Clinical Policy: Off-Label Drug Use

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Line of Business: HIM

Revision Log

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

Description
This policy defines the responsibility of the prescriber when requesting prior authorization (PA) for approval consideration of a medication for an off-label use.

Off-label drug use is the use of a drug, approved by the U.S. Food and Drug Administration (FDA), for other indications, treatment regimens, or patient populations that are not included in approved labeling. When a drug is used for an indication other than those specifically included in the FDA labeling, it is referred to as an off-label use. Many off-label uses are effective, well-documented in the literature, and widely used.

Prescribers requesting PA approval of a medication for an off-label use must submit specified documentation. PA requests that do not meet established criteria for off-label uses will not be approved. Other PA criteria may be enforced prior to approval of a non-formulary medications, despite the prescriber meeting the specifications listed (i.e., trial and failure of two or more formulary medications is required prior to approval of non-formulary agents). Please refer to EPS.PHARM.03B for any exceptions to the policy (California Senate Bill No. 583).

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.

The clinical pharmacist working in the prior authorization department may consider approval of a prior authorization request for an off-label use if the prescriber submits all of the following information:

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. Use must be diagnosis specific as defined by ICD-9 or ICD-10 code(s);
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. Treatment is not for a benefit-excluded use (e.g., cosmetic);
5. Prescribed by or in consultation with an appropriate specialist for the diagnosis;
6. Failure of 2 formulary agents as described below (a, b, c, or d) 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*):
   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 formulary agents are generics (each from a different manufacturer) within the same therapeutic class as the requested agent;
   c. If there is only 1 formulary generic agent within the same therapeutic class as the prescribed agent, member must use at least one additional formulary 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 formulary generic agents within the same therapeutic class, member must use 2 formulary alternatives that are recognized as standards of care for the treatment of the relevant diagnosis, provided that 2 such agents exist;
7. Member has no contraindications to the prescribed agent per the product information label;
8. If applicable, prescriber has taken necessary measures to minimize any risk associated with a boxed warning in the product information label;
9. 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. 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*);
3. Treatment is not for a benefit-excluded use (e.g., cosmetic);
4. Prescribed by or in consultation with an appropriate specialist for the diagnosis;
5. Failure of an adequate trial of at least two FDA-approved drugs for the indication and/or drugs that are considered the standard of care, when such agents exist, at maximum indicated doses, unless clinically significant adverse effects are experienced, all are contraindicated, 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*);
6. Failure of an adequate trial of or clinically significant adverse effects to two generics* (each from a different manufacturer) or the preferred biosimilar(s) of the requested brand name drug, if available, unless one of the following is met (a or b):
   a. Member has contraindications to the excipients in all generics/biosimilars;
   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*);

   **If a second generic of the requested brand name drug is not available, member must try an alternative that is FDA-approved or better supported by standard pharmacopeias (e.g., DrugDex) for the requested indication, provided that such agent exists*
7. Member has no contraindications to the prescribed agent per the product information label;
8. If applicable, prescriber has taken necessary measures to minimize any risk associated with a boxed warning in the product information label;
9. 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)**:***

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

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,

and psychotic disorders [e.g., schizophrenia, bipolar disorder], oncology) with documentation that supports that member has received this medication for at least 30 days 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, 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*);
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
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):

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
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,

Table 2. Strength of Evidence	
	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
OH	Yes	For stage 4 metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions
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.

V. Dosage and Administration

Varies by drug product

VI. Product Availability

Varies by drug product

VII. References

1. Utah Department of Health. Administration of Off-Label Drug use Policy. The Amber Sheet. 2006 Aug; 14:3.
2. BlueShield of Northeastern New York. Drug Therapy Guidelines: Off-Label Drug Use Policy. P&T Newsletter. 2007 Nov.
3. BlueCross BlueShield of Minnesota. Off-Label Use of Phosphodiesterase-5 Inhibitors. Behavioral Health Policy II-67. 2007 May.
4. EPS.PHARM.03B State Specific Addendum

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	12.18.20	01.21 (ad hoc)
Added redirection to generic/biosimilar products, with bypass allowed for states with regulations against redirections in stage IV or metastatic cancer.	03.15.21	
4Q 2021 annual review: revised policy description to remove reference that the policy only applies to non-formulary drugs; to align with approach used in other Centene lines of business revised clinical trial requirements, added specialist requirement, and added requirement for trial of two formulary FDA-approved drugs for the indication and/or drugs that are considered the standard of care, when such agents exist, added requirement for assessment of contraindications and black box warnings, added dosing limits requirement; added Nevada to Appendix F; references reviewed and updated.	07.22.21	11.21
Added criteria set for off-label requests through the medical benefit adapted from CP.PMN.53 (HIM-Medical Benefit line of business removed from this policy); for pharmacy benefit requests, added that "treatment is not for a benefit-excluded use (e.g., cosmetic)"; for continued therapy, added option for State or health plan continuity of care programs; applied redirection bypass for cancer for certain states with regulations to all redirection requests not just biologics; removed general description of "stage IV or metastatic" cancer for states with regulations against redirections.	12.20.21	

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.

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