

## Clinical Policy: Off-Label Use

Reference Number: CP.CPA.09

Effective Date: 08.01.17

Last Review Date: 11.24

Line of Business: Commercial

[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<sup>®</sup> that the off-label use of a drug is **medically necessary** when the following criteria are met:

#### I. Initial Approval Criteria

##### A. Requests for Off-Label Use (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, c, or d):
  - 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 E for additional information*);
  - c. Micromedex DrugDex<sup>®</sup> with strength of recommendation Class I or IIa (*see Appendix D*);
  - d. Non-profit professional association guidelines for mental health and substance use disorders (*see Appendix F*);

4. Request is not for a benefit-excluded use\* (e.g., cosmetic);  
*\*Per California state regulations, **medical** benefit requests for Sculptra<sup>®</sup> and Radiesse<sup>®</sup> for members with HIV is not considered an excluded benefit*
5. Prescribed by or in consultation with an appropriate specialist for the diagnosis;
6. 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:
  - 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;
7. If request is for a non-preferred biologic product with an available biosimilar, member must use the preferred biosimilar product(s), unless contraindicated or clinically significant adverse effects are experienced;
8. Member has no contraindications to the prescribed agent per the product information label;
9. If applicable, prescriber has taken necessary measures to minimize any risk associated with a boxed warning in the product information label;
10. Dosing regimen and duration are within dosing guidelines recommended by clinical practice guidelines and/or medical literature.

**Approval duration:**

**Injectables** – 6 months or to the member’s renewal date, whichever is longer

**All other requests** – Duration of request or 6 months (whichever is less)

## II. Continued Therapy

### A. Requests for Off-Label Use (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, iii, or iv):

- 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 E for additional information*);
  - iii. Micromedex DrugDex with strength of recommendation Class I or IIa (*see Appendix D*);
  - iv. Non-profit professional association guidelines for mental health and substance use disorders (*see Appendix F*);
2. Member is responding positively to therapy;
  3. If request is for a non-preferred biologic product with an available biosimilar, member must use the preferred biosimilar product(s), unless contraindicated or clinically significant adverse effects are experienced;
  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:**

**Injectables** – 6 months or to the member’s renewal date, whichever is longer

**All other requests** – 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*

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).
- 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):

<b>Table 1. Strength of Recommendation</b>		
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

<b>Table 2. Strength of Evidence</b>	
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
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.

Table 2. Strength of Evidence	
	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: 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 F: Non-Profit Association Guidelines for Mental Health and Substance Abuse Disorder*

The following are non-profit professional association guidelines, and these criteria should be referenced to make utilization review decisions. When non-profit association guidelines are not available or are not specific or current enough to address treatment, criteria will follow generally accepted standards of mental health and substance use disorder care and any advancements in technology.

- American Academy of Child and Adolescent Psychiatry
- American Academy of Family Physicians
- American Academy of Neurology
- American Academy of Pediatrics
- American Academy of Sleep Medicine
- American Association for Community Psychiatry

- American College of Physicians
- American Medical Association
- American Psychiatric Association
- American Psychological Association
- American Society of Addiction Medicine
- Canadian Network for Mood and Anxiety Treatments
- Counsel of Autism Providers
- Substance Abuse and Mental Health Services Administration (SAMHSA)
- World Professional Association for Transgender Health (WPATH)

**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 22, 2024.
2. Micromedex<sup>®</sup> Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed July 22, 2024.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2020 annual review: added NCCN 2B as an acceptable level of evidence per Compliance; added redirection to generic/biosimilar products; references reviewed and updated.	07.13.20	11.20
Added bypass to biosimilar redirection for states with regulations against redirections in stage IV or metastatic cancer; added redirection to preferred biosimilar products for continued therapy.	03.15.21	
4Q 2021 annual review: added requirement that request is not for a benefit-excluded use; added Nevada to Appendix F; references reviewed and updated.	07.22.21	11.21
4Q 2022 annual review: removed general description of “stage IV or metastatic” cancer for states with regulations against redirections; 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, added requirement that drug trials be used for at least 30 days; references reviewed and updated.	08.01.22	11.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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: added injectable specific approval duration of “6 months or to the member’s renewal date, whichever is longer”; added clarification for requirement that request is not for a benefit excluded use that per California state regulations, medical benefit requests for Sculptra and Radiesse for members with HIV is not considered an excluded benefit; for redirection to alternative drugs added the following option: 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.	06.23.23	11.23
Removed Appendix F (and references to this appendix) for states with regulations against redirection in cancer as we do not have Commercial business in any of the states listed.	06.10.24	
Due to updates from SB855, added information regarding non-profit professional associations guidelines that should be referenced to make utilization review decisions. Added Appendix F that states “When non-profit guidelines are not available or are not specific or current enough to address treatment, criteria will follow generally accepted standards of mental health and substance use disorder care and any advancements in technology.”	07.17.24	
4Q 2024 annual review: added option for trial of alternative agents to be for an appropriate duration of treatment; added depression and transplant to list of continuity of care programs per current Centene standard approach; references reviewed and updated.	07.25.24	11.24

**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.

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