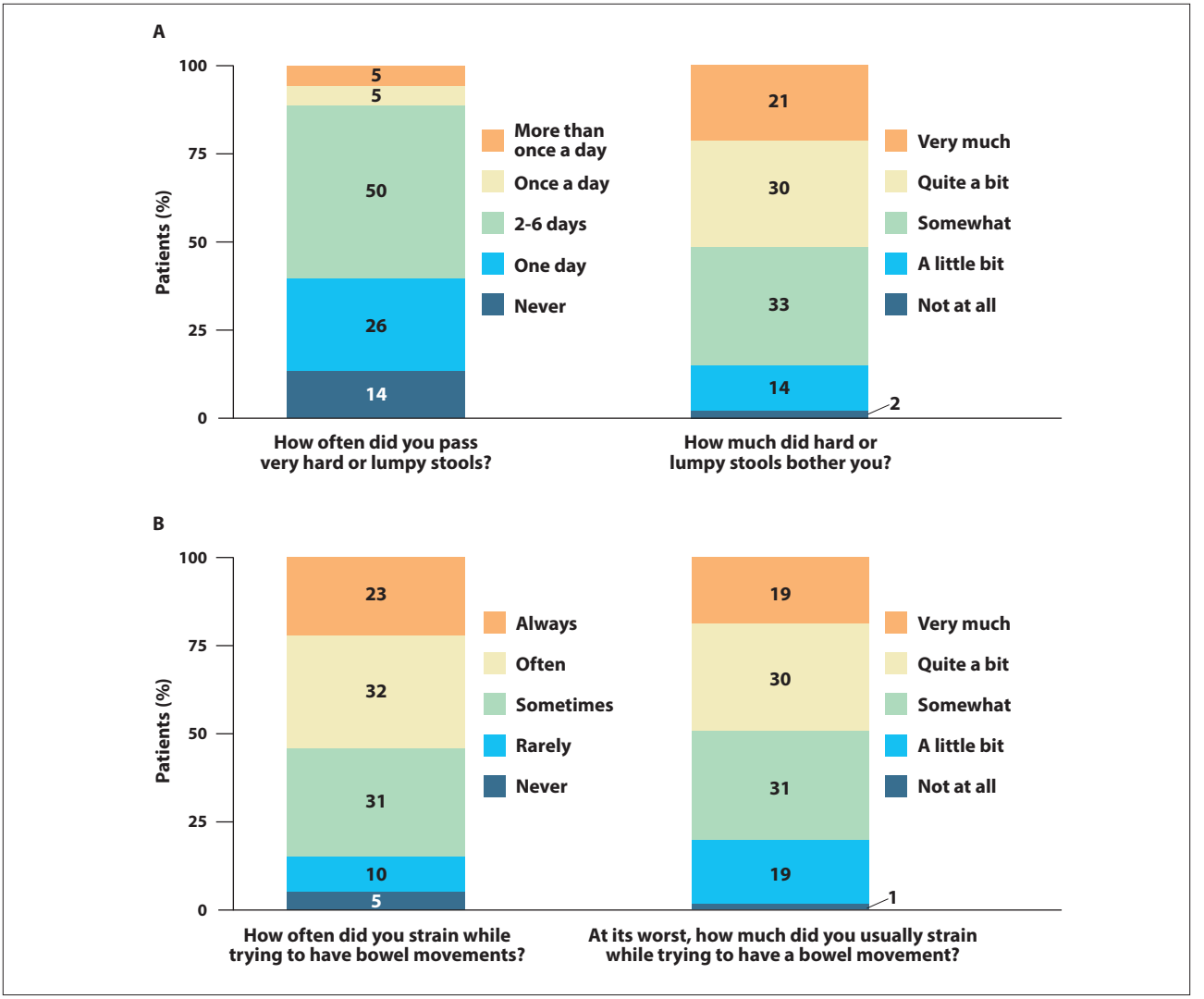

Figure 3. Proportion of patients with irritable bowel syndrome with constipation in the IBS in America 2024 real-world survey who experienced (A) hard or lumpy stools or (B) strain while trying to have a bowel movement in the previous 7 days. Adapted from Moshiree B, et al. Abstract P2235. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[1]

or very bad and interfered with their day-to-day activities quite a bit (20%) or very much (9%).

A total of 104 respondents were either perimenopausal or currently having menstrual cycles. Of these, nearly one-half (48%) felt that menstruation made their constipation symptoms worse, whereas 21% reported they felt no change. More patients felt that menstruation worsened their abdominal pain (82%) and bloating (89%).

