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# PHARMACY / MEDICAL POLICY – 5.01.549

# Off-Label Use of Drugs and Biologic Agents

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| Effective Date: | Aug. 1, 2024 |
| Last Revised: | July 8, 2024 |
| Replaces: | 5.01.01 |

RELATED MEDICAL POLICIES:

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|---|---|
| 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 |
|---|---|
| **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:**<br>• American Hospital Formulary Service – Clinical Drug Information (AHFS-CDI)<br>• Elsevier Gold Standard Clinical Pharmacology Compendium (Clinical Pharmacology)<br>• National Comprehensive Cancer Network Drugs and Biologics Compendium (NCCN)*<br>• Truven Micromedex [formerly known as Thompson Micromedex DrugDex Compendium] (Micromedex)<br>**OR**<br>**Scientific evidence shows that the drug/biologic agent is safe and effective for the off-label indication. The scientific evidence must:**<br>• Consist of an adequate number of well-designed studies with sufficient numbers of participants (related to incidence of the disease)<br>• 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<br>• Show consistent results across all studies<br>• Document a positive health outcome and demonstrate that the drug/biologic agent is as effective or is more effective than established treatment alternatives<br>• Document that the improvements are achievable outside of the research setting<br>**OR**<br>**Any drug or biologic that is approved for Emergency Use Authorization (EUA) under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) may be given temporary coverage for the indication and time period as indicated by the** |

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

| Service | Investigational |
|---|---|
| **Off-label use of a drug or biologic agent** | **Prescription drugs and biologic agents are considered investigational or experimental in the following situations:**<br>• The drug or biologic has not received approval for any indication from the US Food and Drug Administration (FDA).<br>• The FDA determined a drug or biologic to be contraindicated for a specific condition or off-label use.<br>• 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.<br><br>**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.**<br><br>**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).

**Emergency Use Authorization (EUA):** The Emergency Use Authorization (EUA) allows the US 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 June 13, 2024).

**Off-label:** Use of a drug or biologic agent for indications or conditions other than those specifically approved by the US 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 June 13, 2024).

### 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 June 13, 2024).

## 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 June 13, 2024).

## 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 June 13, 2024).

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 that the intervention is appropriate
- Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus that the intervention is appropriate
- Category 2B: The recommendation is based on lower-level evidence and there is non-uniform NCCN consensus (but no major disagreement) that the intervention is appropriate
- Category 3: The recommendation is based on any level of evidence but reflects major NCCN disagreement that the intervention is appropriate

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 June 13, 2024.
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 June 13, 2024.
3. IBM Micromedex DRUGDEX. IBM Watson Health. Compendia transparency statement for Micromedex DRUGDEX. Available at: **https://www.ibm.com/downloads/cas/9OPNDQ51** Accessed June 13, 2024.
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 June 13, 2024.
5. US 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 June 13, 2024.
6. Wolters Kluwer Lexi-Drugs. Clinical Drug Information. **http://www.wolterskluwercdi.com/lexicomp-online/** Accessed June 13, 2024.
7. US 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 June 13, 2024.


## 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 statements. |
| 08/01/24 | Annual Review, approved July 8, 2024. No changes to the policy statements. |



**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.