Clinical Policy: Off-Label Use

Reference Number: CP.PMN.53
Effective Date: 09.12.17
Last Review Date: 11.25
Line of Business: Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Off-label drug use is the utilization of an FDA-approved drug for uses other than those listed in the FDA-approved labeling or in treatment regimens or populations that are not included in approved labeling.

FDA Approved Indication(s)

Varies by drug product.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that all medical necessity determinations for off-label uses be considered on a case-by-case basis by a physician, pharmacist or ad hoc committee, using the guidance provided within this policy.

I. Initial Approval Criteria

A. Requests for Off-Label Use through Pharmacy Benefit (must meet all)**:***

**For medical benefit requests, see Section B below*

1. There are no pharmacy and therapeutic committee approved off-label use criteria for the diagnosis;
2. If a drug-specific clinical policy is available, the request is not for diagnoses or indications listed in Section III of the drug-specific clinical policy;
3. Use is supported by one of the following (a, b, or c):
   a. The National Comprehensive Cancer Network (NCCN) Drug Information and Biologics Compendium level of evidence 1, 2A, or 2B (*see Appendix D*);
   b. Evidence from at least two high-quality, published studies in reputable peer-reviewed journals or evidence-based clinical practice guidelines that provide all of the following (i – iv):
      i. Adequate representation of the member's clinical characteristics, age, and diagnosis;
      ii. Adequate representation of the prescribed drug regimen;
      iii. Clinically meaningful outcomes as a result of the drug therapy in question;
      iv. Appropriate experimental design and method to address research questions (*see Appendix F for additional information*);
   c. Micromedex DrugDex® with strength of recommendation Class I or IIa (*see Appendix D*);

4. Request is not for a benefit-excluded use (e.g., cosmetic);
5. If request is for experimental or investigational use, both of the following (a and b, *see Appendix D*):
   a. Request is for coverage of routine patient costs of qualifying clinical trial services;
   b. Provider must submit the completed Medicaid attestation form on the appropriateness of the qualified clinical trial [https://www.medicaid.gov/resources-for-states/downloads/medicaid-attest-form.docx];
6. Prescribed by or in consultation with an appropriate specialist for the diagnosis;
7. Failure of 2 alternative drugs as described below (a, b, c, d, or e) that are FDA-approved for the requested indication and/or drugs that are considered the standard of care, when such agents exist, tried at maximum indicated doses, each used for at least 30 days or an appropriate duration of treatment, unless contraindicated, clinically significant adverse effects are experienced, request is for a product for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*) or for treatment of a member in a State with limitations on step therapy in certain settings (*see Appendix G*):
   a. The preferred biosimilar(s) of the requested brand name drug has been used, if available, unless member has contraindications to the excipients in all generics/biosimilars;
   b. Both agents are generics (each from a different manufacturer) within the same therapeutic class as the requested agent;
   c. If there is only 1 generic agent within the same therapeutic class as the prescribed agent, member must use at least one additional agent that is recognized as a standard of care for the treatment of the relevant diagnosis, provided that such agent exists;
   d. If there are no generic agents within the same therapeutic class, member must use 2 alternatives that are recognized as standards of care for the treatment of the relevant diagnosis, provided that 2 such agents exist;
   e. There are no generic agents within the same therapeutic class and no alternative agents recognized as standards of care for the treatment of the relevant diagnosis;
8. If request is for a non-preferred biologic product with an available biosimilar, one of the following (a or b):
   a. Member must use the preferred biosimilar product(s), unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for a product for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*) or for treatment of a member in a State with limitations on step therapy in certain settings (*see Appendix G*);
9. Member has no contraindications to the prescribed agent per the product information label;
10. If applicable, prescriber has taken necessary measures to minimize any risk associated with a boxed warning in the product information label;
11. Dosing regimen and duration are within dosing guidelines recommended by clinical practice guidelines and/or medical literature.

Approval duration: Duration of request or 6 months (whichever is less)

B. Requests for Off-label Use through Medical Benefit (must meet all)**:**

1. There are no pharmacy and therapeutic committee approved off-label use criteria for the diagnosis;
2. If a drug-specific clinical policy is available, the request is not for diagnoses or indications listed in Section III of the drug-specific clinical policy;
3. Use is supported by one of the following (a, b, or c):
   a. The National Comprehensive Cancer Network (NCCN) Drug Information and Biologics Compendium level of evidence 1, 2A, or 2B (*see Appendix D*);
   b. Evidence from at least two high-quality, published studies in reputable peer-reviewed journals or evidence-based clinical practice guidelines that provide all of the following (i – iv):
      i. Adequate representation of the member's clinical characteristics, age, and diagnosis;
      ii. Adequate representation of the prescribed drug regimen;
      iii. Clinically meaningful outcomes as a result of the drug therapy in question;
      iv. Appropriate experimental design and method to address research questions (*see Appendix F for additional information*);
   c. Micromedex DrugDex® with strength of recommendation Class I or IIa (*see Appendix D*);
4. Request is not for a benefit-excluded use (e.g., cosmetic);
5. If request is for experimental or investigational use, both of the following (a and b, *see Appendix D*):
   a. Request is for coverage of routine patient costs of qualifying clinical trial services;
   b. Provider must submit the completed Medicaid attestation form on the appropriateness of the qualified clinical trial [https://www.medicaid.gov/resources-for-states/downloads/medicaid-attest-form.docx];
6. Prescribed by or in consultation with an appropriate specialist for the diagnosis;
7. Failure of 2 alternative drugs as described below (a, b, c, d, or e) that are FDA-approved for the requested indication and/or drugs that are considered the standard of care, when such agents exist, tried at maximum indicated doses, each used for at least 30 days, unless contraindicated, clinically significant adverse effects are experienced, or request is for a product for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*) or for treatment of a member in a State with limitations on step therapy in certain settings (*see Appendix G*):
   a. The preferred biosimilar(s) of the requested brand name drug has been used, if available, unless member has contraindications to the excipients in all generics/biosimilars;
   b. Both agents are generics (each from a different manufacturer) within the same therapeutic class as the requested agent;
   c. If there is only 1 generic agent within the same therapeutic class as the prescribed agent, member must use at least one additional agent that is recognized as a

