Clinical Policy: Off-Label Use or Recent Label Changes of Drugs Not on the Statewide Preferred Drug List

Reference Number: PA.CP.PMN.53
Effective Date: 01/2018
Last Review Date: 04/2025

Description
The intent of this policy is to provide coverage criteria when a request for an agent not listed on the Statewide Preferred Drug List (PDL) is received for use of an off-label indication (i.e. 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) or drug specific clinical policies that are pending updates as a result of recent (within the last 6 months) label changes (e.g., newly approved indications, age expansions, new dosing regimens) where no previously approved custom coverage criteria exist.

Policy/Criteria
** Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria **

It is the policy of PA Health & Wellness® that the off-label use of a drug is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Request for a Drug NOT on the Statewide PDL for an Off-label Use (i.e. 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) where No Custom Coverage Criteria Exist (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. Request meets one of the following (a, b, c, or d):
   a. Use is supported by the National Comprehensive Cancer Network (NCCN) Drug Information and Biologics Compendium level of evidence 1, 2A, and 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® with strength of recommendation Class I or IIa (*see Appendix D*);

d. Micromedex DrugDex® with strength of recommendation Class IIb (*see Appendix D*), provided that the request meets the following (i and ii):
   i. Adequate representation of the member's clinical characteristics, age, and diagnosis;
   ii. Adequate representation of the prescribed drug regimen;

4. Request is not for a benefit-excluded purpose (e.g., cosmetic);
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 30 days or an appropriate duration of treatment, unless contraindicated, clinically significant adverse effects are experienced, or request is for a product for treatment associated with Stage IV or metastatic cancer;:
   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, 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 Stage IV or metastatic cancer;
8. Member has no contraindications to 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. Requested dosage regimen and duration is within dosing guidelines recommended by clinical practice guidelines and/or medical literature.

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

B. Labeled Use without Drug-specific Coverage Criteria or Pending Clinical Policy Updates as a Result of Recent Label Changes for a Drug NOT on the Statewide PDL (must meet all)**:**

1. Both of the following (a and b):
   a. Requested drug does not have criteria for requested diagnosis in a drug-specific clinical policy or custom coverage criteria;

b. Requested drug has a drug-specific clinical policy that is pending clinical policy updates as a result of recent (within the last 6 months) label changes (e.g., newly approved indications, age expansions, new dosing regimens);

2. Diagnosis of one of the following (a or b):
   a. A condition for which the product is FDA-indicated and -approved;
   b. A condition supported by the National Comprehensive Cancer Network (NCCN) Drug Information and Biologics Compendium level of evidence 1, 2A, or 2B;
3. Request is not for a benefit-excluded purpose (e.g., cosmetic);
4. Prescribed by or in consultation with an appropriate specialist for the diagnosis;
5. Failure of at least two alternative drugs as described below (a, b, c, d or e) FDA-approved drugs for the indication and/or drugs that are considered the standard of care, when such agents exist, at maximum indicated doses, each used for at least 30 days or an appropriate duration of treatment, unless clinically significant adverse effect are experienced, all are contraindicated, or request is for a product for treatment is for Stage IV or metastatic cancer;
   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;
6. 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 Stage IV or metastatic cancer;
7. For combination product or alternative dosage form or strength of existing drugs, one of the following (a or b):
   a. Medical justification* supports inability to use the individual drug products concurrently or alternative dosage forms or strengths (e.g., contraindications to the excipients of all alternative products)
      **Use of a copay card or discount card does not constitute medical necessity*
   b. Request is for a product for treatment is for Stage IV or metastatic cancer;
   c. Member has no contraindications to the prescribed agent per the prescribing information;
   d. If applicable, prescriber has taken necessary measures to minimize any risk associated with a boxed warning in the product information label;
   e. Request meets one of the following (i or ii):

i. Dose does not exceed the FDA-approved maximum recommended dose for the relevant indication;
ii. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

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

II. Continued Therapy

A. Request for a Drug NOT on the Statewide PDL for an Off-label Use (i.e. 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) where No Custom Coverage Criteria Exist (must meet 1 or 2 thru 4):

1. Currently receiving medication via PA Health & Wellness benefit, or member has previously met initial approval criteria or the Continuity of Care policy (PA.PHARM.01) applies and documentation supports positive response to therapy;
2. Continued use is supported by one of the following (a, b, c, or d):
   a. The 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 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 with strength of recommendation Class I or IIa (*see Appendix D*);
   d. Micromedex DrugDex® with strength of recommendation Class IIb (*see Appendix D*), provided that the request meets the following (i and ii):
      i. Adequate representation of the member's clinical characteristics, age, and diagnosis;
      ii. Adequate representation of the prescribed drug regimen;
3. Member is responding positively to therapy;
4. 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 Stage IV or metastatic cancer;
5. 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 product information label or clinical practice guidelines and/or medical literature.

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

B. Labeled Use without Drug-specific Coverage Criteria or Pending Clinical Policy Updates as a Result of Recent Label Changes for a Drug NOT on the Statewide PDL (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit, or member has previously met all initial approval criteria or the Continuity of Care policy (PA.PHARM.01) applies;
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 Stage IV or metastatic cancer;
4. If request is for a dose increase, request meets one of the following (a or b):
   a. New dose does not exceed the FDA-approved maximum recommended dose for the relevant indication;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

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

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

N/A

IV. Appendices/General Information

Appendix A: Abbreviation 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. 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, 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.*

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. January 2025. Available at: https://www.fda.gov/media/173172/download. Accessed March 24, 2025.
2. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed March 24, 2025.

Reviews, Revisions, and Approvals	Date
2Q 2018 annual review: Added criteria for labeled use without custom criteria; added initial approval criteria for off-label use to align with off-label use policy & procedures; allowed COC for listed disease states in continued approval; added references.	02/2018
2Q 2019 annual review: Clarified use of DrugDex I, IIa and IIb support for off-label use; added criteria for combinations products and alternative dosage forms or strengths of existing drugs; added redirection to PA.CP.PMN.16 for non-PDL agent under the pharmacy and medical benefit; for drugs without custom coverage criteria added requirement for trial and failure of at least two	04/2019

Reviews, Revisions, and Approvals	Date
FDA-approved drugs for the indication and/or drugs that are considered the standard of care, when such agents exist; description section has been rewritten to clarify intent of policy; Added clarification to Labeled use without Coverage Criteria to indicate that combination HIV antiretrovirals products will not require use of individual components; references reviewed and updated.	
09/01/2019 submission for Statewide PDL implementation: revised policy to clarify use for drugs not listed on the Statewide PDL for off-label use where no custom coverage criteria exist	09/2019
4Q 2020 annual review: References reviewed and updated.	09/2020
4Q 2021 annual review: References reviewed and updated.	10/2021
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; references reviewed and updated.	10/2022
2Q 2023 annual review: Retired PA.CP.PMN.255 and add criteria to policy as current policies redirect to PA.CP.PMN.53 if indication not listed	04/2023
2Q 2024 annual review: added redirection for preferred biosimilar products; for Labeled Use without Drug-specific Coverage Criteria or Pending Clinical Policy Updates as a Result of Recent Label Changes for a Drug NOT on the Statewide PDL updated when to use; added consultation with appropriate specialty, not for excluded diagnosis; references reviewed and updated.	04/2024
2Q 2025 annual review: added requirement that alternative drugs be used for at least 30 days; references reviewed and updated.	04/2025