LINZESS® (linaclotide) capsules, for oral use
Medicaid Clinical Summary

Irritable Bowel Syndrome (IBS) and Chronic Idiopathic Constipation (CIC), are chronic and debilitating functional bowel disorders, affecting approximately 11.5 and 28.5 million patients in the United States, respectively. [1-4] In addition to disordered defecation, IBS is also characterized by symptoms of recurrent abdominal pain. If not adequately treated, both IBS-C and CIC can lead to significant symptom burden that impacts health-related quality of life (HRQoL), work productivity, and healthcare resource utilization (HCRU).[5-9]

Both the 2021 American College of Gastroenterology (ACG) and 2022 American Gastroenterological Association (AGA) IBS Guidelines reflect the complexity of the condition and the awareness that IBS is more than a change in bowel habits. These guidelines also emphasize the need for treatment with consistent benefits that treat global symptom s of IBS.[10-11]

Functional constipation (FC) is a common gastrointestinal (GI) disorder in pediatric patients with a global prevalence estimated at about 9.5% and US prevalence of about 14.1% in patients 4 years of age and older.[12,13]

INDICATIONS AND USAGE[14]

Linaclotide is a guanylate cyclase-C (GC-C) agonist indicated in adults for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC). Linaclotide is also indicated for treatment of FC in pediatric patients 6 to17 years of age.

DOSAGE AND ADMINISTRATION[14]

The recommended dose of linaclotide in treatment of IBS-C is 290 mcg orally once daily, and in treatment of CIC is either 145 mcg orally once daily or 72 mcg orally once daily based on individual presentation or tolerability.

Linaclotide should be taken on empty stomach at least 30 minutes prior to the first meal of the day. LIinaclotide capsules or capsule contents should not be crushed or chewed.

IMPORTANT SAFETY CONSIDERATIONS:[14]

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE

Linaclotide is contraindicated in patients less than 2 years of age; in nonclinical studies in neonatal mice, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration.

Risk of Serious Dehydration in Pediatric Patients: Linaclotide is contraindicated in patients less than 2 years of age. In neonatal mice (human age equivalent of approximately 0 to 28 days), linaclotide increased fluid secretion as consequence of age-dependent GC-C intestinal agonism which was associated with increased mortality within the first 24 hours due to dehydration. There was no age-dependent trend in GC-C expression in children 2 to less than 18 years of age; however, there are insufficient data available on GC-C intestinal expression in children less than 2 years of age to assess the risk of developing diarrhea and its potentially serious consequences in these patients. The safety and effectiveness of linaclotide in patients with FC less than 6 years old or in patients with IBS-C less than 18 years of age have not been established.

Diarrhea: In adults, diarrhea was the most common adverse reaction in linaclodtide-treated patients in the pooled IBS-C and CIC double-blind, placebo-controlled trials. The incidence of diarrhea was similar in the IBS-C and CIC populations. Severe diarrhea was reported in 2% of 145 mcg and 290 mcg linaclotide-treated patients, and in <1% of 72 mcg linaclotide-treated CIC patients. In pediatric patients 6 to 17 years of age, diarrhea was the most common adverse reaction in 72 mcg linaclotide-treated patients in the FC double-blind, placebo-controlled trial. Severe diarrhea was reported in one linaclotide-treated patient. If severe diarrhea occurs, dosing should be suspended and the patient rehydrated.

Common Adverse Reactions (incidence ≥2% and greater than placebo) : In IBS-C or CIC adult patients: diarrhea, abdominal pain, flatulence, and abdominal distension. In FC pediatric patients: diarrhea.

