



## **AETNA BETTER HEALTH®**

### **Off-Label Use of FDA-Approved Drugs Policy**

#### **Policy Statement:**

The Plan determines whether certain services or supplies are medically necessary. The Plan established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer-reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). The Plan expressly reserves the right to revise these conclusions as clinical information changes, and welcomes further relevant information. Each benefit program defines which services are covered. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered and/or paid for by the Plan, as some programs exclude coverage for services or supplies that the Plan considers medically necessary. If there is a discrepancy between this policy and a member's benefits program, the benefits program will govern. In addition, coverage may be mandated by applicable legal requirements of a state, the Federal Government or the Centers for Medicare & Medicaid.

#### **Definitions:**

**Indication:** An indication is defined as a diagnosis, illness, injury, syndrome, condition or other clinical parameter for which a drug may be given.

**FDA approval:** Approval for marketing by the Food and Drug Administration (FDA) of drugs that are considered safe and effective.

**FDA-approved indication:** An indication depicted on the drug's official label with prescribing instructions, which includes, but is not necessarily limited to, dosage, route of administration, duration and frequency of administration and population to whom the drug would be administered.

**Standard Drug Reference Compendia:** the following are the compendia accepted and used by Aetna.

- American Hospital Formulary Service-Drug Information (AHFS-DI);
- NCCN Drugs and Biologics Compendium (Oncology);
- Thomson Micromedex DrugDex; and
- Clinical Pharmacology.

**Off-label (also referred to as unlabeled or non-FDA-approved) usage:** Drug usage for an indication that is not listed on the drug's official label; further defined as administration of the drug in a way that deviates significantly from the prescribing information on the official label for a particular indication. This includes, but is not necessarily limited to,

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dosage, route of administration, duration and frequency of administration and population to whom the drug would be administered.

**Guideline:**

Providers may request coverage of off-label usage well in advance to allow time for review, research, &/or decision. Supportive data and clinical documentation substantiating the request must be submitted to the Plan.

The broad range of available evidence must be considered and its quality must be evaluated before a conclusion is reached. After such evidence is received, the Plan will, with guidance of appropriate health care professions, as indicated, make a coverage determination for the off-label use of the drug or biological. The Plan may determine usage to be reasonable and necessary for the treatment of illness or injury if, on the basis of available or presented evidence, it is shown to be safe and effective and does not violate state or federal regulations. The approval will include, but is not limited to, diagnosis, dosage, route of administration, duration and frequency of administration and appropriate patient population.

The determination of coverage for an off-label use of a medication (alone or as part of a larger regimen) may apply to any of the following:

- A single case as exception to current coverage policies, because of case specific circumstances or consideration

OR

- In the absence of a coverage policy currently addressing the drug or the requested use of the drug.

**Criteria for Coverage of Off-label use of FDA approved medication.**

**The Plan may consider coverage for an off-label usage, when the following criteria for the request are met.**

1. The unlabeled use of the drug appears in at least one of the standard drug reference compendia as safe and effective for the situation/use currently being requested. (Appendix A)

OR

2. The use is an accepted standard of medical practice. For example, "Are there non-conflicting published recommendations from specialty societies or in other authoritative evidence-based guidelines" (e.g., a state-of-the-art review article published in a recognized textbook or a reputable publication).

*Note: Acceptance by individual health care practitioners, or even a limited group of health care practitioners, does not typically indicate general acceptance by the medical community.*

*Testimonials indicating such limited acceptance and limited case studies, distributed by sponsors with potential financial conflict of interest in the outcome, are not sufficient evidence of general acceptance by the medical community*

OR

**3.** The FDA has not previously reviewed this use for the requested medication or a review was completed and there was insufficient data to approve the drug for this use and no new determination from the FDA is anticipated.

**THEN**

Supportive data substantiating usage must be submitted to the Plan; the data must include:

**a.** A use supported by clinical research that appears in at least 2 Phase III clinical trials that definitively demonstrate safety and effectiveness.

**OR**

**b.** If no Phase III trial evidence is available, at least 2 Phase II clinical trials with reasonably large patient samples showing consistent results of safety and efficacy. This data may be considered in certain instances (i.e., orphan drugs, in rare disease cases 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).

The Phase III or Phase II trials must come from different centers and be published in national or international peer-reviewed journals (with editorial committees comprised of physicians).

