RXADVANCE
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Clinical Policy Title:	Off-Label Use
Policy Number:	RxA.601
Drug(s) Applied:	Off-Label Use
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

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 labelling.

Clinical Policy

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

I. Initial Approval Criteria

A. All Indications (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 or 2A (*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 Drug Dex® with strength of recommendation Class I or IIa (see Appendix D);
3. Prescribed by or in consultation with an appropriate specialist for the diagnosis;
4. 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 for the same indication at maximum indicated doses, unless no such drugs exist, at maximum indicated doses, unless contraindicated or clinically significant adverse effect are experienced (If only one FDA-approved drug exists, member only need to demonstrate failure of an adequate trial of that drug);
5. Member has no contraindications to the prescribed agent per the product information label;
6. If applicable, prescriber has taken necessary measures to minimize any risk associated with a boxed warning in the product information label;
7. Dosing regimen and duration are within dosing guidelines recommended by clinical practice guidelines and/or medical literature.

This clinical policy has been developed to authorize, modify, or determine coverage for individuals with similar conditions. Specific care and treatment may vary depending on individual need and benefits covered by the plan. This policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. This document may contain prescription brand name drugs that are trademarks of pharmaceutical manufacturers that are not affiliated with RxAdvance.

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

II. Continued Therapy Approval

A. All Indications (must meet all):

1. Member meets one of the following (a, b, or c):
   a. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
   b. Use is supported by one of the following (i, ii, or iii):
      i. The NCCN Drug Information and Biologics Compendium level of evidence 1 or 2A (*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*);
2. Member is responding positively to therapy;
3. 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
Commercial: Duration of request or 12 months (whichever is less)
Medicaid: Duration of request or 12 months (whichever is less)

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

- FDA: Food and Drug Administration

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

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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

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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.

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: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-reprint-practices-distribution-medical-journal-articles-and-medical-or-scientific-reference. Accessed August 17, 2020.
2. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed August 17, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	02/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title Table was updated 2. Continued therapy criteria II.A.1 was rephrased to “Currently receiving medication that has been authorized by RxAdvance…”. 3. References was updated.	10/20/2020	12/07/2020

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