Clinical Policy: Methylnaltrexone Bromide (Relistor)

Reference Number: CP.PMN.169
Effective Date: 12.01.18
Last Review Date: 11.24
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Methylnaltrexone bromide (Relistor®) is an opioid antagonist.

FDA Approved Indication(s)

Relistor tablets and injection are indicated for the treatment of opioid-induced constipation (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.

Relistor injection is indicated for the treatment of OIC in adult patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Relistor is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Opioid Induced Constipation (must meet all)**:**

1. Diagnosis of OIC;
2. Age ≥ 18 years;
3. Member has been taking opioid(s) for ≥ 4 weeks due to chronic pain not caused by active cancer;
4. Failure of one agent from each of the following classes while on opioid therapy, unless clinically significant adverse effects are experienced or all are contraindicated:
   a. Stimulant laxative (e.g., bisacodyl, senna);
   b. Osmotic laxative (e.g., lactulose, polyethylene glycol);
   c. Stool softener (e.g., docusate);
5. Member has used one of the aforementioned agents in the past 30 days, unless contraindicated;
6. Failure of Movantik®, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for Movantik*
7. Dose does not exceed the following one of the following (a or b):
   a. For tablets, both of the following (i and ii):
      i. 450 mg per day;

ii. 3 tablets per day;
b. Injection: FDA-approved weight-based dosing (*see Section V*).

Approval duration:
Medicaid/HIM – 6 months
Commercial – Tablets: 6 months; Injection: 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Opioid Induced Constipation (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member continues to receive opioid therapy;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed one of the following (a or b):
   a. For tablets, both of the following (i and ii):
      i. 450 mg per day;
      ii. 3 tablets per day;
   b. Injection: FDA-approved weight-based dosing (*see Section V*).

Approval duration:
Medicaid/HIM – 12 months
Commercial – Tablets: 6 months; Injection: 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
OIC: opioid induced constipation

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
bisacodyl (Dulcolax®)	Oral: 5 to 15 mg QD Rectal: Enema, suppository: 10 mg (1 enema or suppository) QD	15 mg/day PO; 10 mg/day rectally
senna (Senokot®)	1 to 2 tablets (8.6 to 17.2 mg sennosides) PO BID	68.8 mg sennosides/day (8 tablets/day)
lactulose	10 to 20 g (15 to 30 mL or 1 to 2 packets) daily; may increase to 40 g (60 mL or 2 to 4 packets) PO QD if necessary	40 g/day (60 mL or 2 to 4 packets/day)
polyethylene glycol 3350 (MiraLax®)	17 g (approximately 1 heaping tablespoon) of powder in 120 to 240 mL of fluid given PO QD	34 g/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
docusate sodium (Colace®)	50-300 mg/day PO given in single or divided doses	360 mg/day
Movantik® (naloxegol)	25 mg PO QD, if not tolerated, reduce to 12.5 mg PO QD	25 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction
- Boxed warning(s): none reported

Appendix D: General Information

- Advanced illness is defined as life-ending or terminal disease. In Relistor clinical trials, opioid induced constipation was defined as less than three bowel movements in the preceding week or no bowel movement for 2 days.
- The use of Relistor beyond four months has not been studied.

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>OIC in adult patients with advanced illness or pain caused by active cancer who require opioid dose escalation for palliative care</td><td>The recommended dosage regimen is one dose administered SC QOD, as needed. Do not administer more frequently than one dose per 24-hour period.

<u>Weight-Based Dosing of Relistor Injection</u>
<table>
<tr><th>Weight of Adult Patient</th><th>Subcutaneous Dose and Corresponding Injection Volume</th></tr>
<tr><td>Less than 38 kg</td><td>0.15 mg/kg*</td></tr>
<tr><td>38 kg to less than 62 kg</td><td>8 mg = 0.4 mL</td></tr>
<tr><td>62 kg to 114 kg</td><td>12 mg = 0.6 mL</td></tr>
<tr><td>More than 114 kg</td><td>0.15 mg/kg*</td></tr>
</table>
*Calculate the injection volume for these patients by multiplying the patient weight in kilograms by 0.0075 and then rounding up the volume to the nearest 0.1 mL.</td><td>Refer to dosing regimen</td></tr>
<tr><td>OIC in adult patients with chronic non-cancer pain</td><td>12 mg SC QD or 450 mg PO QD</td><td>12 mg/day SC
450 mg/day PO</td></tr>
</table>

VI. Product Availability

- Tablet: 150 mg

- Injections:
  - 8 mg/0.4 mL methylnaltrexone bromide in a single-dose pre-filled syringe
  - 12 mg/0.6 mL methylnaltrexone bromide in a single-dose pre-filled syringe, or single-dose vial

VII. References

1. Relistor Prescribing Information. Bridgewater, NJ: Salix Pharmaceuticals; May 2024. Available at: https://shared.salix.com/globalassets/pi/relistor-pi.pdf. Accessed July 15, 2024.
2. Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: Pathophysiology, clinical consequences, and management. *Gastroenterology Research and Practice*. 2014;2014:141737. doi:10.1155/2014/141737.
3. Argoff CE, Brennan MJ, Camilleri M, et al. Consensus recommendations on initiating prescription therapies for opioid-induced constipation. *Pain Med*. 2015;16(12):2324-37.
4. Pergolizzi JV, Raffa RB, Pappagallo M, et al. Peripherally acting μ-opioid receptor antagonists as treatment options for constipation in noncancer pain patients on chronic opioid therapy. *Patient preference and adherence*. 2017;11:107-119. doi:10.2147/PPA.S78042.
5. Nelson AD, Camilleri M. Chronic opioid induced constipation in patients with nonmalignant pain: challenges and opportunities. *Therap Adv Gastroenterol*. 2015;8(4):206-20.
6. Nelson AD, Camilleri M. Opioid-induced constipation: advances and clinical guidance. *Ther Adv Chronic Dis*. 2016;7(2): 121–134.
7. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: http://www.clinicalpharmacology-ip.com/.
8. Camilleri M, Lembo A, Katzka DA. Opioids in gastroenterology: Treating adverse effects and creating therapeutic benefits. *Clin Gastroenterol Hepatol*. 2017;15(9):1338-1349.
9. Crockett SD, Greer KB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guidelines on the medical management of opioid-induced constipation. *Gastroenterol*. 2019;156:218-226.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J2212	Injection, methylnaltrexone, 0.1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2020 annual review: no significant changes; references reviewed and updated.	06.30.20	11.20
4Q 2021 annual review: no significant changes; HIM.PHAR.21 revised to HIM.PA.154; added coding implications section; references reviewed and updated.	06.24.21	11.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2022 annual review: no significant changes; general information (appendix D) added; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	07.26.22	11.22
Per February SDC and prior clinical guidance; consolidated commercial line of business and retired CP.CPA.274; added redirection to Movantik.	02.21.23	05.23
4Q 2023 annual review: no significant changes; references reviewed and updated.	07.06.23	11.23
4Q 2024 annual review: no significant changes; references reviewed and updated.	07.15.24	11.24

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise

professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.