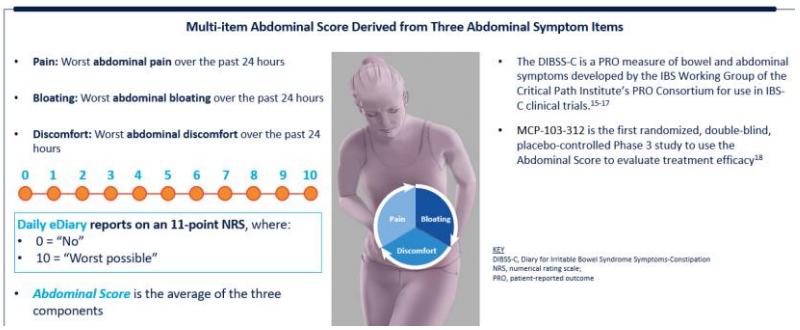
LINZESS (linaclotide) CLINICAL PROGRAM

In 2012, the Food and Drug Administration (FDA) approved LINZESS (linaclotide) based on the safety and efficacy demonstrated in four pivotal, Phase III, randomized, double-blind, multicenter, placebo-controlled studies to determine the efficacy and safety of LINZESS (linaclotide) in both IBS-C and CIC. In 2020, the FDA approved a supplemental New Drug Application (sNDA) based on the results of a Phase 3b, randomized,

LINZESS (linaclotide) CLINICAL PROGRAM cont…

double-blind, parallel-group, placebo-controlled study that evaluated the efficacy and safety of linaclotide 290 mcg on the overall abdominal score (abdominal symptoms including discomfort, pain and bloating) in 614 adults with IBS-C over 12 weeks. The Abdominal Score data was collected from a validated patient-reported outcome (PRO) tool, Diary of Irritable Bowel Syndrome Symptoms- Constipation (DIBSS-C). Additionally, the FDA in 2023, approved LINZESS (linaclotide) for treatment of functional constipation in pediatric patients 6 to17 years of age. In the pivotal, 12-week double-blind, placebo-controlled trial of 328 pediatric patients, linaclotide 72 mcg demonstrated significant improved compared with placebo on the primary endpoint of Least Squares 12-week Mean change from baseline in spontaneous bowel movement (SBM frequency rate with a treatment difference of 1.3 (95% confidence interval [CI] 0.7 to 1.8). SBM frequency improved during week 1 and was maintained throughout the remainder of the 12-week treatment period.

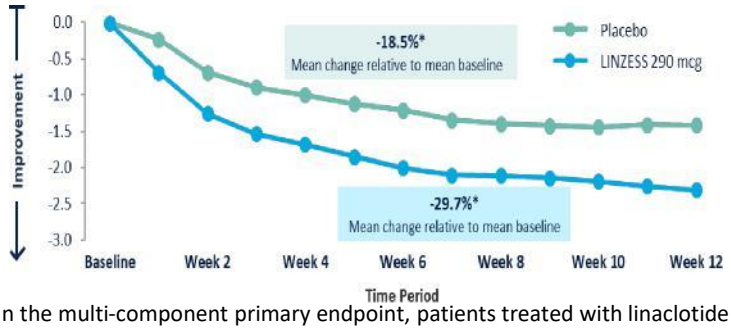
Assessing the Abdominal Symptoms of IBS-C:
DIBSS-C Abdominal Score



ABDOMINAL SCORE RESULTS

PRIMARY EFFICACY ENDPOINT:

Change from baseline in Abdominal Score for the overall treatment period

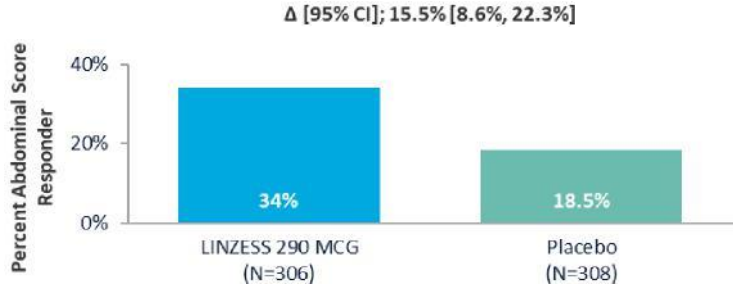


In the multi-component primary endpoint, patients treated with linaclotide showed a 29.7% mean decrease from baseline in their weekly abdominal score (bloating, pain, and discomfort) through the 12-week treatment period, compared to 18.5% of the placebo-treated patients (*p<0.0001).

