MEDICAL POLICY

POLICY TITLE	OFF-LABEL USE OF MEDICATIONS
POLICY NUMBER	MP-2.103

Original Issue Date (Created):	**7/1/2002**
Most Recent Review Date (Revised):	**8/11/2020**
Effective Date:	**11/1/2020**

I. POLICY

Nononcologic Uses of Medications

Off-label drug use for nononcologic indications may be considered **medically necessary** when the drug is administered to improve the functioning of a malformed member of the body or facilitate in the diagnosis or treatment of an illness or injury and **ONE** of the following:

- The drug use is approved under the Federal Food, Drug, and Cosmetic Act; **or**
- The drug use is an accepted standard of medical practice in the United States; **or**
- Drug use is supported by Thomson Micromedex DrugDex®.

Note for Micromedex: The medical necessity of the drug for the requested nononcologic indication is **supported** when the indication is classified as Class I or Class IIA in Thomson Micromedex DrugDex®

A nononcologic use is considered **not supported*** when **one** of the following exists:

- The indication is classified as Class IIB or Class III in Thomson Micromedex DrugDex® **OR**
- The compendium listed above states that the prescription drug and/or biologic is not indicated, is unsupported, is not recommended, or equivalent terms are used regarding the prescription drug and/or biologic.

*The off-label use of erectile dysfunction drugs is not considered supported even when the off-label use is listed in one of the compendia above.

If the FDA determines a prescription drug or biologic to be contraindicated, or if the compendium listed in this policy designate it as “not indicated” for specific conditions, those uses will be considered **investigational** as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Drugs and biologics that have not received FDA approval for any indication are considered **investigational** for all uses. Individual consideration of “off-label use” shall not include use of a

device for treatment of a condition for which the FDA has determined the device to be contraindicated.

Oncologic Uses of Medications

Off-label drug use for oncologic indications may be considered **medically necessary** when the following conditions are met:

1. The drug is administered to improve the functioning of a malformed member of the body or facilitate in the diagnosis or treatment of an illness or injury and **ONE** of the following
   - Drug use is supported by Thomson Micromedex DrugDex® **OR** National Comprehensive Cancer Network (NCCN) Drugs and Biologic Compendium

Note: The compendia support the medical necessity of the drug for the requested oncologic indication when any **ONE** of the following is met:

- The indication is classified as a Category I or IIA in NCCN Drugs and Biologics Compendium
- The indication is classified as Class I or IIA in Thomson Micromedex DrugDex.

Note: An oncologic use is considered not supported by a compendium when **ONE** of the following exists:

- The indication is classified as Category III in NCCN Drugs and Biologics Compendium
- The indication is classified as Class IIB or Class III in Thomson Micromedex DrugDex.
- Any compendia listed above state that the prescription drug and/or biologic is not indicated, is unsupported, or equivalent terms are used regarding the prescription drug and/or biologic.

Orphan Drug Use

An orphan drug may be considered **medically necessary** when it receives FDA **marketing** approval.

Summary of Information regarding supportive or not supportive information:

Thomson Micromedex DrugDex®		**National Comprehensive Cancer Network Drug and Biologics Compendium® (NCCN)**	
Oncology	Non-Oncologic	Oncology	Non-Oncologic
Supported: Class I or IIA	Supported: Class I or Class IIA	Supported: Category I or IIA	Not Applicable

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Not Supported: Class IIB or Class III	Not Supported: Class IIB or Class III	Not Supported: Category III	

Note: The off-label use of a drug is considered not supported when any of the compendia listed in the grid above state that the prescription drug and/or biologic is not indicated, is unsupported, is not recommended, or equivalent terms are used regarding the prescription drug and/or biologic.

For oncologic indications, the complete absence of narrative text or indications listed in Lexi-Drugs® as "Use: Off Label" and rated as "Evidence Level B" or "Evidence Level C" or "Evidence Level G" with an "Equivocal" recommendation for inclusion, are considered neither "supported" nor "identified as not indicated" are considered neither supportive nor non-supportive. Refer to Medicare Benefit Policy Manual Chapter 15 Section 50.4.2.

