# Off-Label/Unproven Specialty Drug Treatment (for Pennsylvania Only)

**Policy Number**: CSPA2026D0054A
**Effective Date**: November 1, 2026

➲ Instructions for Use

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| Related Policies |
| --- |
| None |

## Application

This Medical Benefit Drug Policy only applies to the state of Pennsylvania.

## Coverage Rationale

### Description

This policy provides parameters for coverage of off-label and unproven indications of U.S. Food and Drug Administration (FDA)–approved medications covered under the medical benefit for **one** of the following:

- Provider administered or supervised specialty drug or patient self-administered specialty drug covered under the medical benefit with a corresponding UnitedHealthcare policy that does not address the requested indication; **or**
- Provider administered or supervised specialty drug or patient self-administered specialty drug covered under the medical benefit with a corresponding UnitedHealthcare policy that lists the drug as unproven for the requested indication; **or**
- Provider administered or supervised specialty drug or patient self-administered specialty drug covered under the medical benefit without a UnitedHealthcare drug policy

This policy does **not** address coverage of:

- Self-administered medications covered under the pharmacy benefit. Refer to pharmacy benefit coverage
- Drugs managed by a State policy (such as a Statewide PDL drug)
- Oncology medications (including, but not limited to, octreotide acetate, leuprolide acetate, leucovorin, and levoleucovorin), including therapeutic radiopharmaceuticals, covered under the medical benefit based upon the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium® (NCCN Compendium®); refer to the Medical Benefit Drug Policy titled Oncology Medication Clinical Coverage (for Pennsylvania Only) for more information
- Vaccines

### Indications of Coverage

**A specialty drug may be determined medically necessary for the requested off-label or unproven indication when all of the criteria are met:**

- The drug is approved by the FDA; **and**
- The requested drug is a covered benefit by the member's state Medicaid agency; **and**
- **One** of the following:


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- The requested drug is considered 'unproven' per UnitedHealthcare drug policy, where applicable; **or**
- The indication for the requested drug is not addressed by a UnitedHealthcare drug policy, where applicable; **or**
- A UnitedHealthcare drug policy does not exist for the requested drug

**and**

- The requested drug is intended to treat a chronic and seriously debilitating, or Serious Rare Disease; **and**
- The patient has not failed a previous course or trial of the requested drug; **and**
- The patient is not currently in an eligible clinical trial; **and**
- Documented history of failure, contraindication, or intolerance to standard, conventional therapies to treat or manage the disease or condition, where available; **and**
- Diagnosis is **clinically supported** as a use by at least **one** of the following:
  - **One** of the following compendia:
    - The American Hospital Formulary Service Drug Information (AHFS-DI) under the Therapeutic Uses section; **or**
    - The Elsevier Gold Standard's Clinical Pharmacology under the Indications section; **or**
    - DRUGDEX System by Micromedex® has a Strength of Recommendation rating of Class I, Class IIa, or Class IIb under the Therapeutic Uses section

    **or**
  - Clinical indications supported by InterQual® Specialty Rx; **or**
  - **Two** (2) articles from major peer reviewed medical journals that present data supporting the proposed off-label use or uses as generally safe and effective unless there is validated, and uncontested contradictory evidence presented in a major peer-reviewed medical journal (examples of accepted journals include, but are not limited to, Journal of American Medical Association, New England Journal of Medicine, and Lancet; accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials)

# Definitions

**Serious Rare Disease**: A clinical condition or disease is considered:

- **Serious** if it is life threatening or accompanied by significant major disability or imminent threat of major disability, such as paralysis or limb amputation (modified from Kelley and Bollens-Lund, 2018 and Law Insider); and
- **Rare** if it affects fewer than 200,000 people in the United States at any given time (National Institutes of Health, 2020). Evidence from high quality clinical studies may not exist or is not likely to exist.

**Note**: A Serious Rare Disease is both Serious and Rare as defined in this policy.

# Background

An off label/unlabeled use of a drug is 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. An indication is defined as a diagnosis, illness, injury, syndrome, condition, or other clinical parameter for which a drug may be given. Off-label use is further defined as giving the drug in a way that deviates significantly from the labeled prescribing information for a particular indication.

# Clinical Evidence

In order to meet the requirement that the use of the drug is medically necessary for the treatment of disease, the drugs must be supported by evidence of safety and effectiveness for the intended use. Off-label drug prescribing may be determined medically necessary if scientific evidence and/or compendia support the regimen. A compendium is defined "as 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."

## American Hospital Formulary Service Drug Information (AHFS-DI)

AHFS-DI utilizes the following **levels of evidence rating system**:

- Level 1:
  - High Strength/Quality as defined by at least one of the following:
    - Evidence consists of at least one randomized, double-blind trial without important limitations (i.e., large treatment effect); intent-to-treat analysis used, confidence intervals reported. If more than one trial is available, these trials have consistent results.
    - Evidence consists of a meta-analysis of such trials with consistent results (i.e., low heterogeneity).