Reference

1. Moshiree B, Ruddy J, Gist B, Stremke E, Williams L, Shah E. Patients with irritable bowel syndrome with constipation from the IBS in America 2024 real-world survey experience burdensome symptoms beyond constipation. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P2335.

Many symptoms account for the significant symptom burden in IBS-C, including some extraintestinal. A majority of IBS-C patients report incomplete bowel movements, bloating, cramps, fullness in abdomen, and excessive gas. The most prevalent non-gastrointestinal symptoms reported are fatigue and back pain. Almost half of female participants feel constipation symptoms worsen during menstruation. Exploring hormonal influences on IBS symptom severity is important because IBS has a female predominance, and a cure cannot be promised despite several IBS-C medications available.

—Baharak Moshiree, MD, MSc

Efficacy and Safety of Plecanatide in Treatment of Irritable Bowel Syndrome With Constipation and Chronic Idiopathic Constipation

Plecanatide is approved by the US Food and Drug Administration (FDA) for the treatment of adults with CIC or IBS-C.[1] Ahmed and colleagues reported on the results of a systemic review and meta-analysis that focused on the efficacy and safety of plecanatide in the treatment of these 2 conditions.[2] This analysis included 7 studies consisting of 6316 individuals, of which 4349 received plecanatide and 1967 received placebo. Across the studies, plecanatide was evaluated at different doses, ranging from 0.3 mg once daily up to 9 mg once daily.

Different outcomes were assessed for IBS-C and CIC. A pooled effect size was reported for all outcomes to convey the weighted average of the effect sizes across all studies reporting that outcome. These pooled effect sizes were evaluated for each dose of plecanatide with data for that outcome. Also reported were 2 statistics to evaluate the quality of the meta-analysis. The first of these was the I^2 value, indicating the fraction of variance that is owing to heterogeneity across the publications (with lower percentages indicative of more homogeneity and therefore a suggestion that the treatment will have a similar effect when applied to new patients).[3,4] The second was the Luis Furuya-Kanamori (LFK) index, a measure of the level of bias in a meta-analysis (where values outside of –1 and +1 are suggestive of publication bias).[5]

In patients with IBS-C, 4 outcomes were assessed: change in abdominal pain, change in Bristol Stool Form Scale (BSFS) score, change in complete spontaneous bowel movements (CSBM), and change in straining score. Across each outcome, 8 studies were reported across 5 doses.

For patients with IBS-C, 3 studies were included at the FDA-approved dose of plecanatide 3 mg once daily. For the change in abdominal pain outcome in patients with IBS-C, the pooled effect size was –0.49 (95% CI, –0.88 to –0.09; *P*=.03) (Table). In these studies, the I^2 value was 0%, and the LFK index across all studies of this outcome was 1.02. For the change in BSFS score outcome, the pooled effect size was 0.82 (95% CI, –0.53 to 2.18; *P*=.12). The I^2 value in these 3 studies was 89%, and the LFK index across all studies of this outcome was 1.93. For the change in CSBM outcome, in patients with IBS-C, the pooled effect size was 0.53 (95% CI, –1.77 to 2.83; *P*=.42). The I^2 value for these 3 studies was 90%, and the LFK index across all studies of this outcome was 0.16. Finally, for the change in straining score outcome, at the 3 mg dosage the pooled effect size was 0.39 (95% CI, –1.21 to 1.99; *P*=.40). The I^2 value for these 3 studies was 97%, and the LFK index across all the studies of this outcome was –4.04.

The 4 outcomes assessed in patients with CIC were change in BSFS score (assessed in 10 studies across 6 dosages), change in spontaneous bowel movement (SBM; 8 studies across 6 dosages), change in straining score (5 studies across 4 dosages), and

Table. Clinical Efficacy of Plecanatide for Irritable Bowel Syndrome With Constipation According to Doses

