BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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MOTEGRITY™ (prucalopride)
RELISTOR® (methylnaltrexone bromide)
SYMPROIC® (naldemedine tosylate)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

MOTEGRITY™ (prucalopride)
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Section A. Chronic Idiopathic Constipation (CIC): Motegrity (prucalopride)

- **Criteria for initial therapy:** Motegrity (prucalopride) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist
2. Individual is 18 years of age or older
3. A confirmed diagnosis of **chronic idiopathic constipation**
4. The constipation satisfies **ALL** of the following Rome III/IV criteria:
    a. Less than 3 spontaneous bowel movements per week
    b. Bristol Stool Form Scale of 1 or 2 for at least 25% of bowel movements
    c. Straining during at least 25% of bowel movements
    d. Sensation of incomplete evacuation after bowel movements for at least 25% of bowel movements
    e. Sensation of anorectal obstruction/blockage for at least 25% of bowel movements
5. Documented failure, contraindication per FDA label, or intolerance to at least **ONE** agent from **EACH** of the following:
    a. Oral senna with a stool softener used on schedule (not on an as needed basis)
    b. Oral osmotic agent **OR** saline agent used **EITHER** routinely **OR** on an as needed basis
    c. Oral **OR** rectal stimulant used on an as needed basis
6. Documented failure, contraindication per FDA label, or intolerance to Linzess (linaclotide)
7. There are **NO** FDA label contraindications, such as:
    a. Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megalocolon/megarectum
8. The constipation is not due to any secondary cause or suspected to be drug induced
9. Drugs that are known to cause constipation have been discontinued
10. Individual does not have end-stage renal disease requiring dialysis

Initial approval duration: 6 months

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- **Criteria for continuation of coverage (renewal request):** Motegrity (prucalopride) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist

  2. Individual's condition responded while on therapy
     a. Response is defined as **BOTH**:
        i. Achieved and maintains Type 3 or 4 Bristol Stool Form
        ii. Achieved and maintains 3 or more spontaneous bowel movements per week without laxative use

  3. Individual has been adherent with the medication

  4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
     a. Contraindications as listed in the criteria for initial therapy section
     b. Significant adverse effect such as:
        i. Persistent worsening of depression or the emergence of suicidal thoughts and behaviors, or any unusual changes in mood or behavior
        ii. Severe or persistent diarrhea
        iii. Severe, persistent, or worsening abdominal pain

  5. The constipation is not due to any secondary cause or suspected to be drug induced

  6. Drugs that are known to cause constipation have been discontinued

  7. Individual does not have end-stage renal disease requiring dialysis

  8. There are no significant interacting drugs

  Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of a Non-Cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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Section B. Opioid-Induced Constipation (OIC): Relistor (methylnaltrexone) Symproic (naldemedine)

- **Criteria for initial therapy:** Relistor (methylnaltrexone bromide) or Symproic (naldemedine) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist, Oncologist, or Pain Management Specialist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of **opioid-induced constipation** (OIC) defined as **ALL** of the following:
    a. Less than 3 spontaneous bowel movements per week
    b. Bristol Stool Form Scale of 1 or 2 for at least 25% of bowel movements
    c. Straining during at least 25% of bowel movements
    d. Sensation of incomplete evacuation after bowel movements for at least 25% of bowel movements
    e. Sensation of anorectal obstruction/blockage for at least 25% of bowel movements

4. OIC is **ONE** of the following:
    a. Individual with chronic non-cancer pain who does not require frequent (e.g., weekly) opioid dosage escalation and is to continue with same opioid regimen (same drug, same dose, and same frequency) for pain control **and** there is medical record documentation of a trial and failure of **opioid dose reduction** of $\geq$ 15%
    b. Individual is receiving palliative care for an advanced illness or pain caused by active cancer **AND** requires stable opioid dosage

5. Individual has been taking opiate medication for at least 4 weeks

6. Documented failure, contraindication per FDA label or intolerance to **ONE** agent from each of the following:
    a. Oral senna with a stool softener used on schedule (not on an as needed basis)
    b. Oral osmotic agent **OR** saline agent used **EITHER** routinely **OR** on an as needed basis
    c. Oral **OR** rectal stimulant used on an as needed basis

7. **ONE** of the following:
    a. **For Relistor (methylnaltrexone) tablet only:**
        i. Failure, contraindication per FDA label, or intolerance to Amitiza (lubiprostone)

    b. **For Relistor (methylnaltrexone) subcutaneous injection only, BOTH of the following:**
        i. Failure, contraindication per FDA label, or intolerance to Amitiza (lubiprostone)
        ii. Failure, contraindication per FDA label, or intolerance to the oral Relistor (methylnaltrexone)

c. **For Symproic (naldemedine) only:**
   i. Will not be used in an individual with severe hepatic impairment (Child-Pugh Class C)

