RELISTOR® (methylnaltrexone bromide) oral tablet

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.

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Description:

Relistor (methylnaltrexone) oral tablet is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain and is indicated for the treatment of OIC in adults with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Relistor (methylnaltrexone) is also available as an injection for subcutaneous use. For criteria for use see Medical Coverage Guideline for Relistor (methylnaltrexone bromide).

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.

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.
RELISTOR® (methylnaltrexone bromide) oral tablet (cont.)

Patients may define constipation as straining during defeation or change in stool consistency or frequency. Functional constipation may be defined by the Rome III criteria as the presence of at least two of the following: straining at stool; passage of lumpy or hard stools; sensation of incomplete evacuation or anorectal obstruction or blockage; the need to use manual maneuvers to facilitate defeation; and passing fewer than three stools per week. OIC is a result of use of opioid medications with resultant loss of gastrointestinal tone, contractility, and mobility.

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.

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

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

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.

Definitions:

Laxatives:
- Bulk forming – calcium polycarbophil, methylcellulose, psyllium
- Osmotic – glycerin, lactulose, polyethylene glycol, sorbitol
- Lubricating – mineral oil
- Saline – magnesium citrate, magnesium hydroxide, magnesium sulfate
- Softener – dioctyl calcium sulfosuccinate, dioctyl sodium sulfosuccinate
- Stimulant – bisacodyl, cascara, senna

Prokinetic agent:
- Metoclopramide

Drug related events:
- Ineffective / failure
  Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened
A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

**Adverse Drug Event:** Allergic reaction / Hypersensitivity / Intolerance

Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual’s outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

*Allergic reaction / hypersensitivity* – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

*Intolerance* – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

**Contraindication**

Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

**Non-adherence**

Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

**Precertification:**

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.
RELISTOR® (methylNaltrexone bromide) oral tablet (cont.)

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://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.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Relistor (methylNaltrexone bromide) requires completion of the specific request form in its entirety. 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 email to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Relistor (methylNaltrexone bromide) is considered *medically necessary* when ALL of the following criteria are met:
  1. Individual is 18 years of age or older
  2. Medical record documentation of a confirmed diagnosis of opioid-induced constipation and **ONE** of the following:
      - Individual with non-cancer pain
      - Individual with advanced illness who is receiving palliative care
  3. Medical record documentation that individual has been taking opiate medication for at least 4 weeks **AND** needs to continue opiate medication
  4. Medical record documentation that individual’s response to laxative therapy has not been sufficient **AND** has tried and failed or has a contraindication to **ALL** of the following bowel care regimen:
      - Oral senna with a stool softener used on schedule (not on an as needed basis)
      - Oral osmotic agent OR saline agent used **EITHER** routinely OR on an as needed basis
      - Oral OR rectal stimulant used on an as needed basis
      - Oral prokinetic agent used routinely (not on an as needed basis)
  5. Absence of **ALL** of the following contraindications:
      - Known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction
  6. Absence of **ALL** of the following exclusions:
      - Concomitant use with other opioid antagonists
      - Woman breast feeding an infant or a child
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- Relistor (methylnaltrexone bromide) for all other indications not previously listed is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

Resources:

BCBSAZ Medical Coverage Guidelines for Relistor Injection O572.7.


FDA-approved indication and dosage:

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<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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| RELISTOR is an opioid antagonist. RELISTOR tablets are indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain. | RELISTOR tablets:  
- For OIC in adult patients with chronic non-cancer pain the recommended dosage is 450 mg once daily in the morning.  
- The recommended dosage in adult patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) is 150 mg, once daily in the morning. |
| Limitations of Use: Use beyond four months has not been studied in the advanced illness population. |  |