Select Drugs for Constipation

Policy # 00557
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Current Effective Date: 04/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider select drugs for the treatment of constipation [including, but not limited to Motegrity™‡ (prucalopride) and Ibsrela®‡ (tenapanor)] to be **eligible for coverage**** when the patient selection criteria are met for the requested drug.

Patient Selection Criteria

Coverage eligibility for prucalopride (Motegrity, generics) or Ibsrela (tenapanor) will be considered when the criteria are met for the requested drug:

- Patient has the following diagnosis for the requested drug:
  - For prucalopride (Motegrity, generics) requests:
    - Chronic Idiopathic Constipation (CIC); OR
  - For Ibsrela requests:
    - Irritable Bowel Syndrome with Constipation (IBS-C); AND
- Patient is 18 years of age or older; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) standard therapy for the condition, including use of both fiber and laxative products, unless there is clinical evidence or patient history that suggests the use of fiber and laxative products will be ineffective or cause an adverse reaction to the patient; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- Patient has tried and failed (e.g., intolerance or inadequate response) TWO of the following: generic lubiprostone, Linzess®‡ (linaclotide), or Trulance™‡ (plecanatide), unless there is clinical evidence or patient history that suggests the use of generic lubiprostone, Linzess (linaclotide), or Trulance (plecanatide) will be ineffective or cause an adverse reaction to the patient; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

- If the request is for brand Motegrity, patient has tried and failed (e.g., intolerance or inadequate response) GENERIC prucalopride unless there is clinical evidence or patient history that suggests the use of GENERIC prucalopride will be ineffective or cause an adverse reaction to the patient.
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of prucalopride (Motegrity, generics) or Ibsrela (tenapanor) when the patient has NOT tried and failed fiber and laxative products as well as TWO of the following: generic lubiprostone, Linzess (linaclotide), or Trulance (plecanatide) where applicable, to be **not medically necessary.****

Based on review of available data, the Company considers the use of brand Motegrity when the patient has not tried and failed GENERIC prucalopride to be not medically necessary.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of prucalopride (Motegrity, generics) or Ibsrela (tenapanor) when the patient selection criteria are not met (EXCEPT those denoted as **not medically necessary****) to be **investigational.***

Background/Overview

Motegrity is a serotonin-4 (5-HT_4) receptor agonist indicated for the treatment of CIC in adults. The recommended dosage for Motegrity is 2 mg taken orally once daily and is available in both 1 mg (for renal dosing) and 2 mg tablets.

Ibsrela is a locally acting inhibitor of the sodium hydrogen exchanger 3 (NHE3) indicated for the treatment of IBS-C in adults. The recommended dosage is 50 mg taken orally twice daily. Ibsrela is available in 50 mg tablets.

Chronic Idiopathic Constipation (CIC)

It is estimated that CIC has a prevalence ranging from 12% to 19% in the United States. CIC is more common in women and the elderly. The American Gastrological Association (AGA) and the American College of Gastroenterology (ACG) both recommend fiber as a first line therapy for chronic constipation. The next step would be a stimulant or osmotic laxative. If the CIC is not

controlled with those two options, then newer drugs such as Amitiza®‡, Linzess, or Trulance can be used. Guidelines have been updated to include Trulance and Motegrity. It should be noted that clinical trials with Motegrity were placebo controlled and therefore no superiority claims can be made with Motegrity as compared to other CIC agents, such as Amitiza, Linzess, or Trulance.

Irritable Bowel Syndrome with Constipation (IBS-C)
Irritable Bowel Syndrome (IBS) is defined as recurrent abdominal pain or discomfort at least three days per month in the last three months with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form (appearance) of stool. The prevalence of IBS in North America is approximately 10-15% and is slightly more prevalent in women than in men. IBS can be divided into four categories depending on patient symptoms. IBS-C is IBS in which the patient reports that abnormal bowel movements are usually constipation. Similarly, IBS with diarrhea (IBS-D) requires that abnormal bowel movements are usually diarrhea. Some patients present which IBS-mixed, in which abnormal bowel movements are both constipation and diarrhea (i.e. more than one-fourth of all the abnormal bowel movements were constipation and more than one-fourth were diarrhea). If patients meet diagnostic criteria for IBS but cannot be accurately categorized into one of the other three subtypes, they are considered to have IBS unclassified.

