Pharmacy Management Drug Policy

SUBJECT: Off-Label Use of FDA Approved Drugs **POLICY NUMBER: PHARMACY-32** **EFFECTIVE DATE: 11/2005** **LAST REVIEW DATE: 11/20/2023**
If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application		
Category:	☒ Commercial Group (e.g., EPO, HMO, POS, PPO)	☒ Medicare Advantage
	☒ On Exchange Qualified Health Plans (QHP)	☒ Medicare Part D
	☒ Off Exchange Direct Pay	☒ Essential Plan (EP)
	☒ Medicaid & Health and Recovery Plans (MMC/HARP)	☒ Child Health Plus (CHP)
	☐ Federal Employee Program (FEP)	☐ Ancillary Services
	☒ Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

The FDA approves drugs for specific indications and includes these indications in the drug's labeling. When a drug is used for an indication other than those specifically included in the labeling, it is referred to as an off-label use. Many off-label uses are effective, well documented in peer-reviewed literature, and widely used.

Criteria in drug-specific policies take precedence over the criteria listed in this policy. Therefore, drug-specific policies must be reviewed prior to applying the criteria listed below. However, this policy should be applied when a drug-specific policy is silent for an off-label use of an FDA approved drug or when developing drug-specific medical policies.

Contracts governed by New York State insurance law **may** be subject to the following mandate found in New York State Insurance Law article 3216:

According to New York State Law, every policy which provides coverage for prescribed drugs approved by the FDA for the treatment of certain types of cancer shall not exclude coverage of any such drug on the basis that the drug has been prescribed for the treatment of a type of cancer for which the drug has not been approved by the FDA. However, the drug must be recognized for treatment of the specific type of cancer for which the drug has been prescribed in one of the following references:

- National Comprehensive Cancer Compendium (NCCN) **OR**
- American Hospital Formulary Service Drug Information (AHFS), **OR**
- Truven Health Analytics Micromedex DrugDex **OR**
- Elsevier Gold Standard's Clinical Pharmacology: or other authoritative compendia as identified by the Federal Secretary of Health and Human Services or the Centers for Medicare and Medicaid Services (CMS); or recommended by review article or editorial comment in a major peer reviewed professional journal.

Medicare contracts governed by Federal Law are subject to applicable statutory requirements.

Refer to Corporate Medical Protocol #11.01.03 regarding Experimental and Investigational Services. Refer to Corporate Drug Policies regarding coverage for specific drugs.

Compendia applicability according to state and federal statute:

AMA DE - listed in the NY state oncology mandate and by Medicare Part D as an official compendia. However, this compendia is out of print.
AHFS DI - listed in the NY state oncology mandate, and by Medicare Part D and Medicare Part B as an official compendia, both for anticancer therapeutic regimens and non-cancer requests.
DrugPoints - This is the official successor to USPDI, and as such, is listed in the NY state oncology mandate, and by Medicare Part D as an official compendia for anticancer therapeutic regimen and non-cancer requests.
DrugDex - This is the parent publication of Drug Points. It is a recognized compendia for Medicare Part B and Part D anticancer therapeutic regimen and non-cancer requests.
Clinical Pharmacology - Listed in the NYS Oncology mandate and is a recognized compendia for Medicare Part B or Part D anticancer therapeutic regimen and Medicare Part B non-cancer requests only. It is not appropriate to use this compendia for Part D non-cancer requests.
NCCN Drugs and Biologics Compendium - Listed in the NYS Oncology mandate and is a recognized compendia for Medicare Part B or Part D anticancer therapeutic regimens and Medicare Part B non-cancer requests only. It is not appropriate to use this compendia for Part D non-cancer requests.
Lexi-Drugs - Listed in the NYS Oncology mandate and is a recognized compendia for Medicare Part B or Part D anticancer therapeutic regimens and Medicare Part B non-cancer requests only. It is not appropriate to use this compendia for Part D non-cancer requests.

Decision Tree by request type

Commercial/Exchange/SafetyNet request for non-cancer therapy:

1. Refer to drug specific policy and if the requested use is not addressed, proceed to number 2
2. Consult DrugPoints or DrugDex. Use is considered medically acceptable if the strength of recommendation is listed as Class I or IIa. If use is not listed, or is listed as IIb, proceed to number 3.
3. Consult NCCN Drugs and Biologics Compendium. Use is considered medically acceptable if the indication is given a category of 1 or 2a. If the use is not listed, or is listed as category 2b, proceed to number 4
4. The off-label use is considered medically acceptable if there is supporting published clinical research that meets all the following criteria:
    a. At least one phase III clinical trial that definitively demonstrates safety and effectiveness of the off-label use of the requested drug
    b. The trial must be published in national or international peer-reviewed (editorial committee is comprised of physicians) journal. This excludes case reports, letters, posters, and abstracts
    c. The trial must establish appropriate dose and dosing frequency (approvals will be limited to the dosing regimen established in the literature)
    d. In determining whether the clinical trial is definitively supportive, the following will be assessed:
        i. The prevalence of the disease and subject size sufficient to determine statistical validity
        ii. Whether the clinical characteristics of the patient and the indication are adequately represented in the published evidence
        iii. The effect on the individual's well-being and other responses to therapy that indicate effectiveness (e.g., reduction in mortality, morbidity, and signs and symptoms)
        iv. Whether the study outcomes represent clinically meaningful outcomes experienced by patients
        v. Appropriateness of study design (accepted study design includes, but is not limited to, randomized, double blind, placebo controlled clinical trial)

5. If the request is not supported by compendia or literature as listed above, then the request is not considered medically appropriate and will be denied as experimental and/or investigational.