Outcome	Dose	No. of studies	Plecanatide total events	Control total events	Pooled effect size	CI (*P* value)	I^2	LFK index
Change in abdominal pain	1 mg	1	83	21	-0.01	-0.65; 0.45 (NA)	-	1.02
	9 mg	1	85	21	-0.40	-0.95; 0.15 (NA)	-	
	3 mg	3	814	388	-0.49	-0.88; -0.09 (0.03)	0%	
	6 mg	2	728	366	-0.55	-1.95; 0.84 (0.12)	0%	
	0.3 mg	1	84	22	-0.10	-0.65; 0.45 (NA)	-	
Change in BSFS score	3 mg	3	814	388	0.82	-0.53; 2.18 (0.12)	89%	1.93
	6 mg	2	728	366	0.61	-1.87; 3.09 (0.20)	75%	
	0.3 mg	1	84	22	0.62	0.22; 1.02 (NA)	-	
	1 mg	1	83	21	0.80	0.40; 1.20 (NA)	-	
	9 mg	1	85	21	1.23	0.83; 1.63 (NA)	-	
Change in CSBM	0.3 mg	1	84	22	0.01	-0.71; 0.73 (NA)	-	0.16
	3 mg	3	812	388	0.53	-1.77; 2.83 (0.42)	90%	
	6 mg	2	725	366	-0.13	-8.90; 8.63 (0.88)	95%	
	1 mg	1	83	21	0.85	0.12; 1.58 (NA)	-	
	9 mg	1	85	21	1.17	0.45; 1.89 (NA)	-	
Change in straining score	3 mg	3	814	388	0.39	-1.21; 1.99 (0.40)	97%	-4.04
	6 mg	2	728	366	0.72	0.71; 0.73 (<0.01)	0%	
	0.3 mg	1	84	22	-0.16	-0.41; 0.09 (NA)	-	
	9 mg	1	85	21	-0.32	-0.58; -0.06 (NA)	-	
	1 mg	1	83	21	-0.08	-0.33; 0.17 (NA)	-	

BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement; I^2, heterogeneity; LFK, Luis Furuya-Kanamori.
Adapted from Ahmed S, et al. Abstract P0627. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[2]

change in CSBM (3 studies across 2 dosages).

For the change in BSFS score outcome, which was assessed in 3 studies at the FDA-approved dose of 3 mg once daily, the pooled effect size was 0.83 (95% CI, 0.25-1.41; *P*=.03). The I^2 value for these studies was 71%, and the LFK index across all the studies of this outcome was –2.41. For the change in SBM outcome, assessed in 2 studies at the 3 mg once daily dose, the pooled effect size was 1.55 (95% CI, 0.21-2.88; *P*=.04). The I^2 value for these studies was 0%, and the LFK index across all the studies of this outcome was –1.13. For the change in straining score outcome, assessed in 2 studies at the 3 mg once daily dose, the pooled effect size was –0.20 (95% CI, –1.19 to 0.79; *P* value not available). The I^2 value for these studies was not provided, and the LFK index across all the studies of this outcome was –1.02. For the change in CSBM outcome, no studies were reported at the 3 mg once daily dose. However, in 2 studies at a dose of 1 mg once daily, the pooled effect size was 0.69 (95% CI, –0.23 to 1.60; *P*=.07). The I^2 value for these studies was 0%, and

Once again, plecanatide is shown to be safe and efficacious in improving abdominal pain and bowel frequency despite its side effect of diarrhea. Interpretation of the risk of urinary tract infections with use of plecanatide should be done with caution given the higher known risk of these infections in patients with constipation in general and because baseline urinary symptom data, history of fecal or urinary incontinence, and known objective measures are not reported.

—Baharak Moshiree, MD, MSc

the LFK index across all the studies of this outcome was –1.74.

Two adverse effects were significantly associated with plecanatide: diarrhea (relative risk, 4.11; 95% CI, 2.50-6.77; *P*<.01) and urinary tract infection (relative risk, 1.70; 95% CI, 0.99-2.91; *P*=.05). Other adverse effects reported that were not significantly associated with plecanatide were headache, nausea, nasopharyngitis, and upper respiratory tract infection.

The study authors concluded that the results of this systemic review and meta-analysis supported the efficacy of plecanatide for the treatment of IBS-C and CIC. However, they noted that this benefit should be weighed against the increased risk of diarrhea and urinary tract infection associated with its use.

References

1. Trulance [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2024.
2. Ahmed S, Ahmad E, Akram U, Albustami I. Efficacy and safety of plecanatide in treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P0627.
3. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clin Microbiol Infect*. 2014;20(2):123-129.
4. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. *BMC Med Res Methodol*. 2015;15(1):35.
5. Furuya-Kanamori L, Barendregt JJ, Doi SAR. A new improved graphical and quantitative method for detecting bias in meta-analysis. *Int J Evid-Based Healthc*. 2018;16(4):195-203.

