

## PHARMACY / MEDICAL POLICY – 5.01.549

# Off-Label Use of Drugs and Biologic Agents


Effective Date: June 1, 2023  
Last Revised: May 22, 2023  
Replaces: 5.01.01

### RELATED MEDICAL POLICIES:

2.03.502 Monoclonal Antibodies for the Treatment of Lymphoma  
5.01.517 Use of Vascular Endothelial Growth Factor Receptor (VEGF) Inhibitors and Other Angiogenesis Inhibitors in Oncology Patients  
5.01.546 Medical Necessity Criteria for Compounded Medications  
5.01.603 Epidermal Growth Factor Receptor (EGFR) Inhibitors  
10.01.518 Clinical Trials

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [CODING](#) | [RELATED INFORMATION](#)  
[EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

## 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

Service	Medical Necessity
<b>Off- label use of a drug or biologic agent</b>	<p><b>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:</b></p> <ul style="list-style-type: none"> <li>American Hospital Formulary Service – Clinical Drug Information (AHFS-CDI)</li> <li>Elsevier Gold Standard Clinical Pharmacology Compendium (Clinical Pharmacology)</li> <li>National Comprehensive Cancer Network Drugs and Biologics Compendium (NCCN)*</li> <li>Truven Micromedex [formerly known as Thompson Micromedex DrugDex® Compendium] (Micromedex)</li> </ul> <p><b>OR</b></p> <p><b>Scientific evidence shows that the drug/biologic agent is safe and effective for the off-label indication. The scientific evidence must:</b></p> <ul style="list-style-type: none"> <li>Consist of an adequate number of well-designed studies with sufficient numbers of participants (related to incidence of the disease)</li> <li>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</li> <li>Show consistent results across all studies</li> <li>Document a positive health outcome and demonstrate that the drug/biologic agent is as effective or is more effective than established treatment alternatives</li> <li>Document that the improvements are achievable outside of the research setting</li> </ul> <p><b>OR</b></p> <p><b>Any drug or biologic that is approved for Emergency Use Authorization (EUA) under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&amp;C Act) may be given temporary coverage for the indication and time period as indicated by the</b></p>



Service	Medical Necessity
	<p><b>FDA. EUA is not considered an interim step in the U.S. Food and Drug Administration (FDA) approval process, but a public health emergency use that will be recognized as temporary approval.</b></p> <p><b>Note:</b> *The accepted level of evidence for an off-label clinical indication is Category 1 or Category 2A; not Category 2B or Category 3.</p>

Service	Investigational
<b>Off- label use of a drug or biologic agent</b>	<p><b>Prescription drugs and biologic agents are considered investigational or experimental in the following situations:</b></p> <ul style="list-style-type: none"> <li>• The drug or biologic has not received approval for any indication from the U.S. Food and Drug Administration (FDA).</li> <li>• The FDA determined a drug or biologic to be contraindicated for a specific condition or off-label use.</li> <li>• The Pharmacy and Therapeutics (P&amp;T) Committee classifies as investigational or experimental because the safety and/or efficacy cannot be established after reviewing the published scientific literature.</li> </ul> <p><b>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.</b></p> <p><b>Note:</b> Medical policies that address individual drugs/biologic agents may override this policy (see <a href="#">Related Medical Policies</a>).</p>

## Coding

N/A



### 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).

**Emergency Use Authorization (EUA):** The Emergency Use Authorization (EUA) allows the U.S. Food and Drug Administration (FDA) to provide a pathway to facilitate the availability and use of treatments and tests not otherwise available during public health emergencies. Specific rules on how products will be made available come out with each product that obtains EUA. Additional information regarding EUA and list of all current EUAs are available on the FDA website:

<https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization> (Accessed May 5, 2023).

**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/> (Accessed May 5, 2023).

### 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

This policy adheres to the laws set forth in the Alaska State Statute AS 21.07.020. Required contract provisions for health care insurance policy. Available at:

<https://www.akleg.gov/basis/statutes.asp#21.07.020> (Accessed May 5, 2023).

## 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 May 5, 2023).

## Washington

This policy adheres to the laws set forth in the Washington state administrative code, WAC 284-30-450, Insurance Policies and Contracts – Coverage for Drugs, available at:

<http://apps.leg.wa.gov/WAC/default.aspx?cite=284-30-450> (Accessed May 5, 2023).

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

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## 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

1. American Hospital Formulary Service - Drug Information (AHFS-DI). <http://www.ahfsdruginformation.com> Accessed May 5, 2023.
2. Elsevier Gold Standard Clinical Pharmacology Compendium (Clinical Pharmacology). Editorial statement for Off-Label Drug Data. Available at: <http://www.goldstandard.com/editorial-policy-overview/off-label-drug-data/> Accessed May 5, 2023.
3. IBM® Micromedex® DRUGDEX®. IBM Watson Health. Compendia transparency statement for Micromedex® DRUGDEX®. Available at: <https://www.ibm.com/downloads/cas/9OPNDQ51> Accessed May 5, 2023.
4. National Comprehensive Cancer Network (NCCN). The NCCN Drugs and Biologics Compendium. NCCN Compendium®. Available at: <https://www.nccn.org/compendia-templates/compendia/nccn-compendia> Accessed May 5, 2023.
5. U.S. Food and Drug Administration (FDA). Off-label and investigational use of marketed drugs, biologics, and medical devices. Available at: <https://www.fda.gov/regulatoryinformation/guidances/ucm126486.htm> Accessed May 5, 2023.
6. Wolters Kluwer Lexi-Drugs®. Clinical Drug Information. <http://www.wolterskluwer CDI.com/lexicomp-online/> Accessed May 5, 2023.
7. U.S. Food and Drug Administration (FDA). Emergency Use Authorization. Available at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>. Accessed May 5, 2023.