Note: For patients with late stage metastatic disease (Stage IV), please refer to **MP 2.373** *Step Therapy Treatment in Cancer, Including Treatments for Stage Four, Advanced Metastatic Cancer and Severe Related Health Conditions* for additional guidance.

Cross-reference:

MP 2.373 - Step Therapy Treatment in Cancer, Including Treatments for Stage Four, Advanced Metastatic Cancer and Severe Related Health Conditions

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - The FEP program dictates that all drugs, devices or biological products approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational. Therefore, FDA-approved drugs, devices or biological products may be assessed on the basis of medical necessity.

Notes for Medicare Advantage:

1. Off-label use of FDA approved drugs and biologicals used in an anti-cancer chemotherapeutic regimen for medically accepted indications may be covered under Medicare if the indications are supported in either one or more Medicare recognized compendia or in peer-reviewed literature. Refer to Medicare Benefit Policy Manual

(100-2, Chapter 15, Section 50.4.5- Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen) for the compendia list. *http://www.cms.gov/manuals/Downloads/bp102c15.pdf*

2. FDA approved drugs used for indications other than what is indicated on the FDA approved product label may be covered under Medicare if it is determined that the use is medically accepted, taking into consideration the Medicare recognized national drug compendia, authoritative medical literature and/or accepted standards of medical practice." Refer to Medicare Benefit Policy Manual (100-2, Chapter 15, Section 50.4.2- Unlabeled Use of Drug). *http://www.cms.gov/manuals/Downloads/bp102c15.pdf*

III. DESCRIPTION/BACKGROUND

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The U.S. Food and Drug Administration (FDA) approves drugs and medical devices for specific indications. When a drug or device is used for indications other than those specifically documented in the labeling, it is referred to as an **off-label** use. Many off-label uses are effective, well documented in the peer-reviewed literature, and widely used.

The term "orphan drug" can refer to either a drug or biologic intended for use in a rare disease or condition as defined by the FDA office of Orphan Product Development Program Overview (OOPD). A drug or biologic becomes an "orphan drug" when it receives orphan-drug designation from the Office of Orphan Products Development at the FDA. Orphan drugs may be FDA approved for marketing or experimental. A list of FDA designated orphan products with marketing approval may be accessed at the following FDA website: http://www.fda.gov/orphan/designat/list.htm.

Unapproved or unlabeled uses of drugs include a variety of situations ranging from completely unstudied to thoroughly investigated drug uses where the FDA has not been asked for approval, whereas approved uses of drugs have been proved to be safe and effective by the FDA after the review of adequate and controlled clinical trials that have documented their uses.

IV. RATIONALE

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N/A

V. DEFINITIONS

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COMPENDIA is a comprehensive listing of FDA-approved drugs and biologicals or a comprehensive listing of a specific subset of drugs and biologicals in a specialty compendium, for example a compendium of anti-cancer treatment. A compendium—

i. Includes a summary of the pharmacologic characteristics of each drug or biological and may include information on dosage, as well as recommended or endorsed uses in specific diseases**.**
ii. Is indexed by drug or biological.
iii. Has a publicly transparent process for evaluating therapies and for identifying potential conflicts of interests

OFF-LABEL USE The use of a prescription drug or medical device in the treatment of an illness or injury, which can include different dosing of a medication, for which it has not been specifically approved by the FDA.