*Note: Peer-reviewed medical literature includes scientific and medical publications. It does not include in-house publications of pharmaceutical manufacturing companies or abstracts (including meeting abstracts).*

**4.** Individual patient medical records will be required to determine if the requested off-label use is reasonable and necessary for treatment of a patient's illness or injury, in this case. Regardless of the evidence supporting coverage and the determination of the Plan regarding the general off-label use of a drug, these records must be available to the Plan upon request.

**Limitations**

An approval of coverage for an off-label use may be conditional.

Those conditions may include any or all of the following:

- Use of a formulary alternative(s) that treat the same condition, unless contraindicated, and is either:
  - o Approved for the requested use/indication
  - o Is recommended or accepted by treatment guidelines listed in any compendia, or considered standard of care, as a treatment option of equal or greater efficacy compared to the requested drug/regimen.
  - o Use of an accepted non-pharmacologic interventions of equal or greater efficacy
- Quantity limits
- Have an initial approval period limited to the time needed to evaluate and establish clinical benefit. This time period is dependent on the drug/regimen being requested and the condition being treated.
  - o Continued coverage requires documentation of clinical benefit.

**Exclusions**

Off-label drugs are not covered when the following circumstances are applicable:

1. Coverage will not be provided for off-label usage, unless as outlined in the criteria above.
2. The Plan reserves the right to make the “determination”.
3. If the use, regardless of medical necessity, is specifically excluded from coverage in the Medical Assistance Program.
4. If the drug is not a medication approved for sale and use in the U.S. in humans by the FDA then coverage will not be provided.
5. If a use is identified as not indicated by CMS (in the case of Medicare members) or the FDA, or if a use is specifically identified as not indicated in at least one of the major compendia, or it is determined (based on peer-reviewed literature) that the drug is not safe and effective, then the off-label usage is not supported and therefore not covered.

#### **Appendix A:**

##### **1. NCCN evidence grading (12/2016) [www.nccn.org](http://www.nccn.org)**

- 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.

##### **2. AHFS Levels of Evidence Rating System**

([http://www.ahfsdruginformation.com/off\\_label/levels.aspx](http://www.ahfsdruginformation.com/off_label/levels.aspx))

#### **EVIDENCE LEVEL**

##### **Level 1: High strength/ Quality**

- 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 one more than one trial is available, these trials have consistent results  
Or
- A meta-analysis of such trials with consistent results (i.e., low heterogeneity)  
Or
- Evidence consisting of a non-blinded or single-blinded trial that meets study objective endpoints may be considered as Level 1 evidence in some cancer-related cases (i.e. sponsored cooperative group study or a multi-center trial)

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## **Level 2: Moderate Strength/Quality**

- Evidence consists of at least one non-blinded or single-blinded, randomized clinical trial  
Or
- Evidence consists of at least one non-blinded or single-blinded, non-randomized clinical trial  
Or
- A meta-analysis of randomized, controlled clinical trials with heterogeneous results if reasons for heterogeneity in individual trials are adequately discussed  
Or
- Evidence consists of at least one randomized, controlled clinical trial, but with methodological limitations (e.g. large number of patients lost to follow-up and no intent-to-treat analysis and/or important data not recorded)  
Or
- 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 a strong Level 1 evidence when considered alone)  
Or
- Evidence consisting of a non-blinded, non-randomized trial (e.g., a phase II study) may be considered as Level 2 in some cancer-related cases (e.g., rare cancers or cancers with limited available treatment options)

## **Level 3: Low Strength/Quality**

- 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**

- Expert consensus panel reports or expert reviewer's comments

## **GRADES OF RECOMMENDATION**

### **A- Recommended - Accepted**

(e.g., should be used, is recommended, is useful/effective/beneficial in most cases)

### **B- Reasonable Choice (Accepted, with Possible Conditions) (e.g., option)**

(e.g., is reasonable to use in certain subgroups or clinical scenarios)

### **C- Not Fully Established (Unclear risk/benefit, equivocal evidence, inadequate data and/or experience)**

(e.g., usefulness/effectiveness unknown/unclear/uncertain or not well established relative to standard of care)

### **D- Not Recommended (Unaccepted)**

(e.g., considered inappropriate, obsolete, or unproven)

**3. Micromedex Recommendation, Evidence and Efficacy Ratings (Drugdex® Consults at [www.micromedex.com](http://www.micromedex.com))**

Strength Of <b>Recommendation</b>		
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 <b>Evidence</b>	
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	

<b>Efficacy</b>		
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.