Impact of Weight on the Efficacy, Time to Response, and Safety of Linaclotide in Adults With Chronic Idiopathic Constipation or Irritable Bowel Syndrome With Constipation: Post Hoc Descriptive Analysis by Body Mass Index

Previous studies have provided evidence that constipation may be more prevalent among overweight or obese adults compared with adults of normal weight.[1,2] Linaclotide is FDA-approved for the treatment of adults with IBS-C or CIC.[3] Although differences in body weight and body mass index (BMI) between patients may lead to clinically relevant changes in the pharmacokinetic and pharmacodynamic properties of drugs, there have been no data on the impact of body weight on treatment response in linaclotide-treated patients. Moshiree and colleagues reported on results from a post hoc subgroup analysis evaluating the efficacy and safety of linaclotide in adult patients with IBS-C or CIC stratified by BMI category.[4]

These data were gathered from 7

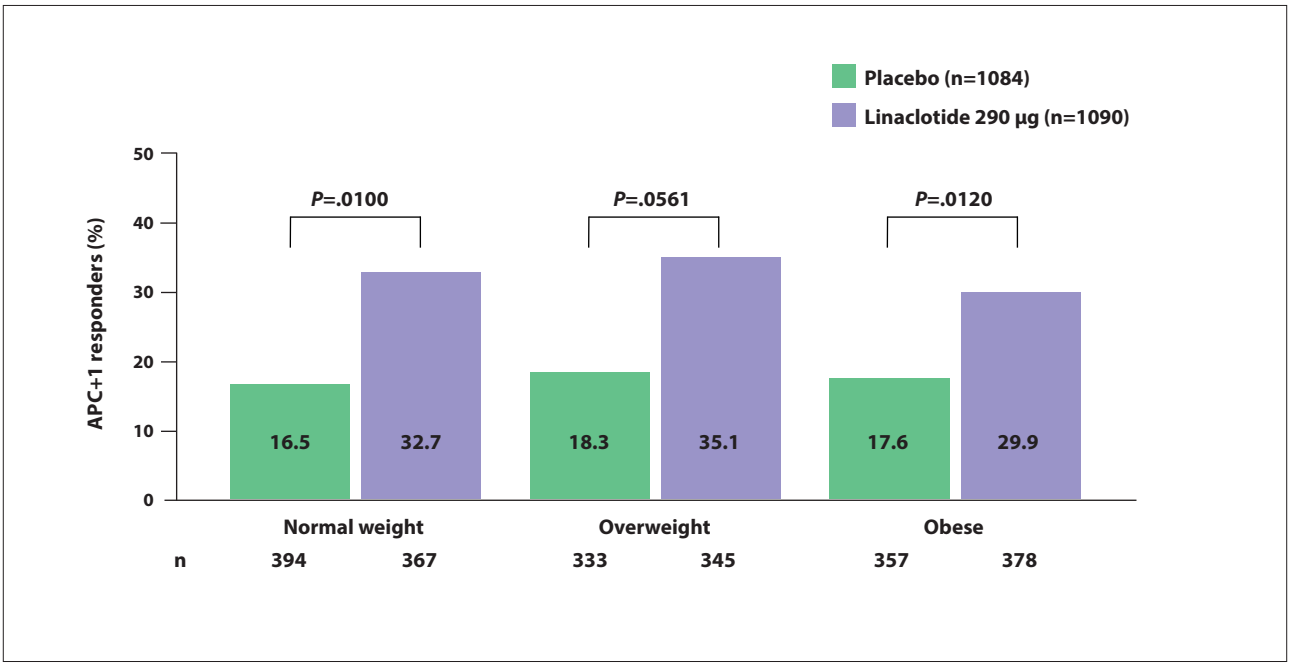

Figure 4. Proportions of APC+1 responders for patients with irritable bowel syndrome with constipation treated with linaclotide or placebo by body mass index category. APC+1, abdominal pain and constipation +1. Adapted from Moshiree B, et al. Abstract P4073. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[4]

A patient's weight has not been previously factored into the efficacy and onset of response of linaclotide for the treatment of IBS-C. In this study, the safety profile of linaclotide is similar across all BMI subgroups, and the same is true for the side-effect profile. Linaclotide, especially given 290 µg once daily, leads to a faster CSBM than placebo across all BMI subgroups. Improvements in abdominal pain and discomfort are also consistently seen across all BMI subgroups with 290 µg once daily. This is in line with its IBS-C indication.

—Baharak Moshiree, MD, MSc

phase 3 clinical trials, all with a randomized, double-blind, placebo-controlled study design. Patients included in this analysis were adults who met modified Rome II or III criteria for IBS-C or CIC and had received either the FDA-approved doses of linaclotide (290 µg once daily for IBS-C or 145 µg once daily for CIC) or placebo for 12 weeks. Patients were stratified into 3 BMI categories: normal weight (18.5 to <25); overweight (25 to <30); and obese (≥30); patients with a BMI less than 18.5 were excluded from this analysis.

A total of 2174 patients with IBS-C were included in this post hoc analysis. Figure 4 shows the percentage of patients with IBS-C who achieved an abdominal pain and constipation +1 (APC+1) response, which was defined as a patient with a 30% or more reduction in abdominal pain score and an increase of 1 or more CSBM per week from baseline for 6 weeks or more of the 12-week treatment period. Across all BMI subgroups, more patients with IBS-C treated with linaclotide met the primary endpoint of APC+1 vs placebo: normal weight (32.7% vs 16.5%; *P*=.0100); overweight (35.1% vs 18.3%; *P*=.0561); and obese (29.9% vs 17.6%; *P*=.0120).