8. There are **NO** FDA label contraindications, such as:
   a. Patients with known or suspected mechanical gastrointestinal obstruction
   b. Patients at increased risk of recurrent obstruction

9. The constipation is not due to any secondary cause or suspected to be drug induced other than from use of opioids

10. Drugs that are known to cause constipation have been discontinued

11. Will not be used with another opioid antagonist

Initial approval duration:
- For OIC chronic non-cancer pain: 6 months
- For OIC palliative care for advanced illness: 4 months

- **Criteria for continuation of coverage (renewal request):** Relistor (methylnaltrexone bromide) or Symproic (naldemedine) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gastroenterologist, Oncologist, or Pain Management Specialist

2. Individual's condition responded while on therapy
   a. Response is defined as **BOTH**:
      i. Achieved and maintains Type 3 or 4 Bristol Stool Form
      ii. Three or more spontaneous bowel movements (SBMs) per week
         – SBM is defined as a bowel movement that occur without laxative use

3. Individual has been adherent with the medication **and** continues to be **ONE** of the following:
   a. Chronic non-cancer pain who does not require frequent (e.g., weekly) opioid dosage escalation and is to continue with same opioid regimen (same drug, same dose, and same frequency) for pain control
   b. Receiving palliative care for an advanced illness or pain caused by active cancer **AND** requires stable opioid dosage

4. Individual has not developed any FDA label contraindications or other significant adverse drug effects that may exclude continued use
   a. Contraindications as listed in the criteria for initial therapy section
   b. Significant adverse effect such as:
      i. Gastrointestinal perforation
      ii. Severe or persistent diarrhea

iii. Severe, persistent, or worsening abdominal pain

5. There are no significant interacting drugs

Renewal duration:
- For OIC chronic non-cancer pain: 6 months
- For OIC palliative care for advanced illness: 6 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of a Non-Cancer Medications**

2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

Motegrity (prucalopride) is a serotonin type-4 (5-HT4) receptor agonist indicated for the treatment of chronic idiopathic constipation (CIC) in adults. Prucalopride is a gastrointestinal (GI) prokinetic agent that stimulates colonic peristalsis (high-amplitude propagating contractions [HAPCs]), which increases bowel motility. In animal studies, prucalopride facilitates acetylcholine release to enhance the amplitude of contractions and stimulate peristalsis and stimulates gastrointestinal motility with contractions starting from the proximal colon to the anal sphincter.

Relistor (methylnaltrexone) oral tablet is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. **Relistor (methylnaltrexone)** injection is indicated for the treatment of OIC in adults with chronic non-cancer pain and the treatment of OIC in adults with advanced illness who are receiving palliative care and response to laxative therapy has not been sufficient. Methylnaltrexone is an antagonist of opioid binding at the mu-opioid receptor. It does not cross the blood brain barrier; it is a peripherally-acting mu-opioid receptor antagonist in tissues, including the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting with the centrally opioid-mediated effects of opioid analgesia.

Symproic (naldemedine) tablets are indicated for the treatment of OIC in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation. Naldemedine is a derivative of naltrexone; where a modification in the chemical structure of naltrexone side chain reduced its ability to cross the blood-brain barrier. As a result, the penetration of naldemedine into central nervous system is expected to be negligible at the recommended dose levels, limiting the potential for interference with centrally-mediated opioid analgesia. Opioid receptors are widely distributed in the central and peripheral nervous system, intestines, and other tissues. There are three types of receptors involved in mediating the effects of opioids. These include delta, kappa, and mu receptors. They belong to the family of G-protein coupled receptors that regulate adenylate cyclase. Stimulation of the receptor results in

inhibition of adenyate cyclase with a reduction of neuron excitability and neurotransmitter release. The end result is inhibition of the affected neuron.

Constipation is a syndrome that may be defined by symptoms of difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation that may occur either alone or due to another medical disorder. The definition of constipation will differ from individual to individual, culture to culture, and even region to region. Patients may define constipation as straining during defecation or change in stool consistency or frequency.

Functional constipation may be defined by the Rome IV criteria as the presence of at least two of the following: straining during at least 25% of bowel movements; passage of lumpy or hard stools at least 25% of bowel movements; sensation of incomplete evacuation at least 25% of bowel movements; anorectal obstruction or blockage at least 25% of bowel movements; the need to use manual maneuvers to facilitate defecation at least 25% of bowel movements; and passing fewer than three stools per week. The criteria also include that loose stools may only rarely be present without the use of laxatives, and that there are insufficient criteria for a diagnosis of irritable bowel syndrome (IBS).