The ACG guidelines recommend that IBS-C be first treated with soluble fiber. If this fails to improve symptoms, patients should then be treated with an osmotic laxative such as polyethylene glycol (PEG), as recommended by the AGA. If the IBS-C is not controlled with those two options, the newer drugs such as Amitiza, Linzess, or Trulance can be used. Guidelines have been updated to include Ibsrela. It should be noted that clinical trials with Ibsrela were placebo controlled and therefore no superiority claims can be made with Ibsrela as compared to other IBS-C agents, such as Amitiza, Linzess, or Trulance.

Opioid Induced Constipation (OIC)
Opioids are an integral component of therapy for severe chronic pain in patients with serious chronic illnesses. Unfortunately, one of the most common side effects associated with the use of opioids is constipation. Initial therapy includes fiber and laxatives, similar to the other constipation variants. Various other medications exist to treat opioid induced constipation, one of which is Amitiza.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Motegrity is a 5-HT_4 receptor agonist approved in late 2018 for the treatment of chronic idiopathic constipation in adults. Ibsrela, an inhibitor of NHE3, was approved in 2019 for the treatment of IBS-C in adults, however it became available in 2022.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Motegrity

The efficacy of Motegrity was established in six randomized, double-blind, placebo-controlled, multicenter studies in patients with CIC. The primary efficacy endpoint was percentage of subjects with ≥ 3 complete spontaneous bowel movements per week over the study period. The percentage of responders in the Motegrity group across the trials ranged from 19% to 38% vs. 10% to 20% in the placebo group. Response rates were statistically significant in 5 of the 6 clinical trials.

Ibsrela

The efficacy of Ibsrela for the treatment of IBS-C was established in two double-blind, placebo-controlled, randomized, multicenter trials in adult patients: Trial 1 and Trial 2. The intent-to-treat analysis population included 620 patients in Trial 1 and 606 patients in Trial 2. In these clinical trials, Ibsrela was administered immediately prior to breakfast or the first meal of the day and immediately prior to dinner.

To enter the trials, all patients met Rome III criteria for IBS-C and were required to meet the following clinical criteria during the 2-week baseline run-in period: 1.) a mean abdominal pain score of at least 3 on a 0-to-10-point numeric rating scale where a score of 0 indicates no pain and 10 indicates very severe pain; 2.) less than 3 complete spontaneous bowel movements per week, where a complete spontaneous bowel movement is defined as a spontaneous bowel movement that is associated with a sense of complete evacuation (a spontaneous bowel movement is a bowel movement occurring in the absence of laxative use); and 3.) less than or equal to 5 spontaneous bowel movements per week.

The trial designs were identical through the first 12 weeks of treatment, and thereafter differed in that Trial 1 continued for an additional 14 weeks of treatment (26 weeks double-blind treatment), whereas Trial 2 included a 4-week randomized withdrawal period.

Efficacy of Ibsrela was assessed using responder analyses based on daily diary entries. In both trials, the primary endpoint was the proportion of responders, where a responder was defined as a patient achieving both the stool frequency and abdominal pain intensity responder criteria in the same week for at least 6 of the first 12 weeks of treatment. The stool frequency (complete spontaneous bowel movements) and abdominal pain responder criteria assessed each week were defined as: 1.) complete spontaneous bowel movement responder: a patient who experienced an increase of at least 1 complete spontaneous bowel movement in weekly average from baseline; 2.) Abdominal pain

responder: a patient who experienced at least a 30% reduction in the weekly average of abdominal pain score compared with baseline. The responder rates for the primary endpoint and components of the primary endpoint (complete spontaneous bowel movements and abdominal pain) were 37% in the Ibsrela group vs. 24% in the placebo group in Trial 1 and 27% in the Ibsrela group vs. 19% in the placebo group in Trial 2.