ABDOMINAL SCORE RESPONDER RATES FOR AT LEAST 6 OUT OF 12 WEEKS

SECONDARY EFFICACY ENDPOINT:

A responder was based on at least a 2.5-point improvement in the Abdominal Score from baseline for at least 6 out of 12 weeks.



In a secondary endpoint, 34% of patients treated with linaclotide 290 mcg showed a clinically meaningful response, as defined by the abdominal symptom score response, compared to 18.5% of patients treated with placebo (p<0.0001).

REFERENCES

1. Saito Y, Schoenfeld P, Locke G. The epidemiology of irritable bowel syndrome in North America: a systematic review. Am J Gastroenterol. 2002 Aug;97(8):1910-15.
2. Andrews E, Eaton S, Hollis K, Hopkins J, Ameen V, Hamm L, et al. Prevalence and demographics of irritable bowel syndrome: results from a large web-based survey. Aliment Pharmacol Ther. 2005 Nov;22(10):935-42.
3. Hungin A, Chang L, GR L, Dennis E, Barghout V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. Aliment Pharmacol Ther. 2005;21:1365-75.
4. Palsson OS, et al. Gastroenterology. 2020;158(5):1262-73.
5. DiBonaventura M, Sun S, Bolge S, Wagner J, Mody R. Health-related quality of life, work productivity and health care resource use associated with constipation predominant irritable bowel syndrome. Curr Med Res Opin. 2011 Nov;27(11):2213-22.
6. Sun S, DiBonaventura M, Purayidathil F, Wagner J, Dabbous O, Mody R. Impact of chronic constipation on health-related quality of life, work productivity, and healthcare resource use: an analysis of the national health and wellness survey. Dig Dis Sci. 2011 Sept;56(9):2688-95.
7. Stephenson J, Buono J, Spalding W, Cai Q, Tan H, Carson R, et al. Impact of irritable bowel syndrome with constipation on work productivity and daily activity among commercially insured patients in the United States. Value Health. 2014 Nov;17(7):A370.
8. Forest Research Institute Inc. Health-related quality of life, work productivity, and daily activity among a sample of commercially insured patients with irritable bowel syndrome with constipation or chronic constipation. Data on file. 2015.
9. Cai Q, Buono J, Spalding W, Stephenson J, Tan H, et al. Impairment in work productivity and daily activity among commercially insured patients with chronic constipation in the United States. Presented at the American Association of Nurse Practitioners National Conference; June 9-14, 2015. New Orleans, LA.
10. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021;116:17-44.
11. Chang, et al. AGA Clinical Practice Guideline on the Pharmacological Management of IBS-C. Gastroenterology. 2022;163:118-36.
12. Koppen IJN. J Pediatr. 2018; 198:121-130.
13. Robin SG. J Pediatr. 2018; 195:134-139
14. LINZESS (linaclotide) [prescribing information]. North Chicago, IL: AbbVie, Inc; Boston, MA : Ironwood Pharmaceuticals, Inc; June 2023.
15. Fehnel SE, Ervin CM, Carson CT, et al. Development of the Diary for IBS Symptoms to Assess Treatment Benefit in Clinical Trials: Foundational Qualitative Research. Value Health. 2017;20(4):618-626.
16. Coon CD, Hanlon J, Abel JL, et al. Psychometric Analysis of the Abdominal Score from the Diary for IBS Symptoms-Constipation Using Phase IIb Clinical Trial Data. Value Health. 2020;23(2):362-369.
17. Coon CD et al. Poster Mo1520 presented at Digestive Disease Week (DDW) 2020, Chicago, IL, USA, May 2-5, 2020.
18. Clinicaltrials.gov. NCT03573908. Accessed March 22, 2023.