Off-Label Use of Drugs and Biologic Agents

Introduction

Before the Food and Drug Administration approves a drug, the drug company must show its drug is safe and effective when used as intended. (Safe doesn’t mean there are no side effects. Rather, safe means the FDA has found that the benefits of using the drug for its intended purpose outweigh the risks.) Based on the submitted information, the FDA approves drug labeling. This labeling tells healthcare providers the conditions the drug is approved to treat, how to use the drug, and its risks. Off-label use is when a drug is used for a condition or in a way the FDA has not approved. A provider can prescribe off-label use of a drug for several reasons. For example, there isn’t a specific drug to treat a medical condition or the drug has been well studied but FDA approval hasn’t been requested yet. Many off-label uses have been widely studied with results published in medical literature. This policy describes when off-label uses of drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
## Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
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| **Off-label use of a drug or biologic agent** | **Off-label use of a drug or biologic agent may be considered medically necessary if the indication for the use is supported by at least one of the following compendia:**  
  - American Hospital Formulary Service - Drug Information (AHFS-DI)  
  - Elsevier Gold Standard Clinical Pharmacology Compendium (Clinical Pharmacology)  
  - National Comprehensive Cancer Network Drugs and Biologics Compendium (NCCN)  
  - Truven Micromedex [formerly known as Thompson Micromedex DrugDex® Compendium] (Micromedex)  
  **OR**  
  **Scientific evidence shows that the drug/biologic agent is safe and effective for the off-label indication. The scientific evidence must:**  
  - Consist of an adequate number of well-designed studies with sufficient numbers of participants (related to incidence of the disease)  
  - Be published in major peer-reviewed scientific journals that publish original manuscripts only after they have been critically reviewed by independent unbiased experts for accuracy, validity and reliability  
  - Show consistent results across all studies  
  - Document a positive health outcome and demonstrate that the drug/biologic agent is as effective or is more effective than established treatment alternatives  
  - Document that the improvements are achievable outside of the research setting |
### Service

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<th>Off-label use of a drug or biologic agent</th>
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### Investigational

Prescription drugs and biologic agents are considered investigational or experimental in the following situations:

- The drug or biologic has not received approval for any indication from the U.S. Food and Drug Administration (FDA).
- The FDA determined a drug or biologic to be contraindicated for a specific condition or off-label use.
- The Pharmacy and Therapeutics (P&T) Committee classifies as investigational or experimental because the safety and/or efficacy cannot be established after reviewing the published scientific literature.

Drugs or biologic agents that are considered investigational or experimental are not covered because the safety and/or efficacy cannot be established after reviewing the published scientific literature.

**Note:** Medical policies that address individual drugs/biologic agents may override this policy (see Related Medical Policies).

### Coding

N/A

### Related Information

**Definition of Terms**

**Compendium:** A comprehensive listing of FDA approved drugs and biologic agents that includes:

- The name of the drug or biologic agent
- Summary of the pharmacologic characteristics
- Dosing information

- Recommended or endorsed uses in specific diseases

**Drug:** A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

**Off-label:** Use of a drug or biologic agent for indications or conditions other than those specifically approved by the U.S. Food and Drug Administration (FDA). The FDA approved use for drugs/biologic agents are stated in the package insert and available on the FDA website: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) (Accessed April 2020)

**Benefit Application**

Health plan contracts may address off-label use of drugs/biologic agents and refer to various compendia. Over time, compendia merge, change names or cease to exist. The clinical review team uses compendia endorsed by the Secretary of HHS and CMS to support coverage decisions when the compendia referenced in individual health plans are no longer in business.

A product or group's health plan contract may exclude coverage of a medication or a class of medications; such exclusion would override any review for a medical necessity determination or the off-label use of drugs/biologic agents addressed in a Medical Policy.

**Alaska**

Oregon

This policy adheres to the laws set forth in the Oregon state revised statutes, Chapter 743A Health insurance: Required reimbursements – Prescription drugs section 743A.062 et al. Available at: http://www.oregonlaws.org/ors/743A.062 (Accessed April 2020).

Washington


The off-label or unapproved use of any drugs/biologic agents dispensed within an approved clinical trial may be covered if the member contract allows for coverage of clinical trials or if the criteria are met as set forth in the Clinical Trials policy (see Related Medical Policies).

Evidence Review

Description

Approved indications or the labeled indications for drugs/biologic agents have been proven to be safe and effective by the FDA after the review of adequate and controlled clinical trials.