In patients with IBS-C, linaclotide provided treatment benefits vs placebo by improving multiple symptoms from baseline across the 3 BMI subgroups. For example, CSBM per week from baseline increased by 2.2, 2.6, and 2.1 in the normal weight, overweight, and obese groups, respectively, with linaclotide compared with 0.7, 0.9, and 0.9 with placebo. SBMs per week also increased from baseline with linaclotide (3.3, 4.0, and 3.3 compared with 1.0, 1.3, and 1.1 in placebo-treated patients, respectively). Abdominal pain was improved from baseline with linaclotide for all 3 weight groups (–2.3, –2.3, and –2.5) compared with placebo (–1.3, –1.5, and –1.5, respectively). Abdominal discomfort was improved with linaclotide across all 3 weight groups (–2.3, –2.4, –2.6) compared with placebo (–1.4, –1.5, and –1.5). Abdominal bloating was improved from baseline with linaclotide across all 3 weight groups (–2.2, –2.4, and –2.6) compared with placebo (–1.4, –1.4, and –1.5).

The frequency of treatment-emergent adverse events was generally similar across weight groups in patients with IBS-C treated with linaclotide (61.3% for normal weight, 56.2% for overweight, and 50.0% for obese) and for those treated with placebo (53.8% for normal weight, 52.3% for overweight, 51.5% for obese). The frequency of diarrhea, the most common treatment-emergent adverse event, was also similar across weight groups (linaclotide: 18.8% for normal weight, 15.9% for overweight, and 13.5% for obese; vs placebo: 9.4% for normal weight, 8.1% for overweight, 4.8% for obese).

In general, the median times to response for improvement in the CSBM weekly rate by an increase of 1 or more from baseline were similar across weight groups, with shorter times achieved with linaclotide (2.0 weeks for normal weight, 1.0 weeks for overweight, and 2.0 weeks for obese) vs placebo (5.0 weeks for normal weight, 4.0 weeks for overweight, and 4.0 weeks for obese).

Similar trends were observed for patients with CIC treated with linaclotide vs placebo. Overall, no significant differences were apparent regarding the efficacy and safety of linaclotide across patient weight groups.

References

1. Xiang N, Xu L, Qian H, Zhang D. Multiple obesity indices suggest a close relationship between obesity and constipation: evidence from NHANES. *BMC Public Health*. 2024;24(1):1273.
2. Silveira EA, Santos ASEAC, Ribeiro JN, Noll M, Dos Santos Rodrigues AP, de Oliveira C. Prevalence of constipation in adults with obesity class II and III and associated factors. *BMC Gastroenterol.* 2021;21(1):217.
3. Linzess [package insert]. North Chicago, IL: AbbVie, Inc; 2023.
4. Moshiree B, Lembo AJ, Cash BD, et al. Impact of weight on the efficacy, time to response, and safety of linaclotide in adults with chronic idiopathic constipation or irritable bowel syndrome with constipation: post hoc descriptive analysis by body mass index. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P4073.

An Association Between IBS Quality of Life Score and Symptoms of Abdominal Pain, Bloating, and Cramping in IBS-C: A Pooled Phase 3 Trial Correlation Analysis

Although abdominal pain and altered stool consistency and frequency are part of the IBS-C diagnostic criteria, other symptoms such as bloating and cramping are also frequently experienced and reported as bothersome for patients.[1,2] Symptom bothersomeness, considered severe enough to impact patient QOL, should be included in the clinical criteria for diagnosis of IBS according to the Rome Foundation.[3] However, whether these bothersome symptoms can be used to predict the burden and impact of IBS remains unclear.

Shah and colleagues conducted an analysis that evaluated the potential relationship between IBS-C symptoms and IBS-related QOL and treatment satisfaction.[4] Data from 2 identically designed, randomized, placebo-controlled, phase 3 trials were pooled and analyzed for this evaluation. Eligible patients were adults with IBS-C according to Rome III criteria, with a worst abdominal pain intensity mean score of 3 or more (range, 0 [none] to 10 [worst possible] during a 2-week pretreatment period). All patients were randomized to treatment with plecanatide 3 mg or 6 mg, or placebo, for 12 weeks.

