

Clinical Policy: Non-FDA Approved Use

Reference Number: MS.PMN.53

Effective Date: 09.12.17

Last Review Date: 05.23

Line of Business: Medicaid

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Non-FDA approved 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 non-FDA approved 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 Non-FDA Approved Use through Pharmacy Benefit (must meet all):

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

1. There are no pharmacy and therapeutic committee approved non-FDA approved 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 IIb or higher and efficacy Class IIa or higher. (*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 a PDL alternative that is FDA-approved or 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)

B. Requests for Non-FDA Approved Use through Medical Benefit (must meet all):

1. There are no pharmacy and therapeutic committee approved non-FDA approved 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 IIb or higher and efficacy Class IIa or higher (*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 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 Non-FDA Approved 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, 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 IIb or higher and efficacy Class IIa or higher (*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

PDL: preferred drug list

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. Non-FDA approved, 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 non-FDA approved 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, 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.

Table 3. 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 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. Food and Drug Administration. Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices. January 2009. Available at: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm>. Accessed July 22, 2021.
2. Micromedex[®] Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed July 22, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2018 annual review: HIM Medical Benefit added; added criteria for combinations products and alternative dosage forms or strengths of existing drugs; added redirection to CP.PMN.16 for non-PDL agent under the pharmacy benefit; for drugs without custom coverage criteria added requirement for trial and failure of at least two FDA-approved drugs for the indication and/or drugs that are considered the standard of care, when such agents exist; references reviewed and updated.	08.14.18	11.18
Removed DrugDex IIb support for off-label use.	02.19.19	05.19
4Q 2019 annual review: added requirement that member does not have any contraindications for labeled use without coverage criteria; references reviewed and updated.	08.27.19	11.19
Clarified for Labeled Use without Coverage Criteria: failure of two FDA-approved agents must be PDL agents for Medicaid pharmacy requests.	03.09.20	
Replaced the terms “PDL” to “formulary” agents for clarity per PA Ops request.	04.22.20	
Revised “formulary agents” to “preferred agents” for clarity per PA Ops request.	05.18.20	
4Q 2020 annual review: removed criteria for drugs without existing coverage criteria and moved to separate policy per PA Ops request; 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: 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 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.”	12.20.21	
Updated “Off-Label” use to “Non-FDA Approved” use throughout the document; policy name changed from CP.PMN.53 to MS.PMN.53; updated criteria to include Micromedex DrugDex with strength of recommendation Class IIb or higher and efficacy Class IIa or higher.	05.06.22	
Annual Review; no changes	05.12.23	

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.

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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.

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