Pharmacy Policy Bulletin

Title:	Off-Label Use
Policy #:	Rx.01.33

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

Prescription pharmaceutical agents available in the United States have FDA approved labeling. The label specifies which disease states a drug can be used to treat. However, use of a pharmaceutical agent may expand past the approved labeling and into what is known as off-label use. Coverage for off-label or experimental use will require Prior Authorization.

Description:

The US Food and Drug Administration (FDA) approves labeling that details uses for which a pharmaceutical agent can be marketed. The approved uses identify the specific disease states that the agent has been shown to be safe, efficacious and meet all clinical requirements set forth by the FDA. An off-label or unlabeled use of a prescription drug or biologic is a use that has not been approved by the US Food and Drug Administration (FDA) and which is not identified in package labeling. Use of a drug for any indication, dose or dose frequency, treatment duration, patient population, or route of administration other than those approved by the FDA and listed on the label or packaging insert is considered an off-label or unlabeled use.Off-label use of prescription drugs and biologics not meeting the medical necessity criteria is considered experimental/investigational and may not be a covered by the prescription drug benefit.

In determining whether there is clinical evidence to support a medical necessity determination, the pharmacy benefits manager will consider the quality of the published evidence as well as an assessment of the following information as submitted by the requesting physician. Off-label uses are medically accepted if they are supported in either of the following:

(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 for the specified medical condition is safe and effective and that the treatment's beneficial effects 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.

Policy:

Off-label uses are medically accepted and thus approved when ONE of the following is met:

1. The narrative text in American Hospital Formulary Service--Drug Information (AHFS-DI®) is supportive of the use; or
2. The use is classified as Category 1 or 2A by National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium™; or
3. The use is classified as Class I or Class IIa in Micromedex®; or
4. Adequate published clinical research (supplied by the provider) as defined below:

Authorization duration: 2 years

PUBLISHED CLINICAL RESEARCH

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

A. 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 a 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).

B. 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. 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 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 or biologic, the

Company considers the quality of the evidence in published, peer-reviewed medical literature. Among other things, such consideration involves the assessment of the following:

1. The prevalence and life history of the disease when evaluating the adequacy of the number of subjects and the response rate

2. 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)

3. Whether the clinical characteristics of the beneficiary and the indication are adequately represented in the published evidence

4. Whether the study is appropriate to address the clinical question, such as:

   a. 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 randomized, double-blind trial, placebos, or crossover)
   b. If non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs
   c. Generally, case reports are considered uncontrolled, are based on anecdotal information, and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.

5. 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	Gynecologic Oncology
American Journal of Psychiatry	International Journal of Radiation, Oncology, Biology and Physics
Annals of Internal Medicine	Journal of Clinical Oncology
Annals of Oncology	Journal of Obstetrics and Gynecology
Annals of Surgical Oncology	Journal of Pediatrics
Archives of Pediatric and Adolescent Medicine	Journal of the National Cancer Institute
Biology of Blood and Marrow Transplantation	Journal of the National Comprehensive Cancer Network (NCCN)
British Journal of Cancer	Journal of Urology
British Journal of Hematology	Lancet
British Journal of Medicine	Lancet Oncology
Cancer	Leukemia
Clinical Cancer Research	Pediatrics
Drugs	Radiation Oncology
European Journal of Cancer	The Journal of the American Medical Association

EXPERIMENTAL/INVESTIGATIONAL

Prescription drugs that are considered experimental/investigational are not covered because the safety and/or efficacy of the drug for those purposes cannot be established by a review of the available published peer reviewed literature. Prescription drugs and biologics are considered experimental/investigational for any of the following:

   a. The prescription drug or biologic has not received FDA approval for any indication
   b. The off-label use of the prescription drug or biologic does not meet the medical necessity criteria listed in this policy (i.e. the off-label use is not recognized by the appropriate compendia or published clinical research)
   c. The FDA determined the prescription drug or biologic to be contraindicated for specific condition(s) or specific off-labels use(s)
   d. The off-label use is not medically accepted or not indicated by a compendium for specific conditions (i.e. the indication is Category # in NCCN, Class III in Micromedex®) or when the narrative text in AHFS-DI® or Clinical Pharmacology® is not supportive

a. The absence of narrative text for an off-label use is considered neither supportive nor non-supportive

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 agency, 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 service.

Black Box Warning as shown in the drug Prescribing Information:

N/A

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

N/A

Applicable Drugs:

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

This policy applies to all drugs that have clinical management policies addressing them.

Cross References:

N/A

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P&T Approval Date:	June 09, 2022
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