At baseline, the mean patient age was 43.5 years and 43.1 years in the plecanatide 3 mg and 6 mg groups, respectively, and 43.9 years in the placebo group. About three-quarters of patients were female (73.8%, 74.1%, and 74.1%), and most were White (72.8%, 71.2%, and 73.5%) in the plecanatide 3 mg, plecanatide 6 mg, and placebo groups, respectively. Abdominal pain, bloating, and cramping were all measured using an 11-point scale, ranging from 0 (no) to 10 (worst possible). At baseline, across the plecanatide 3 mg, plecanatide 6 mg, and placebo groups, the mean abdominal pain score was 6.3, 6.2, and 6.3, respectively. The bloating score at baseline was 6.5, 6.4, and 6.5; and the cramping score at baseline was 6.0, 5.9, and 6.0. The IBS-QOL total score at baseline was 46.5, 45.3, and 44.4 in the plecanatide 3 mg, plecanatide 6 mg, and placebo groups, respectively.

A positive correlation was observed between the IBS-QOL total score and each of the 3 IBS-C symptoms measured over the 12-week treatment period (abdominal pain weekly mean score, +0.38; bloating weekly mean score, +0.41; and cramping weekly mean score, +0.39). This correlation, assessed weekly, is shown in Figure 5.

In contrast, a negative correlation was apparent between treatment satisfaction and each of the 3 IBS-C symptoms over the 12-week treatment period (abdominal pain weekly mean score, –0.30; bloating weekly mean score, –0.30; and cramping weekly mean score, –0.27). The weekly assessment of this correlation began with the first treatment satisfaction assessment at week 4.

The study investigators concluded that there was a modest correlation

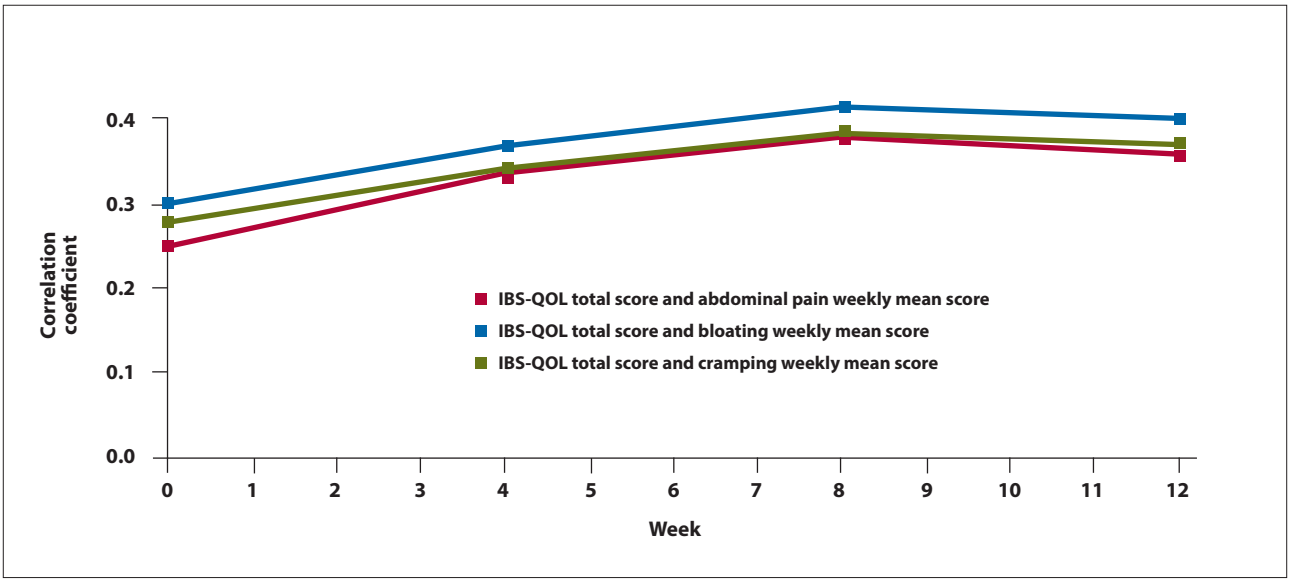

Figure 5. Correlation coefficients comparing IBS-QOL total score and each mean symptom score, by week. IBS-QOL, irritable bowel syndrome quality of life. Adapted from Shah ED, et al. Abstract P2355. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[4]

The pooled phase 3 data in this post hoc analysis of plecanatide indicate that abdominal bloating and cramping (symptoms outside the existing Rome IV definition) also correlate with worsening IBS-related QOL and treatment satisfaction, and perhaps should be considered in future definitions for IBS. This concept of symptom bothersomeness may be a new clinical phenotype added to the existing definitions of many disorders of gut-brain interaction.

—Baharak Moshiree, MD, MSc

between all 3 IBS-C symptoms measured (abdominal pain, bloating, and cramping) and both IBS-QOL as well as treatment satisfaction.

