Off-Label/Unproven Specialty Drug Treatment

Policy Number: 2025D0054M
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➲ Instructions for Use

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Community Plan Policy

- Off-Label/Unproven Specialty Drug Treatment

Coverage Rationale

➲ See Benefit Considerations

Description

This policy provides parameters for coverage of off-label and unproven indications of 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
  - Review under this section requires Drug Policy Interpretation Service (DPIS) research. DPIS staff will:
    - Review clinical evidence to support clinical coverage issues that are not addressed in drug policy
    - Research and summarize the evidence that will focus on the efficacy of the proposed drug for a specific diagnosis based on the best available clinical evidence that is published in the peer-reviewed medical literature and/or compendia
    - Summarize the findings to assist the Medical Director in a coverage decision
- 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
  - Review under this section requires notification to the health plan and approval of a benefit exception for what would otherwise be considered unproven services.
- Provider administered or supervised specialty drug or patient self-administered specialty drug covered under the medical benefit without a UnitedHealthcare drug policy
  - Review under this section requires DPIS research. DPIS staff will:
    - Review clinical evidence to support clinical coverage issues that are not addressed in drug policy
    - Research and summarize the evidence that will focus on the efficacy of the proposed drug for a specific diagnosis based on the best available clinical evidence that is published in the peer-reviewed medical literature and/or compendia
    - Summarize the findings to assist the Medical Director in a coverage decision

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

- Self-administered medications covered under the pharmacy benefit; refer to pharmacy benefit coverage.
- 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 more information.

- Vaccines; refer to the Medical Benefit Drug Policy titled Preventive Vaccines (Immunizations) and the Medical Policy titled Preventative Care Services for additional information on vaccines covered as preventive services.

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 U.S. Food and Drug Administration; **and**
- The requested drug has not been excluded from coverage by UnitedHealthcare due to lack of efficacy, clinical benefit, or administrative program (e.g., exclusion at launch, plan document); **and**
- **One** of the following:
  - The requested drug is considered "unproven" per UnitedHealthcare drug policy, where applicable
  - The indication for the requested drug is not addressed by a UnitedHealthcare drug policy, where applicable
  - 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;[1] **or**
    - The Elsevier Gold Standard's Clinical Pharmacology under the Indications section;[2] **or**
    - DRUGDEX System by Micromedex® has a Strength of Recommendation rating of Class I, Class IIa, or Class IIb under the Therapeutic Uses section[3]

    or
  - Clinical indications supported by InterQual® Specialty Rx;[8] **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: This policy is to be used for a proposed treatment for a clinical condition or disease that 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.

Benefit Considerations

If the coverage review using the NCCN Compendium determines that the drug is unproven, then further review is indicated. Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to

make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Some states also mandate usage of other Compendium references. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

In order to meet the requirement that the use of the drug is medically necessary for the treatment of disease, the drug must be safe and effective relative to other available treatments. 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)."[4]

American Hospital Formulary Service Drug Information (AHFS-DI)

AHFS-DI utilizes the following levels of evidence rating system:[1]

- 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).
  - 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 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:[2]

- 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:[6-7]

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
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 uncertainly 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:[3]

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.
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.	
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

Classification	Type of Evidence
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
09/01/2025	• Corrected formatting error in *References* section

08/01/2025	**Coverage Rationale**
	Description
	• Added review requirements for provider administered or supervised specialty drugs or patient self-administered specialty drugs covered under the medical benefit to indicate:
	  ○ When there is a corresponding UnitedHealthcare drug policy that does not address the requested indication or when there is not a UnitedHealthcare drug policy, review requires Drug Policy Interpretation Service (DPIS) research; DPIS staff will:
	  ▪ Review clinical evidence to support clinical coverage issues that are not addressed in drug policy
	  ▪ Research and summarize the evidence that will focus on the efficacy of the proposed drug for a specific diagnosis based on the best available clinical evidence that is published in the peer-reviewed medical literature and/or compendia
	  ▪ Summarize the findings to assist the Medical Director in a coverage decision
	  ○ When there is a corresponding UnitedHealthcare policy that lists the drug as unproven for the requested indication, review requires notification to the health plan and approval of a benefit exception for what would otherwise be considered unproven services
	Indications of Coverage
	• Replaced language indicating “a specialty drug may be determined medically necessary for the requested off-label or unproven indication when the patient *has not been in or* is not currently in

Date	Summary of Changes
	an eligible clinical trial" with "a specialty drug may be determined medically necessary for the requested off-label or unproven indication when the patient is not currently in an eligible clinical trial" • Removed notation indicating evidence limited to case studies or case series is not sufficient to meet the standard of this criterion (for peer-reviewed articles presented in a major peer-reviewed medical journal) **Definitions** • Updated definition of "Serious Rare Disease" **Supporting Information** • Updated *References* section to reflect the most current information • Archived previous policy version 2024D0054L

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. 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.