Medical Policy Bulletin

Title:
Off-label Coverage for Prescription Drugs and/or Biologics
Policy #:
MA08.012d

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific andmedical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

This policy uses coverage criteria primarily based on applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals and other applicable Medicare coverage documents. In the absence of fully established coverage criteria from these Medicare coverage documents for a specific medical service or item, the criterion/indication/service indicated by an asterisk below (*) is based on internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, regulatory status, and/or expert opinion.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

CRITERIA TO ESTABLISH MEDICAL NECESSITY FOR OFF-LABEL COVERAGE OF US FOOD AND DRUG ADMINISTRATION (FDA)–APPROVED DRUGS AND/OR BIOLOGICS

Off-label use of prescription drugs and/or biologics can include factors such as indications, dosages, frequencies, or routes of administration that are not in accordance with FDA labeling. For off-label use, additional clinical rationale is required to support coverage.

Off-label use of prescription drugs and/or biologics is considered medically necessary and, therefore, covered when the off-label use is supported by either the Medicare-recognized prescription drug and/or biologic compendia, or published clinical research, as outlined below.

1. COMPENDIA FOR ONCOLOGIC USE (ANTI-CANCER CHEMOTHERAPY)

For coverage of an anti-cancer chemotherapy regimen, the off-label
use is considered medically necessary and therefore covered when one of the following criteria is met AND when none of the experimental/investigational criteria exist:

- The narrative text in American Hospital Formulary Service–Drug Information (AHFS-DI®) is supportive of the use.
- The use is classified as Category 1 or 2A by National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium™.

- The use is classified as Class I, Class IIa, or Class IIb in Truven Health Analytics Micromedex® DrugDex® Compendium.
- The narrative text in Elsevier's Clinical Pharmacology® is supportive of the use.
- The use is classified as "Off-Label" and rated as "Evidence Level A" with a "Strong" recommendation in Wolters Kluwer Lexi-Drugs® Compendium.

An anti-cancer chemotherapy regimen is considered experimental/investigational and therefore not covered, even when above criteria have been met and when one of the following exists:

- The use is classified as Category 3 by NCCN® or Class III in Micromedex® DrugDex®.
- The narrative text in AHFS-DI® is not supportive of the use.
- The narrative text in Elsevier's Clinical Pharmacology® is not supportive of the use.
- The use is classified as "Unsupported" with an "Against" recommendation in Wolters Kluwer Lexi-Drugs® Compendium.
- Any of the compendia listed above state that the drug is not indicated, is unsupported, is not recommended, or equivalent terms are used regarding the drug.

When a compendium is considered neither supportive nor nonsupportive (i.e., Category 2B in NCCN, use is classified as "Off-label" and rated as "Evidence Level B, C, or G" with an "Equivocal" recommendation in Wolters Kluwer Lexi-Drugs® Compendium, use is recommended "For" the chemotherapy with a "Strong" recommendation and a "Low or Very Low" Level of Evidence in Elsevier's Clinical Pharmacology®, or an absence of narrative text or evidence classification from any Company-recognized compendium), please refer to the section in this policy entitled Published Clinical Research.

2. COMPENDIA FOR NON-ONCOLOGIC USE*

For coverage of non-oncologic prescription drugs and/or biologics, the off-label use is considered medically necessary and therefore covered when one of the following exists:

- The narrative text in American Hospital Formulary Service–Drug Information (AHFS-DI®) is supportive of the use.
- The use is classified as Class I or Class IIa in Truven Health Analytics Micromedex® DrugDex® Compendium.

Nononcologic prescription drugs and/or biologics are considered experimental/investigational and therefore not covered, even when the above criteria have been met, when one of the following exists:

- The use is classified as Class III in Micromedex® DrugDex®.
- The narrative text in AHFS-DI® is not supportive of the use.
- Either of the compendia listed above state that the drug is not indicated, is unsupported, is not recommended, or equivalent terms are used regarding the drug.

When a compendium is considered neither supportive nor nonsupportive (i.e., Class IIb in Micromedex® DrugDex®, or an absence of narrative text or evidence classification from any Company-recognized compendium), please refer to the section in this policy entitled Published Clinical Research**.**

3. PUBLISHED CLINICAL RESEARCH* (National Government Services, Inc. LCD: L33394. Drugs and Biologicals, Coverage of, for Label and Off-Label Uses. Original 10/01/2015; Revised 07/13/2025.)

In order for an off-label use to be supported by published clinical research, all of the following criteria must be met:

- The prescription drug or biologic must have been studied in at least two clinical trials conducted at different centers, and the results must have been published in national or international peer-reviewed journals with an editorial committee composed of physicians. Peer-reviewed medical literature includes scientific, medical, and pharmaceutical publications. It does not include in-house publications of pharmaceutical manufacturing companies or abstracts (including meeting abstracts).
    - A use is considered supported by clinical research when it appears in at least two Phase III clinical trials that have definitively demonstrated its safety and effectiveness as an appropriate medical treatment for the condition. 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 (e.g., 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).