References

1. Khasawneh M, Shaikh FA, Ng CE, Black CJ, Goodoory VC, Ford AC. Utility of irritable bowel syndrome subtypes and most troublesome symptom in predicting disease impact and burden. *Neurogastroenterol Motil*. 2024;36(4):e14756.
2. Su AM, Shih W, Presson AP, Chang L. Characterization of symptoms in irritable bowel syndrome with mixed bowel habit pattern. *Neurogastroenterol Motil*. 2014;26(1):36-45.
3. Drossman DA, Tack J. Rome Foundation clinical diagnostic criteria for disorders of gut-brain interaction. *Gastroenterology*. 2022;162(3):675-679.
4. Shah ED, Laitman AP, Halton P, McQueen A, Goyal D. An association between IBS quality of life score and symptoms of abdominal pain, bloating, and cramping in IBS-C: a pooled phase 3 trial correlation analysis. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P2355.

Plecanatide Is Efficacious in Patients With Irritable Bowel Syndrome With Constipation and Bloating: Evaluation Using Trisymptom Composite Endpoints

Brenner and colleagues investigated the efficacy of plecanatide among patients with IBS-C using a novel trisymptom composite endpoint, which consisted of abdominal pain, abdominal bloating, and CSBMs.[1] The patient data used in this post hoc analysis were pooled from 2 identically designed, randomized, placebo-controlled, phase 3 trials. Eligible patients were adults 18 to 40 years of age, with IBS-C meeting the Rome III criteria, and a BMI between 18 and 40. At baseline, patients had a bloating score of 1 or higher on a numeric rating scale ranging from 0 (no) to 10 (worst possible); patients were stratified by baseline bloating intensity. For this evaluation, the trisymptom composite endpoint response was defined as simultaneous improvement from baseline in all 3 symptoms (abdominal pain, abdominal bloating, and CSBMs) for 6 or more of the 12 treatment weeks.

A total of 605 patients with IBS-C and bloating at baseline were included in this analysis. Among these patients, the mean patient age was 30.6 years in the plecanatide 3 mg group and 30.3 years in the placebo group. The mean abdominal pain score was similar between the 2 groups (6.2 and 6.4, respectively), as was the mean bloating score (6.4 and 6.6, respectively). Most patients in both groups had bloating considered to be moderate or severe in intensity (70.0% and 73.6%, respectively). At baseline, patients in both groups had a mean of 0.2 CSBMs per week.

Overall, significantly more

A new trisymptom composite endpoint (ie, abdominal pain, bloating, and CSBMs at various thresholds of response) utilized in two phase 3 studies of plecanatide shows improvements in all global symptoms while on plecanatide regardless of baseline bloating severity. Improvements in abdominal bloating follow trends for abdominal pain and CSBM frequency improvements.