standard of care for the treatment of the relevant diagnosis, provided that such agent exists;

d. If there are no generic agents within the same therapeutic class, member must use 2 alternatives that are recognized as standards of care for the treatment of the relevant diagnosis, provided that 2 such agents exist;
e. There are no generic agents within the same therapeutic class and no alternative agents recognized as standards of care for the treatment of the relevant diagnosis;

8. If request is for a non-preferred biologic product with an available biosimilar, one of the following (a or b):
   a. Member must use the preferred biosimilar product(s), unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for a product for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*) or for treatment of a member in a State with limitations on step therapy in certain settings (*see Appendix G*);
9. Member has no contraindications to the prescribed agent per the product information label;
10. If applicable, prescriber has taken necessary measures to minimize any risk associated with a boxed warning in the product information label;
11. Dosing regimen and duration are within dosing guidelines recommended by clinical practice guidelines and/or medical literature.

Approval duration: Duration of request or 6 months (whichever is less)

II. Continued Therapy

A. Requests for Off-Label Use through Pharmacy or Medical Benefit (must meet all)**:**

1. Member meets one of the following (a, b, or c):
   a. Currently receiving medication via Centene benefit;
   b. Member has previously met initial approval criteria;
   c. State or health plan continuity of care programs apply to the requested drug and indication (e.g., seizures, heart failure, human immunodeficiency virus infection, psychotic disorders [e.g., schizophrenia, bipolar disorder], depression, transplant, oncology) with documentation that supports that member has received this medication for at least 30 days (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)* AND use is supported by one of the following (i, ii, or iii):
      i. The NCCN Drug Information and Biologics Compendium level of evidence 1, 2A, or 2B (*see Appendix D);*
      ii. Evidence from at least two, high-quality, published studies in peer-reviewed journals or evidence-based clinical practice guidelines that provide all of the following (1 – 4):
         1) Adequate representation of the member's clinical characteristics, age, and diagnosis;
         2) Adequate representation of the prescribed drug regimen;
         3) Clinically meaningful outcomes as a result of the drug therapy in question;
         4) Appropriate experimental design and method to address research questions (*see Appendix F for additional information*);

iii. Micromedex DrugDex with strength of recommendation Class I or IIa (*see Appendix D*);

2. Member is responding positively to therapy;
3. If request is for a non-preferred biologic product with an available biosimilar, one of the following (a or b):
   a. Member must use the preferred biosimilar product(s), unless contraindicated or clinically significant adverse effects are experienced;
   b. Request is for a product for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (*see Appendix E*) or for treatment of a member in a State with limitations on step therapy in certain settings (*see Appendix G*);
4. If request is for a dose increase (quantity or frequency), member has been titrated up from the lower dose with documentation of partial improvement, and the new dose does not exceed dosing guidelines recommended by the product information label or clinical practice guidelines and/or medical literature.

Approval duration: Duration of request or 12 months (whichever is less)

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Indications or diagnoses in which the drug has been shown to be unsafe or ineffective.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
CMS: Centers for Medicare & Medicaid Services
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives
Varies by drug product

Appendix C: Contraindications/Boxed Warnings
Varies by drug product

Appendix D: General Information

- These criteria are to be used only when specific prior authorization criteria do not exist.
- The U.S. FDA approves drugs for specific indications included in the drug's product information label. The approval by the FDA means that the company can include the information in their package insert. Omission of uses for a specific age group or a specific disorder from the approved label means that the evidence required by law to allow their inclusion in the label has not been submitted to the FDA. Off-label, or "unlabeled," drug use is the utilization of an FDA-approved drug for indications, treatment regimens, or populations other than those listed in the FDA-approved labeling. Many off-label uses are effective and well-documented in the peer-reviewed literature, and they are widely used even though the manufacturer has not pursued the additional indications. Refer to the drug's FDA-approved indication(s) and labeling (varies among drug products).