Unapproved or unlabeled uses of drugs include a variety of situations ranging from completely unstudied to thoroughly investigated uses of the drug/biologic agent, yet approval from the FDA has not been requested.

Many off-label uses are effective, well documented in the literature, and widely used.

National Comprehensive Cancer Network (NCCN) Compendium

The NCCN Drugs and Biologics Compendium is based directly on the NCCN Clinical Practice Guidelines in Oncology. The compendium lists specific panel recommendations for off-label uses of drugs, and each recommendation is supported by a level of evidence category.
The NCCN Categories of Evidence and Consensus used in the recommendations are:

- **Category 1**: The recommendation is based on high level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

- **Category 2A**: The recommendation is based on lower level evidence and there is uniform NCCN consensus.

- **Category 2B**: The recommendation is based on lower level evidence and there is non-uniform NCCN consensus (but no major disagreement).

- **Category 3**: The recommendation is based on any level of evidence but reflects major disagreement.

The accepted level of evidence for an off-label clinical indication is Category 1 or 2A; not 2B. (If a provider chooses to use NCCN level 2B evidence in support of a chemotherapeutic drug used for an off-label indication, The Company expects that the provider will make available for review, copies of significant peer-reviewed Phase II or Phase III studies demonstrating such support.)

**Centers for Medicare and Medicaid Services (CMS) Compendia List**

In 2008 CMS developed an annual review process (including criteria for transparency in the selection process) to recognize *compendia*. CMS may internally generate changes to the list at any time following investigation and public comment. On March 22, 2016, CMS announced the addition of Wolters Kluwer Lexi-Drugs® to their list of compendia used by the Medicare program. The following are recognized as authoritative CMS compendia at this time:

- American Hospital Formulary Service - Drug Information (AHFS-DI)
- Elsevier Gold Standard Clinical Pharmacology Compendium (Clinical Pharmacology)
- National Comprehensive Cancer Network Drugs and Biologics Compendium (NCCN)
- Truven Health Analytics Micromedex® DrugDex® Compendium
- Wolters Kluwer Lexi-Drugs®
References


History

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<th>Date</th>
<th>Comments</th>
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<tbody>
<tr>
<td>03/19/15</td>
<td>Update Related Policies. Remove 11.01.503 and replace with 10.01.518 (policy renumbered).</td>
</tr>
<tr>
<td>10/13/15</td>
<td>Annual Review. Policy reviewed. References put in alphabetical order and broken</td>
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<tr>
<td>Date</td>
<td>Comments</td>
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<tr>
<td>04/01/16</td>
<td>hyperlinks repaired. Policy statement unchanged.</td>
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<tr>
<td>07/01/17</td>
<td>Annual Review, approved June 22, 2017. Policy moved into new format. No changes to policy statements.</td>
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<tr>
<td>07/01/18</td>
<td>Annual Review, approved June 5, 2018. No updates were made for this annual review.</td>
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<tr>
<td>05/01/19</td>
<td>Annual Review, approved April 18, 2019. No changes to policy statement.</td>
</tr>
<tr>
<td>05/01/20</td>
<td>Annual Review, approved April 23, 2020. Added P&amp;T Committee classification of drugs and biologic agents as investigational or experimental to policy.</td>
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</tbody>
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**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2020 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera 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:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5952, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the 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

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):
يكون هذا الإشعار معلومات هامة. قد يكون هذا الإشعار معلومات مهمة تخصك أو أشخاص كبار السن أو ذوي الإعاقة الذين يتبعون في Premera Blue Cross. قد تكون هناك براءات براءة سارية في هذا الإشعار. ينصح أن تقرأ جميع المعلومات المذكورة في هذا الإشعار. تحقق من تحديد محتوى النقاط المذكورة في هذا الإشعار. ينصح بالرجوع إلى هذه المعلومات المفصلة ويرجى الاتصال
800-722-1471 (TTY: 800-842-5357).

Chinese (Chinese):
本通知有重要讯息。本通知可能有关您透过 Premera Blue Cross 提交的申请或保险的重要讯息。本通知内可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保险或费用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):
Daytoy a Pakdaara kat naglaon iti Napateg nga Impormasion. Daytoy a pakdaara mabalin nga adda kat naglaon iti napateg nga impormasion maianggippa ai aplikasyonono yenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelta iti daytoy a pakdaara. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a natiuding nga adda aldaw tapno mapagalatindayyo ti coverage ti salun-atyo yenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukdoyo a pagasaso nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):