Commercial/Exchange/SafetyNet request for the treatment of cancer:

1. Refer to drug specific policy and if the requested use is not addressed, proceed to number 2
2. Consult DrugPoints, DrugDex. Use is considered medically acceptable if the strength of recommendation is listed as Class I or IIa. If use is not listed, or is listed as IIb, proceed to number 3.
3. Consult NCCN Drugs and Biologics Compendium. Use is considered medically acceptable if the indication is given a category of 1 or 2a. If the use is not listed, or is listed as category 2b, proceed to number 4.
4. Consult AHFS and/or Clinical Pharmacology. Use is considered medically acceptable if the narrative text for the indication is supportive. If the use is not listed or supported proceed to number 5.
5. Consult peer-reviewed literature for support. Use is considered medically acceptable if there is at least 1 published article in a major professional peer reviewed journal, which supports the off-label use of the requested drug. Article should reference a sufficient number of subjects in relation to the incidence of the disease being treated. The article should also support that the off-label use is generally safe in relation to the severity of the disease being treated and the other existing treatment options. Evidence of clinically meaningful outcomes should be experienced by patients. If there are no full articles available in peer reviewed literature proceed to number 6.
6. If the request is not supported by compendia or articles as listed above, then the request is not considered medically appropriate and will be denied as experimental and/or investigational.

Medicare Part B request for non-cancer therapy:

1. Refer to drug specific policy and if the requested use is not addressed, proceed to number 2
2. Consult AHFS, DrugPoints/DrugDex, Clinical Pharmacology, or Lexi-Drugs. Use is considered medically acceptable if the strength of recommendation is listed as Class I, IIa, or IIb in DrugDex (A class III recommendation will be considered, as long as the DrugDex narrative/studies are supportive of the indication), Evidence Level A in Lexi-Drugs, or supportive in Clinical Pharmacology or AHFS. If use is not listed proceed to number 3.
3. Consult NCCN Drugs and Biologics Compendium. Use is considered medically acceptable if the indication is given a category of 1 or 2a. If the use is not listed, or is listed as category 2b, proceed to number 4
4. Consult literature for support. The literature must include:
    a. Clinical research that appears in at least two-phase III clinical trials that definitively demonstrate safety and effectiveness.
        i. The Phase III trials must come from different centers and be published in national or international peer-reviewed (editorial committee is comprised of physicians) journals. Peer reviewed medical literature includes scientific and medical publications. It does not include in-house publications of pharmaceutical manufacturing companies or abstracts (including meeting abstracts) **AND**
        ii. In determining whether the clinical trials are definitively supportive, the adequacy of the number of subjects, response rate, effect on key status/survival indications, appropriateness of study design, and the prevalence/life history of the disease will be taken into consideration **OR**
    b. If no phase III trial evidence is available, at least two-phase II clinical trials with reasonably large patient samples showing consistent results of safety and efficacy may be considered in certain instances such as use in rare diseases in which a phase III study might be difficult to complete in a reasonable period of time after completion of the phase II studies, or when overwhelmingly good evidence of safety and effectiveness is noted in the Phase II studies

i. The phase II trials must come from different centers and be published in national or international peer-reviewed (editorial committee is comprised of physicians) journals. Peer reviewed medical literature includes scientific and medical publications. It does not include in-house publications of pharmaceutical manufacturing companies or abstracts (including meeting abstracts) **AND**
ii. In the determining whether the clinical trials are definitively supportive, the adequacy of the number of subjects, response rate, effect on key status/survival indications, appropriateness of study design, and the prevalence/life history of the disease will be taken into consideration **OR**

c. A use that is an accepted standard of medical practice. "Are there published recommendations from specialty societies or in other authoritative evidence-based guidelines?" (For example, a state of the art review article published in a recognized textbook or a reputable publication) It should be noted that acceptance by individual health care practitioners, or even a limited group of health care practitioners normally does not indicate general acceptance by the medical community. Testimonials indicating such limited acceptance, and limited case studies distributed by sponsors with potential financial conflict of interest in the outcome, are not sufficient evidence of general acceptance by the medical community. The broad range of available evidence must be considered, and its quality must be evaluated before a conclusion is reached

5. If the request is not supported by compendia or literature (abstracts and poster presentations are not acceptable) as listed above, then the request is not considered medically appropriate and will be denied.

