PART B DRUG MEDICAL/PHARMACY	ASPIRE HEALTH	**Effective Date** August 15, 2024
	Off-Label Use of Drugs and Biologic Agents	**Policy #** Off-Label Use of Drugs and Biologic Agents
		Review Date 05/28/2024
		Applicable to: ☑ Medicare Advantage ☐ Commercial ☐ Elevance Health HMO ☐ Blue Shield Trio
	Approver's Name & Title QI & UM Drug Subcommittee	

Aspire Health Plan (AHP) applies medical drug clinical criteria as a reference for medical policy information only. Federal and state laws or requirements, contract language, and Plan benefit may take precedence over the application of these clinical criteria. Please consult the applicable certificate or contract for benefit details. This policy is subject to revision at the discretion of the Plan and is therefore subject to change. Refer to the disclaimer section below for more information.

POLICY

This policy addresses the coverage of an off-label use of a drug, defined as a use for a non-FDA approved indication, that is, one that is *not* listed on the drug's official label/prescribing information. AHP will evaluate requests for off-label use on a case-by-case basis in accordance with the criteria set forth in this policy.

FDA approved indications or the labeled indications for drugs/biologic agents have been proven to be safe and effective by the FDA after the review of adequate and controlled clinical trials. An indication is defined as a diagnosis, illness, injury, syndrome, condition, or other clinical parameter for which a drug may be given. When a drug is used for an indication, dosage, route of administration, duration, and frequency of administration, other than those specifically included in the labeling, it is referred to as an off-label use. Numerous off-label uses are effective, well-documented in medical literature, and widely utilized.

This policy shall not be interpreted to require coverage for any drug or biological agent when the FDA has determined its use to be contraindicated.

AHP adheres to Medicare guidelines and coverage determinations will be in compliance with the guidance issued by the Medicare Administrative Contractor (MAC) for Medicare Part B Jurisdiction E (1): Determination of Approved and Accepted Off-label Drug Indications.

APPLICABLE HCPCS

Applicable to Part B physician-administered HCPCS / J-codes that are requested for off-label / unlabeled use.

This policy should only be applied in the absence of a National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare guidance addressing the requested off-label use of an FDA-approved drug.
This policy does not apply to the following request as there is an NCD available, such as the following:

110.17	Anti-Cancer Chemotherapy for Colorectal Cancer NCD
110.22	Autologous Cellular Immunotherapy Treatment NCD
200.1	Nesiritide for Treatment of Heart Failure Patients NCD

CLINICAL CRITERIA

In absence of an NCD, LCD, or Medicare issued guidance, AHP drug-specific policies must be considered before applying this policy. This policy is applicable when an AHP drug-specific policy does not address the requested off-label use of an FDA-approved drug.

I. INITIAL CRITERIA

Off-label / Unlabeled use (indication, dosage, route of administration, duration, and frequency of administration, other than those specifically included in the labeling) of a Part B drug may be authorized, including anti-cancer drugs, in the absence of any statutory, CMS NCD / LCD, or AHP drug-specific policy, if **ALL** the following criteria are met:

A. Prescribed by an appropriate specialist for the indication requested; **AND**

B. Requested drug has been approved as safe and effective by the FDA for at least ONE indication; **AND**

C. Prescriber attests to, or has submitted documentation, the requested drug is not contraindicated by the FDA for the off-label use prescribed and the member does not have any FDA-labeled contraindications; **AND**

D. The member has tried and failed, or has a contraindication to, the current treatment guideline recommended formulary alternatives, which are regarded the standard of care and are of equal or greater efficacy compared to the requested drug for the member's diagnosis; **AND**

E. Member meets **ONE** of the following with documentation:

1. Off-label use requested (including indication, dosage, frequency, route of administration, age, patient population) is supported by at least **ONE** of the CMS-approved compendia with an appropriate †level of evidence of efficacy.

   The evidentiary levels of efficacy discussed in these compendia determine whether a drug may be covered for a given indication.

   †"Medically accepted" definitions by compendium:
   1. NCCN: The level of evidence for the indication is Category 1 or 2A. (If a provider chooses to use NCCN level 2B in support of a chemotherapeutic drug used for an off-label indication, it is expected that the provider will make available significant peer reviewed phase II or phase III studies demonstrating such support.)
   2. DrugDex: The level of evidence for the indication is a Class I, Class IIa, or Class IIb.
   3. AHFS-DI or Clinical Pharmacology: The narrative text is supportive.
   4. Lexi-Drugs: The indication is listed as "Use: Off-Label" and rated as "Evidence Level A."