Chronic constipation can result in hemorrhoid formation, rectal pain and burning, bowel obstruction, bowel rupture, as well as upper gut dysfunctions, including gastroesophageal reflux disease, nausea, and abdominal distention.

OIC is a result of use of opioid medications with ensuing loss of gastrointestinal tone, contractility, and mobility. OIC is defined as: new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy and must include two or more of the symptoms defining functional constipation (see above) with the same frequency cutoff (25%). The cause of OIC is multifactorial and includes: inhibition of gastric emptying; reduction of mucosal secretions; reduced bowel tone and contractility; decreased peristalsis with delayed transit; and increased fluid and electrolyte absorption from increased contact time. Tolerance to opioid induced gastrointestinal adverse effects does not occur.

Opioid medications are increasingly used not only for the management of acute pain but also for the long term management of cancer related and non-cancer related chronic pain syndromes. With increased use of opioids for pain there is also an increase in adverse effects from their use which includes OIC and opioid bowel dysfunction.

Definitions:

The Bristol Stool Form Scale (BSFS) – seven types:

- Type 1: separate hard lumps, like nuts (hard to pass), also known as *goat feces*
- Type 2: sausage-shaped, but lumpy
- Type 3: like a sausage but with cracks on its surface
- Type 4: like a sausage or snake, smooth and soft
- Type 5: soft blobs with clear-cut edges (passed easily)
- Type 6: fluffy pieces with ragged edges, a mushy stool
- Type 7: watery, no solid pieces, entirely liquid

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Types 1 and 2 indicate constipation, with types 3 and 4 indicating the ideal stools (especially the latter), as they are easy to defecate while not containing excess liquid, and types 5, 6 and 7 specify diarrheal stools

Rome III/IV Diagnostic criteria for functional gastrointestinal disorders:

Functional Constipation - adult

ALL of the following diagnostic criteria - Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis:

- Must include ***two or more*** of the following:
  - Straining during at least 25% of bowel movements
  - Lumpy or hard stools in at least 25% of bowel movements
  - Sensation of incomplete evacuation for at least 25% of bowel movements
  - Sensation of anorectal obstruction/blockage for at least 25% of bowel movements
  - Manual maneuvers to facilitate at least 25% of bowel movements (e.g., digital evacuation, support of the pelvic floor)
  - Fewer than three bowel movements per week
  - Loose stools are rarely present without the use of laxatives
  - Insufficient criteria for irritable bowel syndrome

Laxatives:

Bulk forming – calcium polycarbophil, cellulose, fiber, malt soup, methylcellulose, psyllium
Osmotic – glycerin, lactulose, polyethylene glycol, sodium phosphate, sorbitol
Lubricating – mineral oil
Saline – magnesium citrate, magnesium hydroxide, magnesium oxide, magnesium sulfate
Softener – dioctyl calcium sulfosuccinate, dioctyl sodium sulfosuccinate
Stimulant/Irritant – bisacodyl, cascara, senna
Other – castor oil, ceo-two

Partial mu-opioid receptor antagonist (PAMORA):

Relistor (methylnaltrexone) – quaternary derivative of naltrexone
Symproic (naldemedine)
Movantik (naloxegol) – naloxone conjugated with a polyethylene glycol polymer

Type 2 chloride channel activator – Secretagogue:

Amitiza (lubiprostone)

Guanylate cyclase-C receptor agonist – Secretagogue:

Linzess (linaclotide)
Trulance (plecanatide)

5HT4 receptor agonist – Prokinetic agent:

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Resources:

Motegrity (prucalopride) product information, revised by Takeda Pharmaceuticals America, Inc. 11-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on March 26, 2021.

Relistor (methylnaltrexone) product information, revised by Salix Pharmaceuticals, Inc. 04-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on March 26, 2021.

Symproic (naldemedine) product information, revised by BioDelivery Sciences International, Inc. 05-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on March 26, 2021.

Wald A. Management of chronic constipation in adults. In: UpToDate, Talley NJ, Grover S (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on March 26, 2021.

Portenoy RK, Mehta Z, Ahmed E. Prevention and management of side effects in patients receiving opioids for chronic pain. In: UpToDate, Abrahm J, Savarese DMF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on March 26, 2021.

Rao SSC. Constipation in the older adult. In: UpToDate, Talley NJ, Schmader KE, Grover S (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on March 26, 2021.

Crockett SD, Greer KB, Heidelbaugh JJ, et al.: American Gastroenterology Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. Gasterenterol 2019 Jan; 156 (1):218-226. Accessed March 29, 2021.