- Reliable evidence must demonstrate that the proposed off-label use for the specified medical condition is safe and effective and that the beneficial effects of the treatment outweigh its risks.
- In determining whether there is supportive clinical evidence for a particular use of a prescription drug and/or biologic, the quality of the evidence in published, peer-reviewed medical literature is considered. Among other things, such consideration involves the assessment of the following:
    - The prevalence and life history of the disease when evaluating the adequacy of the number of subjects and the response rate
    - 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)
    - Whether the clinical characteristics of the beneficiary and the use are adequately represented in the published evidence
    - Whether the administered chemotherapy regimen is adequately represented in the published evidence
    - Whether the reported study outcomes represent clinically meaningful outcomes experienced by individuals
    - Whether the study is appropriate to address the clinical question, such as:
        - If the study design is appropriate to address investigative questions (e.g., in some clinical studies, it may be unnecessary or not feasible to use randomization, double-blind trials, placebos, or crossover)
        - If nonrandomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of prescription drugs and/or biologics
        - Generally, case reports are considered uncontrolled, are based on anecdotal information, and do not provide adequate supportive clinical evidence for determining accepted uses of prescription drugs and/or biologics
- The off-label use is supported by published clinical research, and the results have been published in major peer-reviewed medical journals such as, but not limited to:

American Journal of Medicine
Annals of Internal Medicine
Annals of Oncology
Annals of Surgical Oncology
Biology of Blood and Marrow Transplantation
Blood
Bone Marrow Transplantation
British Journal of Cancer
British Journal of Hematology
British Medical Journal
Cancer
Clinical Cancer Research
Drugs
European Journal of Cancer
Gynecologic Oncology
International Journal of Radiation, Oncology, Biology, and Physics
Journal of Clinical Oncology
Journal of the National Cancer Institute
Journal of the National Comprehensive Cancer Network (NCCN)
Journal of Urology
Lancet
Lancet Oncology
Leukemia
Radiation Oncology
The New England Journal of Medicine
The Journal of the American Medical Association

EXPERIMENTAL/INVESTIGATIONAL

If a use is identified as not indicated by the Centers for Medicare and Medicaid Services (CMS) or the FDA, or if a

use is specifically identified as not indicated in one or more of the compendia listed, or if analysis of peer-reviewed medical literature determines that a particular use of a drug is not safe and effective, the off-label usage is not supported and, therefore, the drug is not covered and is considered experimental/investigational.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the prescription drug and/or biologic.

Guidelines

This policy is consistent with Medicare's coverage criteria. The Company's reimbursement methodology may differ from Medicare.

BENEFIT APPLICATION

A prescription drug and/or biologic may be covered through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the prescription drug and/or biologic is prescribed, dispensed, or administered. This medical policy only addresses instances when prescription drugs and/or biologics are covered under a member's medical benefit. It does not address instances when prescription drugs and/or biologics are covered under a member's pharmacy benefit.

Description

OFF-LABEL USE

Off-label use of prescription drugs and/or biologics can include factors such as indications, dosages, frequencies, or routes of administration that are not in accordance with US Food and Drug Administration (FDA) labeling. For off-label use, additional clinical rationale is required to support coverage.

Off-label uses are generally recognized as medically accepted indications if they are supported in either 1) one or more authoritative compendia, and none list it as not indicated, unsupported, not recommended, or equivalent terms; or 2) in peer-reviewed medical literature. Reliable evidence must demonstrate that the proposed off-label use to treat the specified medical condition is safe and effective, and that the beneficial effects of the treatment outweigh its risks.

Peer-reviewed medical literature includes 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. In order for a use to be supported by clinical research, it must have been studied in at least two clinical trials conducted at different centers, and the results must have been published in national or international peer-reviewed journals with an editorial committee composed of physicians. Peer-reviewed medical literature does not include in-house publications of pharmaceutical manufacturing companies or abstracts (including meeting abstracts).

According to the National Cancer Institute, clinical trials are usually conducted in a series of steps called phases. These are outlined as follows:

Phase 0 trials are the first step in testing a new agent in people. Phase 0 trials will evaluate how the new agent is processed in the body and how it exerts its clinical effects in the body. Phase 0 trials enroll a small number of individuals (10-15 individuals) who are administered a very small amount of the new agent.

Phase I trials evaluate what dose is safe, how a new agent should be given (by mouth, injected into a vein, or

injected into the muscle), and how often. Researchers watch closely for any harmful side effects. Phase I trials usually enroll a small number of individuals (20 or more individuals) and take place at only a few locations. The dose of the new therapy or technique is increased a little at a time. The highest dose with an acceptable level of side effects is determined to be appropriate for further testing.

Phase II trials study the safety and effectiveness of an agent or intervention, and evaluate how it affects the human body. Phase II studies usually focus on a particular aspect of a disease, and include fewer than 100 patients.