Conclusion
The patient selection criteria presented in this policy takes into consideration the FDA approved indications of these drugs as well as other therapeutic alternatives that currently exist for these conditions. There have been no direct, head-to-head comparisons of Motegrity or Ibsrela to other drugs in this treatment category (e.g., Amitiza, Linzess, Trulance) that would indicate Motegrity or Ibsrela are more efficacious than any of the existing treatment modalities.

References

1. Trulance [package insert]. Synergy Pharmaceuticals, Inc. New York, New York. Updated February 2018.
2. Trulance Drug Evaluation. Express Scripts. Updated February 2017.
3. Amitiza [package insert]. Takeda Pharmaceuticals, Sucampo Pharma. Deerfield, Illinois/Rockville, Maryland. Updated September 2016.
4. Linzess [package insert]. Allergan. Irvine, California. Updated January 2017.
5. Bharucha AE, Dorn SD, Lembo A, et al. American Gastroenterological Association medical position statement on constipation. Gastroenterology. 2013;144:211-217. Available at: http://www.gastrojournal.org/article/S0016-5085(12)01545-4/pdf. Accessed on February 7, 2017.
6. Chang, L., Chey, WD. et al. American Gastroenterological Association-American College of Gastroenterology Clinical Practice Guideline: Pharmacological Management of Chronic Idiopathic Constipation. The American Journal of Gastroenterology 118(6):p 936-954, June 2023. | DOI: 10.14309/ajg.0000000000002227
7. Chang, L., Sultan, S., et al. AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Constipation. Gastroenterology 2022;163:118-136. Available at: https://www.gastrojournal.org/action/showPdf?pii=S0016-5085%2822%2900390-0. Accessed on June 23, 2023.
8. Ford AC, Moayyedi P, Lacy BE. American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation. Am J Gastroenterol. 2014;109:S2-S26. Available at: http://gi.org/wp-content/uploads/2014/08/IBS_CIC_Monograph_AJG_Aug_2014.pdf. Accessed on January 24, 2017
9. UpToDate. Treatment of Irritable Bowel Syndrome in Adults. Accessed March 2018.
10. UpToDate. Clinical Manifestations and diagnosis of irritable bowel syndrome in adults. Accessed March 2018.
11. Motegrity [package insert]. Shire US. Lexington, Massachusetts. Updated December 2018.

12. Motegrity Drug Evaluation. Express Scripts. Updated January 2019.
13. Lubiprostone [package insert]. Par Pharmaceuticals. Chestnut Ridge New York. Updated November 2020.
14. Ibsrela [package insert]. Ardelyx, Inc. Waltham, Massachusetts. April 2022.

Policy History

Original Effective Date: 04/19/2017
Current Effective Date: 04/01/2025
Medical Policy Committee review

04/19/2017	Medical Policy Implementation Committee approval. New policy.
04/05/2018	Medical Policy Committee review
04/18/2018	Medical Policy Implementation Committee approval. Added IBS-C indication with relevant background information and rationale
04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2019	Medical Policy Committee review
06/19/2019	Medical Policy Implementation Committee approval. Title changed from "Trulance (plecanatide)" to "Select Drugs for Constipation". Added a new product, Motegrity, to this policy and updated relevant Background, FDA, and Rationale sections.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Added newly approved, Zelnorm, to the policy. Updated relevant policy sections.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/02/2021	Medical Policy Committee review
12/08/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. Added branded Lubiprostone to the policy with applicable criteria. Updated the remainder of the policy with relevant information regarding the new drug addition.
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. Added a new product, Ibsrela, to the medical policy and updated relevant sections.
07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. Removed branded Lubiprostone as a targeted product from policy. Removed branded Amitiza as a

	prerequisite product and added generic lubiprostone as a prerequisite product. Updated relevant sections.
08/01/2024	Medical Policy Committee review
08/14/2024	Medical Policy Implementation Committee approval. Removed Trulance as a targeted product from this policy. Updated PA criteria to read as requiring "TWO of the following" and included Trulance in options for trial and failure. Removed discontinued product, Zelnorm, from policy. Updated relevant sections.
03/06/2025	Medical Policy Committee review
03/12/2025	Medical Policy Implementation Committee approval. Generic prucalopride added to the policy with new criterion requiring trial of generic prucalopride prior to brand Motegrity.

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.