Medical Drug Clinical Criteria

Subject:	Off-Label Drug and Approved Orphan Drug Use		
Document #:	CC-0141	**Publish Date:**	07/24/2023
Status:	Reviewed	**Last Review Date:**	06/12/2023

Table of Contents

Overview

The U.S. Food and Drug Administration (FDA) approves drugs for specific use(s) that are listed in the drug's product information label. Off-label or "unlabeled" drug use is the utilization of an FDA-approved drug for uses other than those listed in the FDA-approved labeling or in treatment regimens or populations that are not included in approved labeling. Many off-label uses are effective, well documented in the peer-reviewed literature and widely used.

American Hospital Formulary Service Drug Information (AHFS, Bethesda, MD) uses the “dagger” symbol to indicate off-label drug use. If the AHFS indicates an off-label use, but qualifies that statement with “but additional study is needed” or “further study is needed to evaluate safety and efficacy,” the qualifying language does not support an off-label indication as approvable.

DrugDex® (Truven Health Analytics, Greenwood Village, CO) is a comprehensive drug information source which includes all FDA approved indications and all off-label indications. For purposes of this document, indications listed in DrugDex are approvable when the Strength of Recommendation is Class I or IIa **and** Strength of Evidence is Category A or B **and** Efficacy is Class I or IIa.

The Truven Health Analytics Efficacy, Strength of Evidence and Strength of Recommendation definitions are outlined below:

Table 1. 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	

Table 2. 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	

Table 3. 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.

The National Comprehensive Cancer Network (NCCN) Drug & Biologics Compendium is a listing of appropriate uses of agents as defined in and derived from the NCCN Clinical Guidelines in Oncology®. The compendium lists both FDA-approved uses and NCCN designated off-label indications. According to the NCCN, the identified off-label indications are based upon evaluation of evidence from scientific literature integrated with expert judgment in an evidence-based process. Indications are categorized in a systematic approach that describes the type of evidence available for and the degree of consensus underlying each recommendation. For purposes of this document, any indication listed in the NCCN Drug & Biologics Compendium with a Category of Evidence and Consensus 1 or 2A is considered approvable.

Definitions for NCCN Categories
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

The Company takes into account credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community. “Peer-reviewed medical literature” does not include publications or supplements to publications that are sponsored to a significant extent by a pharmaceutical manufacturing company or health carrier.

An "orphan drug" is a product that treats a rare disease (e.g., affecting fewer than 200,000 Americans or affecting more than 200,000 Americans with no reasonable expectation that the cost of drug development will be recovered from sales of the drug in the U.S.). The safety and efficacy of the drug must be established through clinical studies. If the designated product meets the standard FDA regulatory requirements and process for obtaining marketing approval, it is given an FDA approved orphan drug designation status (for example, “Designated/Approved”).

Note: These criteria apply to drugs which fall under the medical benefit. It does not apply to those medications falling under the pharmacy benefit, which include, but are not limited to oral agents.

- **Any entity’s clinical criteria document on a specific drug takes precedence over this guideline.**
- Please check appropriate state mandates for laws that will supersede this document when applicable, such as those governing off-label use of prescription drugs.
- Verify benefits and benefit exclusions. Excluded products or treatments are not covered under this document (e.g., agents for impotency or weight loss).
- This document shall not be construed to require coverage for any drug when the FDA has determined its use to be contraindicated.
- The document shall not be construed to require coverage for any drug when the benefit plan excludes drug coverage.
- The document shall not be construed to require coverage for any drug when the benefit plan includes drug benefit limitations based on a formulary and the off-label drug is not part of the formulary.

Clinical Criteria

Off-Label Drug Use

In the absence of an applicable clinical criteria document, requests for off-label drug use may be approved if the following criteria are met:

I. The drug is approved by the U.S. Food and Drug Administration (FDA); **AND**
II. The drug is being prescribed to treat a medical condition not listed in the product label and for which medical treatment is approvable; **AND**
III. The prescribed drug use is supported in any **one** or more of the following:
    A. American Hospital Formulary Service Drug Information (AHFS); **OR**
    B. Truven Health Analytics Inc., DrugDex meeting each of the following:
        1. Strength of Recommendation Class I or IIa; **AND**
        2. Strength of Evidence Category A or B; **AND**
        3. Efficacy Class I or IIa;

    OR
    C. National Comprehensive Cancer Network (NCCN) Drug & Biologics Compendium Category of Evidence and Consensus 1 or 2A; **OR**

D. Two articles from major scientific or medical peer-reviewed journals (excluding case reports, letters, posters, and abstracts), or published studies having validated and uncontested data, which support the proposed use for the specific medical condition as safe and effective:
    1. Examples of accepted journals include, but are not limited to, *Journal of American Medical Association, New England Journal of Medicine,* and *Lancet;*
    2. Accepted study designs include, but are not limited to, randomized, double blind, placebo controlled clinical trials.

In the absence of an applicable clinical criteria document, off-label drug use may not be approved when the above criteria are not met.

Orphan Drug Use

Use of an FDA designated orphan drug is not approvable when FDA has not approved the drug for marketing.

Use of an approved drug for a designated orphan use before the FDA has approved this use for marketing* is considered “off-label” and is subject to the criteria above.

**Once the orphan drug use has been approved for marketing, the FDA considers the drug “Designated/Approved”.*

Document History

Reviewed: 06/12/2023
Document History:

- 06/12/2023 – Annual Review: No changes.
- 06/13/2022 – Annual Review: No changes.
- 06/14/2021 – Annual Review: No changes.
- 08/21/2020 – Select Review: Wording and formatting updates for clarity; update orphan drug use language.
- 06/08/2020 – Annual Review: Update DrugDex as drug information source name.
- 05/17/2019 – Annual Review: Wording and formatting changes.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
4. NCCN Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.