   †Not "medically accepted" by a compendium:
   1. NCCN: The level of evidence for the indication is Category 3 in NCCN.
   2. DrugDex: The level of evidence for the indication is Class III in DrugDex.
   3. AHFS-DI or Clinical Pharmacology: The narrative text is "not supportive" (or equivalent term).
   4. Lexi-Drugs: Indication is listed as "Use: Unsupported."

   NOTE: The complete absence of narrative text on a use is considered neither supportive nor non-supportive. **The off-label use of the requested drug (including requests for off-labeled dose, will not be authorized for coverage if it is listed as "unsupported," "not indicated," "not recommended" (or equivalent terms) in any of the CMS-approved compendia.**

OR

2. Submitted peer-reviewed literature by requesting Prescriber supporting evidence for the off-label use of the requested drug includes **ONE** of the following:

    a. Full-text articles from at least TWO (2) major *peer-reviewed journals (*medical literature may appear in scientific, medical, and pharmaceutical publications in which original manuscripts are published, only after having been critically reviewed for scientific accuracy, validity, and reliability by unbiased, independent experts prior to publication) providing evidence of both safety and efficacy for the requested off-label use; **or**

    b. A use supported by clinical research that appears in at least **TWO *published* Phase III clinical trials** that definitively demonstrate safety and effectiveness.

        i. Phase III trials must be conducted at multiple centers and published in peer-reviewed journals with physician editorial committees. Medical literature includes scientific and medical publications. Excludes in-house publications of pharmaceutical manufacturing companies and abstracts.

        ii. 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 considered to determine if the clinical trials are definitively supportive.

    or

    c. **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. (LCD L33394)

        i. The Phase III or 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).

        ii. 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 considered to determine if the clinical trials are definitively supportive.

    or

    d. A use that is an accepted standard of medical practice: Published recommendations from specialty societies or in other authoritative evidence-based guidelines.
    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.

AND

F. Additional medical records and other relevant documentation as requested by AHP must be submitted by the Provider. **NOTE:** Insufficient or unfurnished documentation may result in an untimely review or the denial of the off-label use request.

II. REAUTHORIZATION / CONTINUATION OF THERAPY CRITERIA

Reauthorization: Continuation of treatment requires supporting documentation of ongoing positive response, such as improvement of symptoms or stability in the disease state or overall condition.

Continuation of off-label treatment with the requested drug will be taken into consideration with the current preferred formulary, which may require consideration of cost-effective treatment alternatives that are accepted standards of care or guideline-supported drug therapy (i.e., generics, biosimilars).

1. Member continues to meet the 'Initial Criteria' section above. NOTE: Newly enrolled AHP members on off-label therapy must also meet the initial criteria; **and**

2. Adherence to therapy at least 85% of the time (as verified by the prescriber or member medication fill history), OR adherence less than 85% of the time due to the need for surgery, treatment of an infection or adverse event mitigation, causing temporary discontinuation: Review with Prescriber and Aspire Clinical Reviewer may be required; **and**

3. Prescriber attests to, or clinical reviewer has found, no evidence of intolerable adverse effects or unacceptable toxicity with the requested drug; **and**

4. Documentation of positive response to therapy as evidenced by improvement/stabilization in disease activity or member's clinical function / symptoms. *Documentation may include medical records, progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit that support the continued use of the requested product is medically necessary;* **and**

5. Prescriber attests to ongoing safety monitoring per FDA label for the requested drug

III. EXCLUSIONS

Experimental/Investigational Use: Off-label medical use not supported by CMS recognized compendia or acceptable peer-reviewed literature.

*Medically accepted indications are defined by CMS as those uses of a covered drug that are approved under the federal Food, Drug and Cosmetic Act, or the use of which is supported by one or more citations included or approved for inclusion in any of the compendia described in section 1927(g)(1)(B)(i) of the Act. These compendia guide review of off-label and off-evidence prescribing and are subject to minimum evidence standards for each compendium. Currently, this review includes the following references when applicable and may be subject to change per CMS:

- American Hospital Formulary Service-Drug Information (AHFS-DI)
- National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
- Truven Health Analytics Micromedex DrugDEX
- Elsevier/Gold Standard Clinical Pharmacology
- Wolters Kluwer Lexi-Drugs

STEP THERAPY

Step Therapy: NOT APPLICABLE

DOSAGE AND AUTHORIZATION TIMEFRAMES

1. Recommended Dose: The requested dose must align with CMS-approved authoritative compendia or supported by acceptable peer-reviewed literature or treatment guidelines.

   NOTE: If request is for a dose increase, new dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

2. Quantity: Not to exceed limits in CMS-approved authoritative compendia or accepted peer-reviewed articles submitted by Provider.