Medicare part D request for non-cancer therapy:

1. Refer to drug specific policy if the requested use is not addressed proceed to number 2
2. Consult DrugPoints or DrugDex. Use is considered medically acceptable if the strength of recommendation is listed as Class I, IIa, or IIb. A class III recommendation will be considered, as long as the DrugDex narrative/studies are supportive of the indication. If use is not listed proceed to number 3.
3. Consult AHFS. Use is considered medically acceptable if the narrative text for the indication is supportive. If the use is not listed or supported proceed to number 4.
4. If the request is not supported by DrugPoints/DrugDex or AHFS, then the request is not considered medically appropriate and will be denied. Support from primary literature or listing in alternative compendia is not sufficient.

Medicare part B or D request for anticancer therapeutic regimens

1. Refer to drug specific policy if the requested use is not addressed proceed to number 2.
2. Consult AHFS, DrugPoints/DrugDex, Clinical Pharmacology, or Lexi-Drugs. Use is considered medically acceptable if the strength of recommendation is listed as Class I, IIa, or IIb in DrugDex, Evidence Level A in Lexi-Drugs, or supportive in Clinical Pharmacology/AHFS. If use is not listed proceed to number 3.
3. Consult NCCN Drugs and Biologics Compendium. Use is considered medically acceptable if the indication is given a category of 1 or 2a. If the use is not listed, or is listed as category 2b, proceed to number 4.
4. Consult peer-reviewed literature for support. Use is considered medically acceptable if there is at least 1 published article in a major peer-reviewed journal that supports the off-label use of the requested drug as defined in CMS Chapter 15 Section 50.4.5.C
5. If the request is not supported by compendia or literature (abstracts, including meeting abstracts, are not acceptable) as listed above, then the request is not considered medically appropriate and will be denied.

POLICY GUIDELINES:

1. Drugs that are not FDA approved are not eligible for coverage.
2. The requested off label use (indication AND regimen) will be reviewed using the criteria set forth above.
3. For Commercial/Exchange/SafetyNet, non-cancer therapy may include supportive therapy in oncology, precancerous conditions, complications associated with the treatment of cancer, and conditions associated with an increased risk of developing cancer.
4. Standard approval time frame will be for up to 6 months and will depend on expected period to determine safety and efficacy of the drug. Approval time frame will be individualized based on case-specific factors and may vary. Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition. Such documentation may include progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit which support that continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary [Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e., generics, biosimilars, or other guideline-supported treatment options)] and the requested dose must continue to meet FDA approved or off-label/guideline supported dosing.
5. The provider requesting reimbursement must provide appropriate evidence to support the off-label use of the drug.
6. The Health Plan may create policies/protocol(s) related to coverage for off-label use of specific drugs under the following circumstances:
   - When a drug is being used for off-label indications determined to have marginal benefit; or
   - When asked to approve reimbursement for certain drug specific procedures (e.g., creation of a code for a new procedure which uses an off- label indication of a drug).

7. DrugDex classification of recommendations and evidence

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	
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.	

8. NCCN Categories of Evidence and Consensus

Class I	Based upon **high**-level evidence, there is **uniform** NCCN consensus that the intervention is appropriate
Class IIa	Based upon **lower**-level evidence, there is **uniform** NCCN consensus that the intervention is appropriate
Class IIb	Based upon **lower**-level evidence, there is NCCN consensus that the intervention is appropriate
Class III	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

UPDATES:

Date:	Revision:
11/20/2023	Revised
11/14/2023	Revised
11/8/2023	Revised
10/24/2023	Revised
10/17/2023	Revised
8/17/2023	Revised
8/3/2023	Revised
5/11/2023	Reviewed / P&T Committee Approval 5/11/2023
5/22	Revised / P&T Committee Approval 5/5/2022
5/21	P&T Committee Approval 5/6/2021
01/21	Revised
07/20	Reviewed
5/20	P&T Committee Approval 5/7/2020
06/19	Revised
02/19	P & T Committee Approval 2/7/2019
01/19	Reviewed
08/18	Revised
11/17	Revised
9/17	Reviewed/P&T Approval
7/16	Reviewed
6/15	Revised
6/14	Reviewed
8/13	P&T Approval
6/13	Revised
6/12	Reviewed
10/10	Revised
11/09	Reviewed
1/09	Revised

REFERENCES:

1. New York State Consolidated Law § 3216 (12) (A).
2. Medicare Benefit Policy Manual Chapter 15. Rev 12171, 08/03/2023 <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c15.pdf>
3. Medicare Prescription Drug Benefit Manual Chapter 6. Rev 18, 1/15/16 < https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Part-D-Benefits-Manual-Chapter-6.pdf>
4. Medicare Modernization Act 1680D-2(e)

5. NCCN Compendia. Available at <http://www.nccn.org/professionals/drug_compendium/content/contents.asp>
6. Compendia 1861 (t)(2). Centers for Medicare @ Medicaid Services. Available at <http://www.cms.gov/Medicare/Coverage/CoverageGenInfo/compendia.html>
7. Micromedex Compendia. Available at <https://www.micromedexsolutions.com/home>
8. CMS Local Coverage Determination L33394 , Drugs and Biologics, Coverage of, for Label and OFF-LABEL Uses. Rev 11/01/2022 < https://www.cms.gov/medicare-coverage-database>