RELISTOR® (methylnaltrexone bromide) INJECTION FOR SUBCUTANEOUS USE

Non-Discrimination Statement and Multi-Language Interpreter Services information are located at the end of this document.

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

This Medical 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.

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

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

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

Description:

Relistor is an opioid antagonist indicated for:

- Treatment of opioid-induced constipation in adults with chronic non-cancer pain
- Treatment of opioid-induced constipation in adults with advanced illness who are receiving palliative care and response to laxative therapy has not been sufficient
DEFINITIONS:

Adult: Age 18 years and older

SIGNIFICANT ADVERSE DRUG EVENT:
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.

CRITERIA:

See Resources section for FDA-approved dosage.

- FDA-approved dosage of Relistor for the treatment of opioid-induced constipation in adults is considered medically necessary with documentation of ALL of the following:
  1. ONE of the following:
     - Chronic non-cancer pain
     - Receiving palliative care for an advanced illness
  2. Individual has been taking opiate medication for at least 4 weeks AND needs to continue opiate medication
  3. Response to laxative therapy has not been sufficient
  4. No documentation of known or suspected mechanical GI obstruction
  5. Failed response to the oral form of Relistor with documentation of ANY of the following:
     - Individual’s condition has not improved or has worsened
     - Individual experienced a significant adverse drug event to the oral form of the medication
     - Individual is intolerant to the oral form of the medication

- Relistor for all other indications not previously listed or if above criteria not met 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.
RELISTOR (methylnaltrexone bromide) INJECTION FOR SUBCUTANEOUS USE (cont.)

Resources:

Literature reviewed 12/20/16. We do not include marketing materials, poster boards and non-published literature in our review.

Relistor Package Insert:

- FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
</table>
| Opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain | For subcutaneous use only. Administer in the upper arm, abdomen or thigh. Do not inject at the same spot each time (rotate injection sites).
12 mg. once daily. Discontinue all maintenance laxative therapy prior to initiation of Relistor. Laxative(s) can be used as needed if there is a suboptimal response to Relistor after three days. Re-evaluate the continued need for Relistor when the opioid regimen is changed to avoid adverse reactions. Discontinue Relistor if treatment with the opioid pain medication is also discontinued. In adult patients with severe renal impairment (creatinine clearance less than 30 mL/min as estimated by Cockcroft-Gault), dose reduction of Relistor by one-half is recommended. No dosage adjustment is recommended for adult patients with mild to moderate renal impairment. Safety and effectiveness of Relistor have not been established in pediatric patients. |
RELISTOR (methylnaltrexone bromide) INJECTION FOR SUBCUTANEOUS USE (cont.)

Resources: (cont.)

Relistor Package Insert: (cont.)

- FDA-approved indication and dosage: (cont.)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid-induced constipation (OIC) in adult patients with advanced illness</td>
<td>For subcutaneous use only. Administer in the upper arm, abdomen or thigh. Do not inject at the same spot each time (rotate injection sites).</td>
</tr>
<tr>
<td></td>
<td>Inject one dose, every other day, as needed, but no more frequently than one dose in a 24-hour-period.</td>
</tr>
<tr>
<td></td>
<td>Weight of Adult Patient</td>
</tr>
<tr>
<td>Less than 38 kg</td>
<td>0.15mg/kg</td>
</tr>
<tr>
<td>38 kg to less than 62 kg</td>
<td>8 mg</td>
</tr>
<tr>
<td>62 kg to 114 kg</td>
<td>12 mg</td>
</tr>
<tr>
<td>More than 114 kg</td>
<td>0.15 mg/kg</td>
</tr>
</tbody>
</table>

¹ The injection volume for these patients should be calculated using the following method: Multiply the patient weight in kilograms by 0.00075 and round up the volume to the nearest 0.1 mL.

Use beyond four months has not been studied.

In adult patients with severe renal impairment (creatinine clearance less than 30 mL/min as estimated by Cockcroft-Gault), dose reduction of Relistor by one-half is recommended. No dosage adjustment is recommended for adult patients with mild to moderate renal impairment.

Safety and effectiveness of Relistor have not been established in pediatric patients.

Discontinue Relistor if treatment with the opioid pain medication is also discontinued.
RELISTOR (methylaltrexone bromide) INJECTION FOR SUBCUTANEOUS USE
(cont.)

Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ’s Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ’s Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1-800-368-1019, 800-537-7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html

Multi-Language Interpreter Services:

Spanish: Si usted, o alguien a quien usted está ayudando, tiene preguntas acerca de Blue Cross Blue Shield of Arizona, tiene derecho a obtener ayuda y información en su idioma sin costo alguno. Para hablar con un intérprete, llame al 602-864-4884.

