Policy Number	**RX503.001**
Policy Effective Date	**06/15/2025**
Policy End Date	**12/31/2025**

Off-Label Use of Drugs Without a Medical Policy

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Louisiana, R.S. 22:999 prohibits excluding coverage for a drug prescribed for the treatment of cancer even where the FDA has not approved the product for that indication so long as that drug is recognized for treatment of the covered indication in a standard reference compendia or in substantially accepted peer reviewed medical literature. Coverage requirement also includes all medically necessary services related to the administration of the product. Coverage is not required where use of the product for the prescribed indication is contraindicated. "Medical literature" means scientific studies published in a journal specified by the United States Department of Health and Human Services pursuant to Section 1861(t)(2)(B) of the Social Security Action, 107 Stat. 591 (1993), 42 U.S.C. 1395x(t)(2)(B), as amended. "Standard reference compendia"

means authoritative compendia as identified by the secretary of the United States Department of Health and Human Services.

EXCEPTION: For HCSC members residing in the state of Louisiana, R.S. 22:1054.1 requires coverage for a minimum initial treatment period of not less than three months for medically necessary drugs prescribed for the treatment of metastatic or unresectable tumors or other advanced cancers even where the drug is not FDA approved to treat the specific tumor type or a cancer of the location of the body afflicted so long as the drug is FDA approved for the treatment of cancer with the specific genetic mutation. Continued coverage of the prescribed drug shall be provided after the initial treatment period if the treating physician certifies the prescribed drug is medically necessary for the treatment of the patient's cancer based on documented improvement of the patient. Coverage may be denied only if an alternative treatment has proven to be more effective in published randomized clinical trials and is not contraindicated in the patient.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and is not to be used for current claims adjudication or business purposes. See RX501.087 FDA – Drugs, Biological, Cellular and Gene Therapies for dates of service 01/01/2026 and after.

Please check the appropriate state mandate for laws governing off-label use of prescription drugs within individual plans that may supersede this medical policy when applicable.

Off-label use of U.S. Food and Drug Administration (FDA) approved drugs as prescribed by a physician to treat chronic, disabling, or life-threatening illnesses **may be considered medically necessary** when approved by the FDA for at least one indication, **AND** one of the following:

- Is recognized in one of the following prescription drug reference compendium for treatment of the indication for which the drug is prescribed:
  1. American Hospital Formulary Service Drug Information (AHFS-DI);

2. Micromedex DrugDex Compendium (DrugDex);
3. Clinical Pharmacology (Elsevier/Gold Standard, Inc.);
4. Lexi-Drugs (Wolters Kluwer);
5. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium; **OR**

- Is supported by qualified clinical research that appears in peer-reviewed scientific literature specific for treatment of the indication for which the drug is prescribed.

NOTE 1: Qualified peer-reviewed literature means a published scientific study including a trial that is large, multi-centered and prospective, double blinded and randomized, OR high-quality research with applicable controls in circumstances where a large, randomized, double-blind trial was not feasible or currently unavailable. Qualified peer-reviewed medical literature does not include publications or supplements to publications sponsored to a significant extent by a pharmaceutical company or an issuer of a health benefit plan.

A published scientific study is further defined as a journal article or other publication in which original manuscripts are published only after they have been critically reviewed by unbiased independent experts in the same field for scientific accuracy, validity, and reliability, and have been determined by the International Committee of Medical Journal Editors to have met the Uniform Requirements for Manuscripts submitted to biomedical journals.

NOTE 2: Coverage of a drug that meets the coverage criteria shall also include medically necessary services associated with the administration of the drug.

Off-label use of FDA approved drugs **is considered non-covered** when the FDA has determined its use to be contraindicated for treatment of the condition for which coverage is requested.

Off-label use of a FDA approved drug that does not meet the medically necessary coverage criteria as addressed in this medical policy or any specific HCSC drug medical policy, **is considered experimental, investigational and/or unproven.**

NOTE 3: If there is an HCSC medical policy regarding a specific drug, such medical policy supersedes use of this Off-Label Use policy.

Orphan Drugs
Use of an orphan drug **may be considered medically necessary** when used to treat rare diseases and disorders as defined by the Orphan Drug Act of the U.S. Food and Drug Administration.

NOTE 4: An Orphan Drug is defined in the 1984 amendments of the Orphan Drug Act as "a drug intended to treat a condition affecting fewer than 200,000 persons in the United States or will not recover development cost, plus a reasonable profit, within seven years following FDA approval." The Orphan Drug Act was signed into law on January 4, 1983.

Policy Guidelines

None.

Description

Off-label or unlabeled drug use is the use of a drug approved by the U.S. Food and Drug Administration (FDA) for other uses or in treatment regimens or patient populations that are not included in approved labeling.

The FDA approves drugs for specific indications that are included in the drug's labeling. When a drug is used for an indication other than those specifically included in the labeling, it is referred to as an off-label use. Many off-label uses are effective, well-documented in the literature, and widely used.

Unapproved or unlabeled uses of drugs include a variety of situations ranging from completely unstudied to thoroughly investigated drug uses where the FDA has not been asked for approval, whereas approved uses of drugs have been shown to be safe and effective by the FDA after the review of adequate and controlled clinical trials that have documented their uses.

Compendium

A compendium is a comprehensive listing of FDA-approved drugs and biologics. In some cases, compendia specialize in a particular subset of drugs, such as those used for anti-cancer treatment. Compendia include a summary of how each drug works in the body, as well as information for health care practitioners about proper dosing and whether the drug is recommended or endorsed for use in treating a specific disease. A compendium may be used as one of several tools to determine whether a drug should be covered.

Rationale

In certain instances, scientific evidence may support using a drug to treat a disease even if the drugs U.S. Food and Drug Administration (FDA) approved label does not include those clinical conditions. In these circumstances, the compendia or scientific peer-reviewed literature specific for the indication in question may recommend uses beyond those included in the FDA approved labels. Medical policies on specific drugs are reviewed for consideration of change when valid new scientific literature emerges.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	Dependent on drug

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

1. Medicare Benefit Policy Manual, Chapter 15, Section 50.4.5. (Publication 100-02) (October 4, 2024). Available at: <https://www.cms.gov> (accessed April 15, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
06/15/2025	Reviewed. No changes.
05/15/2024	Document updated with literature review. Coverage unchanged. No new references added.
06/01/2023	Reviewed. No changes.
12/01/2022	Document updated with literature review. Coverage unchanged. Updated reference 1; one reference removed.
07/01/2021	Reviewed. No changes.
01/15/2021	Document updated with literature review. The following change was made to Coverage: Updated drug reference compendium list.
10/15/2019	Reviewed. No changes.
11/01/2018	Document updated with literature review. Document updated with literature review. The following statement was added to coverage. "Off-Label use of a FDA approved drug that does not meet the medically necessary coverage criteria as addressed in this medical policy or any specific

	HCSC drug medical policy, is considered experimental, investigational and/or unproven". In addition, the United States Pharmacopoeia-Drug Information compendium added to the listing of accepted compendia. Some wording in coverage modified for clarification.
03/01/2017	Reviewed. No changes.
03/01/2016	Document updated with literature review. Coverage unchanged.
07/01/2015	Reviewed. No changes.
12/01/2014	Document updated with literature review. Coverage unchanged.
08/01/2012	Document updated with literature review. Coverage statements modified to add current compendium.
09/15/2007	Revised/Updated Entire Document
02/27/2004	Revised/Updated Entire Document
06/01/1996	Revised/Updated Entire Document
03/01/1996	Revised/Updated Entire Document
04/01/1994	New medical policy