## History



Date	Comments
11/11/13	New policy. Replaces BC policy 5.01.01. Coverage remains unchanged.
11/20/14	Annual Review. Policy reviewed. Definition of terms moved to Policy Guidelines section. In the Benefit Application section hyperlinks added to state statutes. No new references added reference 10 removed. Policy statements unchanged.
03/19/15	Update Related Policies. Remove 11.01.503 and replace with 10.01.518 (policy renumbered).
10/13/15	Annual Review. Policy reviewed. References put in alphabetical order and broken hyperlinks repaired. Policy statement unchanged.
04/01/16	Annual Review, approved March 9, 2016. Policy reviewed. Policy statements unchanged. Added Wolters Kluwer Lexi-Drugs® to the list of CMS approved compendia. Added reference 10.
07/01/17	Annual Review, approved June 22, 2017. Policy moved into new format. No changes to policy statements.
07/01/18	Annual Review, approved June 5, 2018. No updates were made for this annual review.
05/01/19	Annual Review, approved April 18, 2019. No changes to policy statement.
05/01/20	Annual Review, approved April 23, 2020. Added P&T Committee classification of drugs and biologic agents as investigational or experimental to policy.
09/01/20	Interim Review, approved August 31, 2020. Updated policy coverage criteria to include drugs that are approved for Emergency Use Authorization (EUA) under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).
10/01/21	Annual Review, approved September 23, 2021. Updated references and no changes to policy statement.
01/01/23	Annual Review, approved December 23, 2022. Added a note regarding the accepted level of evidence for the NCCN Compendium. Changed the wording from "patient" to "individual" throughout the policy for standardization.
06/01/23	Annual Review, approved May 22, 2023. No changes to the policy statement.

**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). ©2023 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 (Premera) complies with applicable Federal and Washington state civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability, sex, gender identity, or sexual orientation. Premera provides free aids and services to people with disabilities to communicate effectively with us, such as qualified sign language interpreters and written information in other formats (large print, audio, accessible electronic formats, other formats). Premera 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, 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, sex, gender identity, or sexual orientation, you can file a grievance with: Civil Rights Coordinator — Complaints and Appeals, PO Box 91102, Seattle, WA 98111, Toll free: 855-332-4535, Fax: 425-918-5592, TTY: 711, Email [AppealsDepartmentInquiries@Premera.com](mailto: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 <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Ave SW, Room 509F, HHH Building, Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD). Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

**Washington residents:** You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at <https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status>, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at <https://fortress.wa.gov/oic/online-services/cc/pub/complaintinformation.aspx>.

**Alaska residents:** Contact the Alaska Division of Insurance via email at [insurance@alaska.gov](mailto:insurance@alaska.gov), or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

## Language Assistance

**ATENCIÓN:** si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).

**PAUNAWA:** Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 800-722-1471 (TTY: 711).

**注意:** 如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 800-722-1471 (TTY: 711)。

**CHÚ Ý:** Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 800-722-1471 (TTY: 711).

**주의:** 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 800-722-1471 (TTY: 711) 번으로 전화해 주십시오.

**ВНИМАНИЕ:** Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 800-722-1471 (телетайп: 711).

**LUS CEEV:** Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 800-722-1471 (TTY: 711).

**MO LOU SILAFIA:** Afai e te tautala Gagana fa'a Sāmoa, o loo iai auaunaga fesoasoan, e fai fua e leai se totagi, mo oe, Telefoni mai: 800-722-1471 (TTY: 711).

**ໂປດຊາບ:** ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ຄ່າ, ຄມມຸນິພົມໃຫ້ທ່ານ. ໂທ 800-722-1471 (TTY: 711).

**注意事項:** 日本語を話される場合、無料の言語支援をご利用いただけます。800-722-1471 (TTY: 711) まで、お電話にてご連絡ください。

**PAKDAAR:** Nu saritaem ti Ilocano, ti serbisyo para ti baddang ti lengguahe nga awanan bayadna, ket sidadaan para kenyam. Awagan ti 800-722-1471 (TTY: 711).

**УВАГА!** Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 800-722-1471 (телетайп: 711).

**ប្រយ័ត្ន:** បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតល្បួល គឺអាចមានសំរាប់អ្នក។ ចូរ ទូរស័ព្ទ 800-722-1471 (TTY: 711)។

**ማስታወሻ:** የሚናገሩት ቋንቋ አማርኛ ከሆነ የትርጉም አርዳታ ድርጅቶች በነጻ ሊያግዝዎት ተዘጋጅተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ 800-722-1471 (መስማት ለተሳናቸው: 711)፡

**XIYYEEFFANNAA:** Afaan dubbattu Oroomiffa, tajaajjila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bililaa 800-722-1471 (TTY: 711).

**ملحوظة:** إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 800-722-1471 (رقم هاتف الصم والبكم: 711).

**मिआन सिउ:** ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 800-722-1471 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।

**เรียน:** ถ้าคุณพูดภาษาไทยคุณสามารถใช้บริการช่วยเหลือทางภาษาได้ฟรี โทร 800-722-1471 (TTY: 711).

**ACHTUNG:** Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 800-722-1471 (TTY: 711).

**UWAGA:** Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 800-722-1471 (TTY: 711).

**ATANSYON:** Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 800-722-1471 (TTY: 711).

**ATTENTION:** Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 800-722-1471 (ATS: 711).

**ATENÇÃO:** Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 800-722-1471 (TTY: 711).

**ATTENZIONE:** In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 800-722-1471 (TTY: 711).

**توجہ:** اگر بہ زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 800-722-1471 (TTY: 711) تماس بگیرید.