Navajo: Díí kwe’é atah niilínígíí Blue Cross Blue Shield of Arizona haada yit’éego bina’idílíkidgo élí doodago Háída bí já aniyeedíígilí t’áadoo leé yíña’idílíkidgo bée hazaadk’ehíí háká a’óówolgo bée haza’ doó báñh ilínígóó. Ata’ halné’iígilí kojí’ bíchí’ hödilinh 877-475-4799.

Chinese: 如果您，或是您正在協助的對象，有關於插入項目的名稱 Blue Cross Blue Shield of Arizona 方面的問題，您有權利免費以您的母語得到幫助和訊息。洽詢一位翻譯員，請撥電話 請在此插入數字 877-475-4799。

Vietnamese: Nếu quý vị, hay người mà quý vị đang giúp đỡ, có câu hỏi về Blue Cross Blue Shield of Arizona quý vị sẽ có quyền được giúp và có thêm thông tin bằng ngôn ngữ của mình miễn phí. Để nói chuyện với một thợ dịch viên, xin gọi 877-475-4799.

Arabic:

إن كان لديك أو لدى شريكك أسئلة بخصوص Blue Cross Blue Shield of Arizona المستوردة بلغتك من دون دعم لغوي، للتحدث مع مترجم اتصل ب 877-475-4799.
RELISTOR (methylnaltrexone bromide) INJECTION FOR SUBCUTANEOUS USE
(cont.)

Multi-Language Interpreter Services: (cont.)

Tagalog: Kung ikaw o ang iyong tinitulungan, ay may mga katanungan tungkol sa Blue Cross Blue Shield of Arizona, may karapatan ka na makakuha ng tulong at impormasyon sa iyong wika ng walang gastos. Upang makausap ang isang tagasalin, tumawag sa 877-475-4799.

Korean: 만약 귀하 또는 귀하가 돕고 있는 어떤 사람이 Blue Cross Blue Shield of Arizona 에 관해서 질문이 있다면 귀하는 그러한 도움과 정보를 귀하의 언어로 비용 부담없이 원할 수 있는 권리가 있습니다. 그렇게 동역사와 얘기하기 위해서는 877-475-4799 로 전화하십시오.

French: Si vous, ou quelqu’un que vous êtes en train d’aider, a des questions à propos de Blue Cross Blue Shield of Arizona, vous avez le droit d’obtenir de l’aide et l’information dans votre langue à aucun coût. Parler à un interprète, appelez 877-475-4799.

German: Falls Sie oder jemand, dem Sie helfen, Fragen zum Blue Cross Blue Shield of Arizona haben, haben Sie das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Um mit einem Dolmetscher zu sprechen, rufen Sie bitte die Nummer 877-475-4799 an.

Russian: Если у вас или лица, которому вы помогаете, имеются вопросы по поводу Blue Cross Blue Shield of Arizona, то вы имеете право на бесплатное получение помощи и информации на вашем языке. Для разговора с переводчиком позвоните по телефону 877-475-4799.

Japanese: ご本人様、またはお客様の身の回りの方でも、Blue Cross Blue Shield of Arizona についてご質問がございましたら、ご希望の言語でサポートを受けたり、情報を探すしたりすることができます。料金はかかりません。通訳とお話しされる場合、877-475-4799 までお電話ください。

Farsi: آگر شما یا کسی که شما به او کمک می‌کنید، سوالی در مورد اطلاعاتی به زبان خود را به طور رایگان دریافت نمایید 877-475-4799.

Assyrian: Blue Cross Blue Shield of Arizona ناسیسی گەواسترا، ناسیسی گەواسترا، ناسیسی گەواسترا، ناسیسی گەواسترا، ناسیسی گەواسترا، ناسیسی گەواسترا، ناسیسی گەواسترا, 877-475-4799.

Serbo-Croatian: Ukoliko Vi ili neko kome Vi pomazete ima pitanje o Blue Cross Blue Shield of Arizona, imate pravo da besplatno dobijete pomoć i informacije na Vašem jeziku. Da biste razgovarali sa prevodiocem, nazovite 877-475-4799.

Thai: หากคุณ หรือผู้ที่คุณช่วยเหลือมีคำถามเกี่ยวกับ Blue Cross Blue Shield of Arizona คุณสามารถติดต่อได้โดยไม่ต้องเสียค่าช่าง ติดต่อที่ 877-475-4799