ORPHAN DRUG RARE DISEASE OR CONDITION refers to the FDA designation as any disease or condition which (a) affects less than 200,000 persons in the U.S. or (b) affects more than 200,000 persons in the U.S. but for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

***Specific Procedure Coding does not apply to this policy**

IX. REFERENCES

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1. *Centers for Medicare and Medicaid Services (CMS) Medicare Benefit Policy Manual. Publication 100-02. Chapter 15. Section 50.4.2. Unlabelled Use of Drug. Effective 10/01/03. [Website]: http://www.cms.gov/manuals/Downloads/bp102c15.pdf. Accessed August 8, 2020*
2. *Centers for Medicare and Medicaid Services (CMS) Medicare Benefit Policy Manual. Publication 100-02. Chapter 15. Section 50.4.5. Off-Label Use of Anti-Cancer Drugs and Biologicals. [Website]: http://www.cms.gov/manuals/Downloads/bp102c15.pdf. Accessed August 8, 2020.*
3. *National Comprehensive Cancer Network®. NCCN Drugs & Biologic Compendium™ (electronic version). [Website]: http://www.nccn.org. Accessed August 8, 2020*
4. *Radley DC, Finkelstein SN, Stafford RS. (2006). Off-label prescribing among office-based physicians. Arch Intern Med., 166(9), 1021-6.*
5. *Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. N Engl J Med. 2008 Apr 3;358(14):1427-9.*
6. *Taber's Cyclopedic Medical Dictionary, 19th edition.*
7. *U.S. Food and Drug Administration (FDA). Guidance for industry: 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. Last updated 9/27/18. [Website]: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-reprint-practices-distribution-medical-journal-articles-and-medical-or-scientific-reference Accessed August 8, 2020.*
8. *U.S. Food and Drug Administration (FDA). Office of Orphan Products (OOPD) Overview. Updated 4/23/19. [Website]: https://www.fda.gov/about-fda/office-special-medical-programs/office-orphan-products-development. Accessed August 8, 2020.*

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X. POLICY HISTORY

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MP 2.103	**CAC 4/27/04**
	CAC 6/28/05
	CAC 7/26/05
	CAC 7/31/07
	CAC 11/25/08
	CAC 11/24/09 Consensus review. No change in policy statement. References updated.
	CAC 11/30/10 Consensus review. No change in policy statements. References updated.
	CAC 11/22/11 Consensus review.
	7/23/13 Administrative update. Coding review complete
	CAC 11/26/13 Minor review. References updated. Minor editing for policy clarification. Nationally recognized compendia list updated. Compendia criteria for necessary level of evidence for medically necessity were added to the policy. Note removed that policy only applies to drugs and biologics that are not the subjects of specific medical policies. Policy title revised to "Off-Label Use of Prescription Drugs". Criteria regarding off-label use of devices removed from title and policy. Medicare and FEP variations removed.
	CAC 11/25/14 Consensus review. No change to policy statements.
	CAC 6/2/15 Minor review. Changed format of policy statements for clarity. New Title.
	CAC 1/26/16 Minor review. Added Wolters Kluwer Lexi-Drugs® to list of approved compendia. References updated.
	11/10/16 Administrative Update Variation reformatting
	CAC 1/31/17 Minor revision. Two statements that were in the policy guidelines were moved to the policy statement to include the following: • If the FDA determines a prescription drug or biologic to be contraindicated, or if the compendia listed in this policy designate it as "not indicated" for specific conditions, those uses will be considered investigational as there is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure. • Drugs and biologics that have not received FDA approval for any indication are considered investigational for all uses. Individual consideration of "off-label use" shall not include use of a device for treatment of a condition for which the FDA has determined the device to be contraindicated. References updated. No codes on policy to review.
	12/4/17 Consensus Review. No change to the policy statements. References updated.
	10/8/18 Consensus Review. No change to policy statements. References updated.
	6/24/19 Consensus Review. No change to policy statements. References updated.

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	8/29/19 Minor revision. Removed American Hospital Formulary Service Drug Information (AHFS-DI) as a recognized compendia source and updated the class/category of supported compendia. Effective 1/1/2020.
	4/10/20 Administrative update. Note added for patients with late stage metastatic disease (Stage IV), please refer to MP 2.373 Step Therapy Treatment in Cancer, Including Treatments for Stage Four, Advanced Metastatic Cancer and Severe Related Health Conditions for additional guidance.
	8/11/20 Consensus review. No change to policy statement. References reviewed.

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