3. Authorization Period: May authorize up to 6 months depending on the discretion of Aspire's Pharmacy/Medical Director of the expected period to determine safety and efficacy of the drug. May vary based on individualized, case-specific factors as determined by Aspire Medical Director.

DRUG INFORMATION

PHARMACOLOGIC CATEGORY: N/A

ROUTE OF ADMINISTRATION: In accordance with the FDA approved labeling, CMS-approved authoritative compendia, or accepted peer-reviewed articles submitted by Provider for requested off-label use.

INDICATIONS: In accordance with the FDA approved labeling, CMS-approved authoritative compendia, or accepted peer-reviewed articles submitted by Provider for requested off-label use.

COMPENDIAL APPROVED OFF-LABELED USES: In accordance with the FDA approved labeling, CMS- approved authoritative compendia, or accepted peer-reviewed articles submitted by Provider for requested off-label use.

CONTRAINDICATIONS: In accordance with the FDA approved labeling, CMS-approved authoritative compendia, or accepted peer-reviewed articles submitted by Provider for requested off-label use.

CLINICAL SUMMARY / APPENDIX

Centers for Medicare and Medicaid Services (CMS) Compendia
CMS established an annual review procedure for recognizing compendia in 2008, which included transparency requirements in the selection process. CMS may make modifications to the list internally at any time after investigation and public comment. CMS has established five drug compendia as authoritative sources (listed in the CMS Internet Only Manual (IOM) Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, Section 50.4.5) as follows in no particular order:

- American Hospital Formulary Service - Drug Information (AHFS-DI)
- Elsevier Gold Standard Clinical Pharmacology Compendium (Clinical Pharmacology)
- National Comprehensive Cancer Network Drugs and Biologics Compendium (NCCN)
- Truven Health Analytics Micromedex® DrugDex® Compendium
- Wolters Kluwer Lexi-Drugs®

REFERENCES

Government Agency

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database: National coverage determination (NCD) (search: off-label use). Accessed on May 2024. Available from CMS:
   - 110.17 Anti-Cancer Chemotherapy for Colorectal Cancer NCD
   - 110.22 Autologous Cellular Immunotherapy Treatment NCD
   - 200.1 Nesiritide for Treatment of Heart Failure Patients NCD
2. Centers for Medicare and Medicaid Services (CMS). CMS IOM, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, Section 50.4.5
3. Centers for Medicare and Medicaid Services (CMS). CMS Transmittal 96, Change Request (CR) 6191 dated October 24, 2008
4. Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)]: Noridian Medicare Available at: Determination of Approved and Accepted Off-label Drug Indications . (noridianmedicare.com). Accessed on May 2024.

IMPORTANT REMINDER

This Medicare Part B Step Therapy Medical Necessity Guideline is provided for informational purposes only and neither constitutes nor replaces professional medical advice. Physicians, hospitals, and other providers are expected to administer or use drugs/biologicals in the most effective and clinically appropriate manner.

Treating physicians and other health care providers is solely responsible for all medical care decisions. In accordance with the member's Evidence of Coverage (EOC), every benefit plan has its own coverage provisions, limitations, and exclusions. In the event of a conflict between this policy and the member's EOC, the member's EOC provisions will take precedence.

Aspire Health Plan (AHP) adheres to Medicare guidelines, including National Coverage Determination (NCD), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs), and other relevant Medicare manuals established by CMS. Compliance with these guidelines is required when applicable. Refer to the CMS website at http://www.cms.hhs.gov. For the most up-to-date Medicare policies and coverage, please search the Medicare Coverage Database. All LCDS are the same for each state within a Jurisdiction. Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)]: Active LCDs - JE Part B – Noridian (noridianmedicare.com). In the event of a discrepancy between this policy and the Medicare NCD or LCD, the Medicare NCD/LCD will govern.

This policy is utilized by AHP to determine coverage in the absence of applicable CMS Medicare guidelines. Please refer to the links provided in the References section below to access the Medicare source materials that were used for developing this resource document. This document does not serve as a substitute for the official Medicare source materials that provide detailed information on Medicare coverage requirements. In the event of a conflict between this document and Medicare source materials, the Medicare source materials will take precedence.

The inclusion of a code in this policy does not imply that the health service it describes is covered or not covered. Benefit coverage for health services is determined by the member-specific plan document and applicable laws that may mandate coverage for a particular service. Inclusion of a code does not imply or guarantee reimbursement or payment of a claim. Other Policies and Standards may also apply. Providers are expected to retain or have access to the necessary documentation when requested in order to support coverage.

POLICY HISTORY

Version	Approval Date	Revision Author/Title	Summary of Changes
1	5/28/2024		New Policy