- The Center for Medicaid and CHIP Services (CMCS) requires Medicaid state plans ensure coverage of routine patient costs associated with participation in qualifying clinical trials. Routine patient cost includes any item or service provided to prevent, diagnose, monitor, or treat complications resulting from participation in the qualifying clinical trial, to the extent that the provision of such items or services to the beneficiary would otherwise be covered outside the course of participation in the qualifying clinical trial under the state plan or waiver. Routine patient cost does not include any item or service that is provided to the beneficiary solely to satisfy data collection and analysis for the qualifying clinical trial that is not used in the direct clinical management of the beneficiary and is not otherwise covered under the state plan, waiver, or demonstration project. To qualify for coverage, Medicaid Attestation Form on the Appropriateness of Qualified Clinical Trial must be submitted for each Medicaid member enrolled in a qualifying clinical trial for whom Medicaid reimbursement is requested, prior to providing treatment in the trial. This form can be downloaded here: https://www.medicaid.gov/resources-for-states/downloads/medicaid-attest-form.docx
- NCCN Categories of Evidence and Consensus:
  - Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
  - Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
  - Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
  - Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.
- Micromedex DrugDex Strength of Evidence, Strength of Recommendation, and Efficacy Definitions (Tables 1, 2, and 3):

Table 1. Strength of Recommendation		
Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa	Recommended, In Most Cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases
Class IIb	Recommended, In Some Cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not Recommended	The given test, or treatment is not useful, and should be avoided.
Class Indeterminate	Evidence Inconclusive	Not applicable

Table 2. Strength of Evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients

Table 2. Strength of Evidence	
Category B	Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies)
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series
No Evidence	Not applicable

Table 3. Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Class IIa	Evidence Favors Efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is Inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

Appendix E: States with Regulations against Redirections in Cancer

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes≠	For stage 4 advanced, metastatic cancer or associated conditions. ≠Exception if clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes^	For stage 4 advanced metastatic cancer, metastatic blood cancer, and associated conditions ^Exception if step therapy is for AB-rated generic equivalent, interchangeable biological product, or biosimilar product to the equivalent brand drug

State	Step Therapy Prohibited?	Notes
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

Appendix F: Appropriate Experimental Design Methods

- Randomized, controlled trials are generally considered the gold standard; however:
  - In some clinical studies, it may be unnecessary or not feasible to use randomization, double-blind trials, placebos, or crossover.
  - Non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- Case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.

Appendix G: States with Limitations against Redirections in Certain Settings

State	Step Therapy Prohibited?	Notes
AR	Yes	For the treatment of psychosis and serious mental illness through antipsychotic prescription drugs, no step therapies allowed.
NV	No	For typical or atypical antipsychotic or anticonvulsant medications, step therapy is limited to one PDL drug.

V. Dosage and Administration

Varies by drug product

VI. Product Availability

Varies by drug product

VII. References

1. Food and Drug Administration. Guidance for Industry: Distribution of Scientific and Medical Publications on Unapproved New Uses- Recommended Practices. October 2023. Available at: https://www.fda.gov/media/173172/download. Accessed July 10, 2025.
2. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed August 20, 2025.
3. Department Of Health & Human Services – Centers for Medicare & Medicaid Services: Mandatory Medicaid Coverage of Routine Patient Costs Furnished in Connection with Participation in Qualifying Clinical Trials. April 13, 2022. Available at: https://www.medicaid.gov/federal-policy-guidance/downloads/smd21005.pdf. Accessed August 20, 2025.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2021 annual review: no significant changes; added Ohio and Nevada to Appendix F; references reviewed and updated.	07.22.21	11.21
Removed HIM-Medical Benefit line of business (criteria from this policy added to HIM.PA.154 for medical benefit requests); applied	12.20.21	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
State-mandated redirection bypass for cancer for all redirection requests not just biologics; removed general description of "stage IV or metastatic" cancer for states with regulations against redirections; created separate criteria set for medical benefit requests to distinguish that formulary/PDL verbiage is not applicable; revised references from "formulary" to "PDL."		
4Q 2022 annual review: added requirement if a drug-specific clinical policy is available, the request is not for diagnoses or indications listed in Section III of the drug-specific clinical policy; clarified drug failure requirements by consolidating multiple requirements and including various scenarios for biosimilars and generics, separated the following as an additional option for added clarity: "There are no generic agents within the same therapeutic class and no alternative agents recognized as standards of care for the treatment of the relevant diagnosis"; references reviewed and updated.	08.16.22	11.22
Added clarification to initial authorization if request is for a non-preferred biologic with an available biosimilar, member must use the preferred biosimilar product(s).	12.21.22	
Added reference to CC.PHARM.03A and CC.PHARM.03B to Section II for state or health plan continuity of care programs.	02.06.23	
4Q 2023 annual review: no significant changes; references reviewed and updated.	07.11.23	11.23
4Q 2024 annual review: added requirement that alternative drugs be used for at least 30 days; added bypass to all redirections for States with regulations against redirections in certain settings (Appendix G); added depression and transplant to list of continuity of care programs per current Centene standard approach; references reviewed and updated.	07.29.24	11.24
4Q 2025 annual review: added requirements if request is for experimental or investigational use with resources to the attestation form per CMS requirements; references reviewed and updated.	07.10.25	11.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.