—Baharak Moshiree, MD, MSc

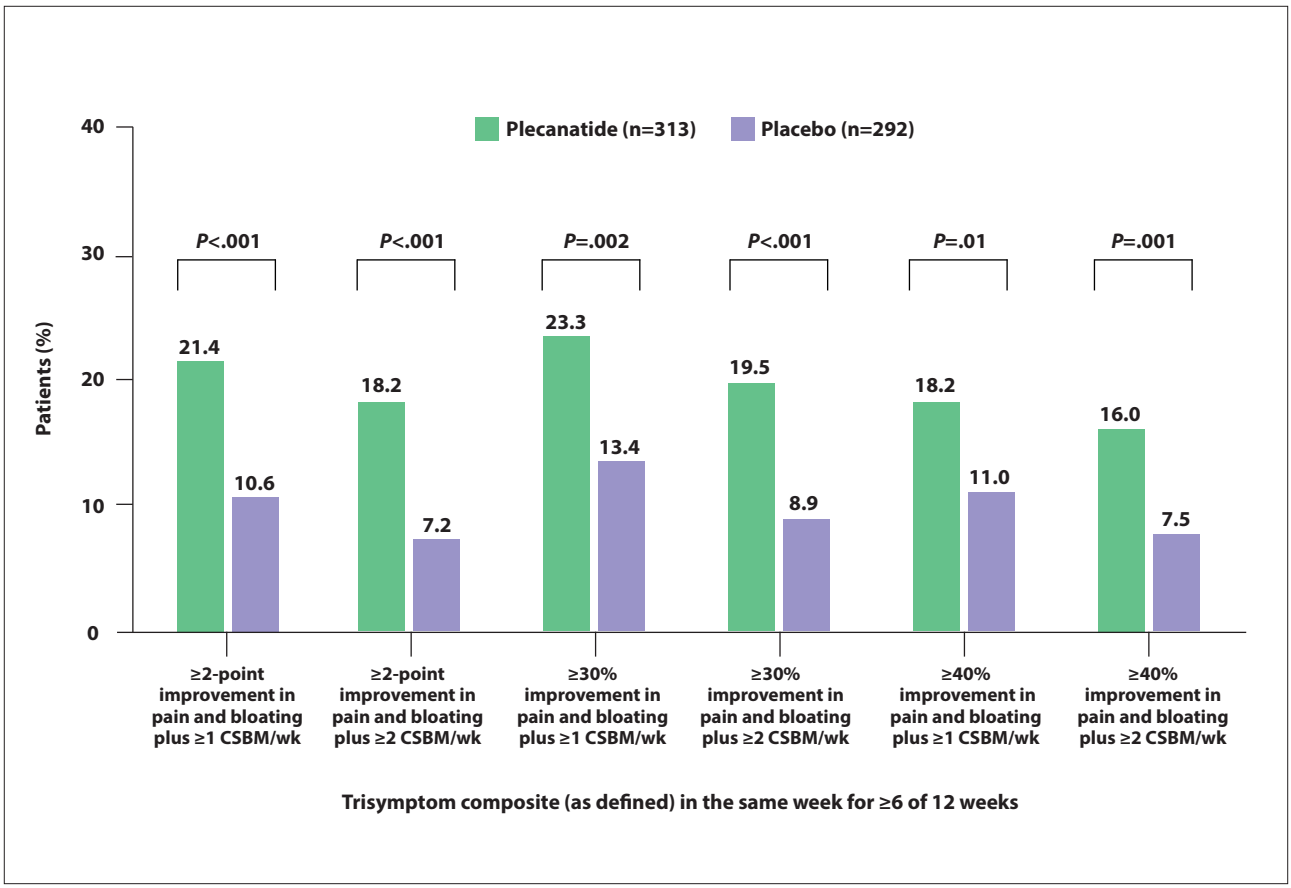

Figure 6. Irritable bowel syndrome with constipation trisymptom composite (abdominal pain, bloating, and CSBM) responders (overall population) to plecanatide vs placebo. CSBM, complete spontaneous bowel movement. Adapted from Brenner DM, et al. Abstract P2363. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, Pennsylvania.[1]

patients in the plecanatide group compared with the placebo group achieved a trisymptom composite response (Figure 6). This was true across several thresholds, including a 2-point or greater improvement in pain and bloating plus 1 or more CSBM per week (21.4% with plecanatide vs 10.6% with placebo; *P*<.001); a 2-point or greater improvement in pain and bloating plus 2 or more CSBMs per week (18.2% vs 7.2%, respectively; *P*<.001); a 30% or greater improvement in pain and bloating plus 1 or more CSBM per week (23.3% vs 13.4%, respectively; *P*=.002); a 30% or greater improvement in pain and bloating plus 2 or more CSBMs per week (19.5% vs 8.9%, respectively; *P*<0.001); a 40% or greater improvement in pain and bloating plus 1 or more CSBM per week (18.2% vs 11.0%, respectively; *P*=.01); and a 40% or greater improvement in pain and bloating plus 2 or more CSBM per week (16.0% vs 7.5%, respectively; *P*=.001).

An analysis by baseline bloating intensity revealed that the rates of trisymptom composite response were maintained across baseline bloating intensities. For example, using a threshold of a 2-point or greater improvement in pain and bloating plus 2 or more CSBMs per week, 16.0% (plecanatide-treated) and 5.2% (placebo-treated) of patients with mild bloating at baseline achieved the trisymptom composite response (*P*=.02) compared with 19.2% and 7.9% (*P*<.001), respectively, of patients with moderate or severe bloating at baseline. A similar observation was noted across all other thresholds used, such as a 30% or greater improvement in pain and bloating plus 2 or more CSBMs per week (mild bloating at baseline group: 20.2% with plecanatide vs 9.1% with placebo; *P*=.04; moderate/severe bloating at baseline group: 19.2% with plecanatide vs 8.8% with placebo; *P*=.002).

Reference

1. Brenner DM, Shin AS, Laitman AP, Kunkel DC. Plecanatide is efficacious in patients with irritable bowel syndrome with constipation and bloating: evaluation using trisymptom composite endpoints. Presented at: American College of Gastroenterology 2024 Annual Scientific Meeting; October 25-30, 2024; Philadelphia, PA. Abstract P2363.

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/1.73m^2). 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/1.73m^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).

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 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 effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. 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)*]. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. 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.

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

IBSRELA® (tenapanor) tablets
50 mg BID

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