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    - Evidence consisting of a non-blinded or single-blinded trial that meets study objective end points may be considered as Level 1 evidence in some cancer-related cases (e.g., NCI-sponsored cooperative group study or a multicenter trial).
- Level 2:
    - Moderate Strength/Quality as defined by at least one of the following:
        - Evidence consists of at least one non-blinded or single-blinded, randomized clinical trial.
        - Evidence consists of at least one non-blinded or single-blinded, non-randomized clinical trial.
        - Evidence consists of a meta-analysis of randomized, controlled clinical trials with heterogeneous results if reasons for heterogeneity in individual trials are adequately discussed.
        - Evidence consists of at least one randomized, controlled clinical trial, but with important methodological limitations (e.g., large number of patients lost to follow-up and/or no intent-to-treat analysis and/or important data not recorded).
        - Evidence is inconsistent (i.e., two or more randomized controlled trials with unexplained, widely varying estimates of treatment effects, even if results of individual trials would constitute strong Level 1 evidence when considered alone).
    - Evidence consisting of a non-blinded, non-randomized trial (i.e., a phase II study) may be considered as Level 2 evidence in some cancer-related cases (i.e., rare cancers or cancers with limited available treatment options).
- Level 3:
    - Low Strength/Quality is defined as:
        - Evidence consists of observational studies, case reports, or case series; may also include randomized clinical trials with multiple serious deficiencies or study limitations.
- Level 4:
    - Opinion/Experience is defined as:
        - Evidence consists of expert consensus panel reports or expert reviewers' comments.

AHFS-DI utilizes the following **grades of recommendation**:
- Recommended (Accepted):
    - The drug or biologic should be used, is recommended/indicated, or is useful/effective/beneficial in most cases.
- Reasonable Choice (Accepted, With Possible Conditions) (e.g., treatment option):
    - The drug or biologic is reasonable to use under certain conditions (e.g., in certain patient groups), can be useful/effective/beneficial, or is probably recommended or indicated.
- Not Fully Established (Unclear Risk/Benefit, Equivocal Evidence, Inadequate Data and/or Experience):
    - Usefulness and/or effectiveness is unknown, unclear, or uncertain, or is not well established relative to the standard of care.
- Not Recommended (Unaccepted):
    - The drug or biologic is considered inappropriate, obsolete, or unproven; is not recommended, is not indicated, or is not useful/effective/beneficial; or may be harmful.

## Clinical Pharmacology

Off-label drug indication data are included within clinical pharmacology when identified as a clinically relevant or as an emerging treatment that are adequately supported by a systematic review of the evidence. Off-label data are primarily identified for inclusion in the database through a regular and comprehensive review of:
- Primary published literature
- New or updated national practice guidelines
- Surveillance of other accepted sources of medical information (e.g., FDA, CDC, NIH communications)
- Dialogue with customers or other external reviewers of the compendia content

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system is used to evaluate and rate the quality of evidence to determine qualities of evidence levels and recommendations as follows:

| Grade of Recommendation | Clarity of Risk/Benefit | Quality of Supporting Evidence | Implications |
|---|---|---|---|
| 1A. Strong recommendation; High quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. | Strong recommendation, can apply to most patients in most circumstances without reservation |


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| Grade of Recommendation | Clarity of Risk/Benefit | Quality of Supporting Evidence | Implications |
|---|---|---|---|
| 1B. Strong recommendation; Moderate quality evidence | Benefits clearly outweigh risk and burdens, or vice versa | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. | Strong recommendation, likely to apply to most patients |
| 1C. Strong recommendation; Low quality evidence | Benefits appear to outweigh risk and burdens, or vice versa | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain. | Relatively strong recommendation; might change when higher quality evidence becomes available |
| 2A. Weak recommendation; High quality evidence | Benefits closely balanced with risks and burdens | Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. | Weak recommendation, best action may differ depending on circumstances or patients or societal values |
| 2B. Weak recommendation; Moderate quality evidence | Benefits closely balanced with risks and burdens, some uncertainty in the estimates of benefits, risks, and burdens | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise), or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. | Weak recommendation, alternative approaches likely to be better for some patients under some circumstances |
| 2C. Weak recommendation; Low quality evidence | Uncertainty in the estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens | Evidence from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain. | Very weak recommendation; other alternatives may be equally reasonable |

## DRUGDEX (Micromedex)

The DRUGDEX (Micromedex) efficacy, strength of evidence, and strength of recommendation definitions are outlined below:

| DRUGDEX (Micromedex): Strength of Recommendation, Strength of Evidence and Efficacy | | |
|---|---|---|
| **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. |
| **Strength of Recommendation** | | |
| Class Indeterminate | Evidence Inconclusive | |


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| DRUGDEX (Micromedex): Strength of Recommendation, Strength of Evidence and Efficacy | | |
|---|---|---|
| **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. | |
| No evidence | | |
| **Efficacy** | | |
| Class I | Effective | Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective. |
| Class IIa | Evidence Favors Efficacy | Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy. |
| Class IIb | Evidence is Inconclusive | Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy. |
| Class III | Ineffective | Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective. |

## InterQual® Specialty Rx

The InterQual clinical content development is generally consistent with:

- AHRQ Methods Guides, the Cochrane Handbook, and the NICE guideline development manual for literature searching, critical appraisal, and combining results of studies.
- GRADE methodology for compiling evidence and determining recommendations.

**Evidence classification and quality of evidence definitions are outlined below**:

| Classification | Type of Evidence |
|---|---|
| Class I | Meta-analysis, technology assessment, or systematic review |
| Class II | Randomized controlled clinical trial |
| Class III | Observational or epidemiologic study |
| Class IV | Evidence-based guideline |
| Class V | Expert opinion, panel consensus, literature review, text or reference book, descriptive study, case report, or case series |
| High | Additional research is considered very unlikely to change our confidence in the estimate of effect |
| Medium | Further research is likely to have an important impact on the estimate of effect |
| Low | Further research is very likely to change the estimate of effect |
| Very Low | Our estimate of effect is very uncertain |

# References


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# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 11/01/2026 | **Template Update**<br>• Created state-specific policy version<br>**Coverage Rationale**<br>• Added language to indicate this policy does not address coverage of drugs managed by a state policy (such as a Statewide PDL drug)<br>**Supporting Information**<br>• Archived previous policy version CS2026D0054R |

# Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.


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