Select Drugs for Constipation

Policy # 00557
Original Effective Date: 04/16/2017
Current Effective Date: 08/14/2023

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 Trulance™‡ (plecanatide), Motegrity™‡ (prucalopride), Zelnorm™‡ (tegaserod), 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 Trulance (plecanatide), Motegrity (prucalopride), Zelnorm (tegaserod), 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 Trulance requests:
    - Chronic Idiopathic Constipation (CIC); OR
    - Irritable Bowel Syndrome with Constipation (IBS-C); OR
  - For Motegrity requests:
    - Chronic Idiopathic Constipation (CIC); OR
  - For Zelnorm and Ibsrela requests:
    - Irritable Bowel Syndrome with Constipation (IBS-C); AND
- Patient meets the following for the requested drug:
  - For Trulance, Ibsrela, and Motegrity requests:
    - Patient is 18 years of age or older; OR
  - For Zelnorm requests:
    - Patient is a female; AND
    - Patient is at least 18 years of age AND less than 65 years of age; AND

- For all requests: 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)*
- For all requests: Patient has tried and failed (e.g., intolerance or inadequate response) both generic lubiprostone and Linzess®‡ (linaclotide) unless there is clinical evidence or patient history that suggests the use of both generic lubiprostone and Linzess (linaclotide) 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 Trulance (plecanatide), Motegrity (prucalopride), Zelnorm (tegaserod), or Ibsrela (tenapanor) when the patient has NOT tried and failed fiber and laxative products as well as generic lubiprostone and Linzess (linaclotide), where applicable, 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 Trulance (plecanatide), Motegrity (prucalopride), Zelnorm (tegaserod), or Ibsrela (tenapanor) when the patient selection criteria are not met (EXCEPT those denoted as **not medically necessary****) to be **investigational.***

Background/Overview

Trulance is a guanylate cyclase-C agonist indicated in adults for the treatment of CIC and IBS-C. The recommended adult dosage of Trulance for both indications is 3 mg taken orally once daily. Trulance is available in 3 mg tablets.

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.

Zelnorm is a 5-HT_4 receptor agonist indicated for the treatment of adult women less than 65 years of age with IBS-C. The recommended dosage for Zelnorm is 6 mg taken orally twice daily and is available in 6 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®‡ or Linzess can be used. Guidelines have been updated to include Trulance and Motegrity. It should be noted that clinical trials with Trulance and Motegrity were placebo controlled and therefore no superiority claims can be made with Trulance or Motegrity as compared to other CIC agents, such as Amitiza or Linzess.

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 or Linzess can be used. Guidelines have been updated to include Zelnorm and Ibsrela. It should be noted that clinical trials with Trulance, Zelnorm, and Ibsrela were placebo controlled and therefore no superiority claims can be made with Trulance, Zelnorm, or Ibsrela as compared to other IBS-C agents, such as Amitiza or Linzess. As a side note, of all the available products, Zelnorm carries a contraindication for cardiovascular disease, which will limit its place in therapy.

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)
Trulance is a guanylate cyclase-C agonist indicated in adults for the treatment of chronic idiopathic constipation. In January 2018, Trulance received the additional indication for the treatment of adults with IBS-C. Motegrity is a 5-HT_4 receptor agonist approved in late 2018 for the treatment of chronic idiopathic constipation in adults. Zelnorm is a 5-HT_4 receptor agonist indicated for the treatment of adult women less than 65 years of age with IBS-C. Note that Zelnorm was voluntarily withdrawn from U.S. marketing in 2007 due to concerns over a possible cardiovascular safety signal but was re-introduced in 2019. 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 federal regulations, other plan medical policies, and accredited national guidelines.

Trulance
The efficacy of Trulance in chronic idiopathic constipation was evaluated in two, 12 week, double-blind, placebo-controlled, randomized, multi-center clinical studies in adult patients. Subjects were randomized 1:1 to either receive placebo or Trulance 3 mg daily. The efficacy of Trulance was assessed using a responder analysis and change-from-baseline complete spontaneous bowel movements and spontaneous bowel movements. This was assessed using information provided by patients on a daily basis in an electronic diary. A responder is defined as a patient who had at least 3 complete spontaneous bowel movements in a given week and an increase of at least 1 complete spontaneous bowel movement from baseline in the same week for at least 9 weeks out of the 12 week treatment period and at least 3 of the last 4 weeks of the study. In the first study, the Trulance group had a 21% responder rate vs. a 10% responder rate in the placebo group (a difference of 11%). In study 2, the Trulance group had a 21% responder rate vs. a 13% responder rate in the placebo group (a difference of 8%).

The efficacy of Trulance for the management of symptoms of IBS-C was established in two 12-week, double-blind, placebo-controlled, randomized, multicenter clinical studies in adult patients. In both studies, patients were randomized 1:1 to receive Trulance 3 mg once daily or placebo. Patients were required to meet the Rome III criteria for IBS for at least 3 months prior to the screening visit, with symptom onset for at least 6 months prior to diagnosis. Efficacy was assessed using a responder analysis of patient-kept daily electronic diaries based on abdominal pain intensity and a stool frequency responder endpoint. A responder was defined as a patient who met both the abdominal pain intensity and stool frequency responder criteria in the same week for at least 6 of the 12 treatment weeks. In the first study, 30% of patients were responders compared to 18% of placebo patients (a difference of 12%). In the second study, 21% of patients were responders compared to 14% of placebo patients (a difference of 7%).

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.

Zelnorm
The efficacy of Zelnorm was established in three multicenter, double-blind, placebo-controlled trials, which enrolled 2,470 women (mean age 43 years [range 17 to 89 years]) with at least a 3-month history of IBS-C symptoms prior to the baseline period that included abdominal pain, bloating and constipation. Patients received either Zelnorm 6 mg twice daily or placebo. The design for the three trials consisted of a 4-week placebo-free baseline period followed by a 12-week double-blind treatment period. Studies 1 and 2 evaluated a fixed dose regimen of Zelnorm 6 mg twice daily while Study 3 utilized a dose-titration design. Each week of the 4-week placebo-free baseline period and the 12-week double-blind treatment period, patients were asked the question, "Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain and altered bowel habit. Compared to the way you usually felt before entering the trial, how would you rate your relief of symptoms during the past week?" The response variable consisted of the following five categories: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Patients were classified as responders within a month if they were considerably or completely relieved for at least two of the four weeks, or if they were at least somewhat relieved for each of the four weeks. In study 1 at month 1, there was a 31% responder rate in the Zelnorm group vs. 17% in the placebo group. In study 2 at month 1, there was a 35% responder rate in the Zelnorm group vs. 22% in the placebo group. In study 3 at month 1, there was a 34% responder rate in the Zelnorm group vs. 20% in the placebo group. At 3 months, the responder rates were 39%, 44%, and 43% in studies 1, 2, and 3, respectively. The placebo responder rate at 3 months was 28%, 29%, and 38%, respectively.

In two randomized, placebo-controlled, double-blind trials enrolling 288 males, efficacy response rates were similar between Zelnorm and placebo in the male subgroup

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 Trulance, Motegrity, Zelnorm, or Ibsrela to other drugs in this treatment category (e.g., Amitiza, Linzess) that would indicate Trulance, Motegrity, Zelnorm, or Ibsrela are more efficacious than any of the existing treatment modalities.

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References

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Policy History

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04/06/2017	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

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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.
Next Scheduled Review Date: 07/2024

*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.