Phase III trials compare a new agent or intervention (or new use of a standard one) with the current standard therapy. Participants are randomly assigned to the standard group or the new group, usually by computer. This method, called randomization, helps to avoid bias and ensures that human choices or other factors do not affect the study's results. In most cases, studies move into Phase III testing only after they have shown promise in Phases I and II. Phase III trials often include large numbers of individuals across the country.

Phase IV trials are conducted to further evaluate the long-term safety and effectiveness of a treatment. They usually take place after the treatment has been approved for standard use. Several hundred to several thousand people may take part in a Phase IV study. These studies are less common than Phase I, II, or III trials.

In the field of oncology, there are many reasons to consider a medically supported off-label use of a prescription drug and/or biologic for a cancer chemotherapy agent. Prescription drugs and/or biologics may be effective for many other cancers in addition to those that were considered in the primary labeling of the prescription drug and/or biologic, and many chemotherapeutic agents are given in combinations (regimens). Any of the prescription drugs and/or biologics in the combination may not have been approved in the initial labeling of the products. In addition, the combination of effective chemotherapeutic agents changes over time. Healthcare providers are often left with few approved treatment options if initial treatment regimens have failed.

ORPHAN DRUGS

According to the US Food and Drug Administration (FDA), an orphan drug is "a product that treats a rare disease that either affects fewer than 200,000 individuals in the United States or affects more than 200,000 individuals in the United States with no reasonable expectation that the cost of drug development will be recovered from sales of the drug in the United States." If the designated product meets the standard FDA regulatory requirements and process for obtaining marketing approval, it is given an FDA orphan drug designation status.

The Orphan Drug Act (ODA) provides for granting special status, orphan drug designation, to a product to treat a rare disease or condition upon request of a sponsor. The product to treat the rare disease or condition must meet certain criteria. Orphan designation qualifies the sponsor of the product for specific benefits from the FDA.

An orphan drug designation does not imply FDA approval or medically accepted use. FDA approval of a drug means that data on the drug’s effects have been reviewed by the Center for Drug Evaluation and Research (CDER), and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population. Consideration for coverage requires sufficient evidence of drug safety and efficacy established through clinical studies.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
N/A

HCPCS Level II Code Number(s)
N/A

Revenue Code Number(s)
N/A

Policy History

Revisions From MA08.012d:

12/15/2025	This version of the policy will become effective 12/15/2025. The intent of this policy remains unchanged; however, the policy was revised in accordance with: • Centers for Medicare & Medicaid Services (CMS). Medicare Benefit Policy Manual. Chapter 15: Covered medical and other health services. §50.4.5: Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen. • National Government Services, Inc. LCD: L33394. Drugs and Biologicals, Coverage of, for Label and Off-Label Uses. [National Government Services, Inc. Web site]. Original 10/01/2015; Revised 07/13/2025. Available at: LCD - Drugs and Biologicals, Coverage of, for Label and Off-Label Uses (L33394). Accessed July 16, 2025. • Centers for Medicare & Medicaid Services (CMS). *Medicare Prescription Drug Benefit Manual.* Chapter 6: Part D Drugs and Formulary Requirements. 10.6 - Medically-Accepted Indication. Rev. 18, 01-15-16.

Revisions From MA08.012c:

03/28/2025	This policy has been reissued in accordance with the Company's annual review process.
05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
03/22/2023	This policy has been reissued in accordance with the Company's annual review process.
02/23/2022	This policy has been reissued in accordance with the Company's annual review process.
03/24/2021	This policy has been reissued in accordance with the Company's annual review process.
05/04/2020	This version of the policy will become effective 05/04/2020. This policy was updated to clarify the coverage for off-label use of oncologic conditions by the Medicare-recognized compendia, Micromedex® DrugDex® to include Category IIB, to include a definition of orphan drug designation, as well as requirements for consideration of coverage.

Revision From MA08.012b:

06/03/2019	This policy was updated to communicate a clarification of the components of off-label use of prescription drugs and/or biologics, such as indications, dosages, frequencies, or routes of administration.

Revisions From MA08.012a:

09/12/2018	This policy has been reissued in accordance with the Company's annual review process.
08/02/2017	This policy has been reissued in accordance with the Company's annual review process.
11/30/2016	This policy communicates the addition of a new compendium, Wolters Kluwer Lexi-Drugs® Compendium, to Medicare's list of drug compendia used for the evaluation of an off-label use for drug and biologics. Elsevier Gold Standard's Clinical Pharmacology Compendium (Clinical Pharmacology®), name was revised to Elsevier's Clinical Pharmacology® and further levels of evidence were incorporated into the Policy. This policy also clarifies the scenario of when a compendium is considered neither supportive nor non-supportive. The drug compendium name, Micromedex® Compendium, was revised to Micromedex® DrugDex® Compendium.

Revisions From MA08.012:

07/22/2015	The policy has been reviewed and reissued to communicate the Company's continuing position on Off-label Coverage for Prescription Drugs and/or Biologics.
01/01/2015	This is a new policy.

Version Effective Date:
12/15/2025
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12/15/2025
Version Reissued Date:
N/A