BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 11/17/16**
SECTION: DRUGS	**LAST REVIEW DATE: 11/16/17**
	LAST CRITERIA REVISION DATE: 11/16/17
	ARCHIVE DATE:

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.

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.**

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

Description:

Relistor (methylnaltrexone) oral tablet is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. Relistor (methylnaltrexone) is also available as an injection for subcutaneous use. For criteria for use see Medical Coverage Guideline for Relistor (methylnaltrexone bromide).

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.

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.

Opioids & Constipation:

- 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
    - Patients may define constipation as straining during defecation or change in stool consistency or frequency

- Bristol Stool Form Scale – seven types of stool are:
    - 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

    - Types 1 and 2 indicate constipation, with types 3 and 4 indicainge 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

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

- 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
  - Passing fewer than three stools per week

- 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
    - 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
  - 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
  - Upper gut dysfunctions, including gastroesophageal reflux disease, nausea, and abdominal distention

Definitions:

Laxative types:

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

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

Prokinetic agent:
Metoclopramide

Relistor (methylnaltrexone bromide) oral

Medication class:
Gastrointestinal agent, opioid antagonist

FDA-approved indication(s):
- Treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation

Recommended Dose:
- 450 mg once daily

Maximum dosage
- 450 mg once daily

Available Dosage Forms:
- 150 mg tablets

Warnings and Precautions:
- If there is a change in opioid regimen, re-evaluate continued need for Relistor
- Discontinue if opioid pain medication is discontinued
- Discontinue all maintenance laxatives before starting Relistor, may resume them if there is a suboptimal response to Relistor after 3 days
- Discontinue for severe, persistent or worsening abdominal pain
- Discontinue for severe or persistent diarrhea
- Avoid concomitant use with other opioid antagonists
- Monitor for opioid withdrawal symptoms such as excessive sweating, chills, diarrhea, abdominal pain, anxiety, and yawning
- Decrease dose to 150 mg once daily in individuals with moderate and severe renal impairment (CrCl < 60 mL/min)
- Decrease dose to 150 mg once daily in individuals with moderate or severe hepatic impairment (Child-Pugh Class B or C)
- Woman who is breast feeding an infant or a child should stop breast feeding

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

Criteria:

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

1. Individual is 18 years of age or older
2. A confirmed diagnosis of opioid-induced constipation (OIC) in an individual with chronic non-cancer pain
3. Individual has been taking opiate medication for at least 4 weeks **AND** needs to continue opiate medication
4. Medical record documentation of a trial and failure of opioid dose reduction of ≥ 15%
5. Individual has failure, contraindication or intolerance to **ALL** the following agents:
    - Oral senna with a stool softener used on schedule (not on an as needed basis)
        - Preferred regimen Sennoside tablet with dioctyl calcium sulfosuccinate, dioctyl sodium sulfosuccinate
    - Oral osmotic agent **OR** saline agent used **EITHER** routinely **OR** on an as needed basis
        - Preferred oral agents include:
            1. Lactulose, polyethylene glycol, sodium phosphate, sorbitol
        - Preferred oral saline agents include:
            1. Magnesium citrate, magnesium hydroxide, magnesium oxide, magnesium sulfate
    - Oral **OR** rectal stimulant used on an as needed basis
        - Preferred oral stimulant agents include:
            1. Bisacodyl or sennoside
        - Preferred rectal stimulant includes:
            1. Bisacodyl
    - Oral prokinetic agent used routinely (not on an as needed basis)
        - Preferred prokinetic agent includes
            1. Metoclopramide
6. There are **NO** contraindications:
    - Patients with known or suspected mechanical gastrointestinal obstruction and patients at increased risk of recurrent obstruction

Initial approval duration: 6 months

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

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

1. Individual's condition responded while on therapy
   - Response is defined as:
     - Type 3 or 4 Bristol Stool Form
     - Three or more spontaneous bowel movements (SBMs)/week
     - SBM is defined as a bowel movements that occur without laxative use

2. Individual has been adherent with the medication **and** continues to require same opioid regimen (same drug, same dose, and same frequency) for pain control

3. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section

4. There are no significant interacting drugs

Renewal duration: 12 months

Resources:

BCBSAZ Medical Coverage Guidelines for Relistor Injection O572.7.

Relistor. Package Insert. Revised by manufacturer 7/2016. Accessed 9/26/16.

UpToDate: Prevention and management of side effects in patients receiving opioids for chronic pain. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/prevention-and-management-of-side-effects-in-patients-receiving-opioids-for-chronic-pain?source=search_result&search=opioid%20induced%20constipation&selectedTitle=1~40

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.