09-J0000-68

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Reviewed: 05/14/25

Revised: 06/15/25

Subject: Drugs and Biologics without a Medical Coverage Guideline (Orphan Drugs and Off-Label and Labeled Use of FDA Approved Drugs)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

The sale and use of drugs are regulated in almost all countries by governmental agencies. In the United States, the Food and Drug Administration (FDA) oversees the drug evaluation process and grants approval for marketing of new drug products. Drug companies seeking FDA approval to sell a drug in the United States must evaluate the drug in various ways. This will include laboratory and animal tests, and finally, test in humans to determine if the drug is safe and effective when used to treat or diagnose a disease.

After testing the drug, the company then sends the FDA an application called a New Drug Application (NDA), or for new biologic drugs, a Biologics License Application (BLA). Whether an NDA or a BLA, the application includes

- Drug's test results
- Manufacturing information to demonstrate the company can properly manufacture the drug
- Proposed label for the drug

The label provides necessary information about the drug, including uses for which it has been shown to be effective, possible risks, and how to use it. If a review by FDA physicians and scientists shows the drug's benefits outweigh its known risks and the drug can be manufactured in a way that ensures a quality product, the drug is approved and can be marketed in the United States.

When a drug is used for an indication other than those specified in the labeling, it is referred to as an off-label (or "unlabeled") use. Many off-label uses are effective, well documented in the literature, and widely used.

Unapproved or unlabeled uses of drugs include a variety of situations ranging from completely unstudied to thoroughly investigated drug uses where the FDA has not been asked for approval.

Orphan drug designation is a special status granted under the provisions of the Orphan Drug Act of the U.S. Food and Drug Administration (FDA) based on specific criteria. The Orphan Drug Designation program provides orphan status to drugs and biologicals that are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the United States, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug. Orphan drug designations can be found at http://www.fda.gov/orphan/designat/list.htm.

This medical coverage guideline (MCG) applies **ONLY** to agents that **DO NOT** have an existing MCG developed by Florida Blue or a relevant Prime Therapeutics criteria document. For agents with an existing Florida Blue MCG or relevant Prime Therapeutics criteria document, refer to that MCG/document for medical necessity criteria. Additionally, Table 1 lists specific drugs and biologics that should be reviewed using this MCG. This list is not comprehensive.

POSITION STATEMENT:

A drug or biologic product **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Requested product has been approved by the United States Food and Drug Administration (FDA)
2. One of the following is met:
    a. Requested product is not included in an existing medical coverage guideline developed by Florida Blue (or relevant Prime Therapeutics criteria document)
    b. Requested product is listed in Table 1
3. One of the following is met:
    a. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
    b. Requested product is designated as an orphan drug by the FDA for the requested indication (i.e., "Designated/Approved", "Designated") (Orphan drug designations can be found at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/)
    c. Requested product meets **ONE** of the following:
        i. Oncology medications (including interferons for oncology use): Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

ii. All others: Indication **AND** usage is recognized in one or more of the standard reference compendium listed in Table 2

d. Indication **AND** usage of requested product is supported by the results of **TWO or more** published clinical studies – prescriber must submit full text copies of each article

NOTE:

- Case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support for use.
- Clinical studies must be supportive of use for a similar patient population (e.g., indication, diagnosis, disease severity, genetic or tumor mutations) and for the intended treatment plan, including any concomitant therapy.

4. Xiaflex only:
    a. Documentation from the medical record of member's diagnosis and indication for use must be provided
5. Dose does not exceed maximum FDA-approved dose and frequency with the following exceptions:
    a. Dose and frequency for indication are supported by standard reference compendium listed in Table 2
    b. Dose and frequency for indication are supported by the results of **TWO** or more published clinical studies – prescriber must submit full text copies of each article

    NOTE: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use
6. Dose and/or dispensed quantity does not exceed the following product-specific limits:
    a. iDose TR: 1 implant per eye per lifetime
    b. Sinuva: 1 implant (1350 mcg) per nostril per lifetime
    c. Zilretta: 1 intra-articular injection (32 mg) per knee per lifetime
    d. Targretin (bexarotene) gel: 4 g per day (two 60 g tubes/month)
    e. Xiaflex:
        i. Dupuytren's contractures: 0.58 mg per dose injected into a palpable cord
        ii. Peyronie's disease: 0.58 mg per dose injected into penile plaque with a maximum of 2 injection procedures per cycle and a maximum of 8 injections per treatment course (4 treatment cycles = 1 treatment course)

Approval duration: 6 months; 1 year (Pluvicto only)

Coverage for an off-label use of the prescribed drug or biologic product **does not meet the definition of medical necessity** when any of the following apply:

1. The FDA determines the drug or biological to be contraindicated for the specific requested condition(s).
2. The drug has not received FDA approval for any indication.

3. The compendia list the drug as "not indicated" or “not recommended”.
4. The requested off-label use is not supported by adequate clinical research as determined by Florida Blue,
5. The drug is not recognized as described above in at least one of the identified compendium.

For Medicare Part B and Medicare Advantage members, the reviewer shall refer to National and Local Coverage Determinations. National and Local Coverage Determinations can be found at: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx.

Table 1

Drugs and biologics that must meet medical necessity criteria. **(NOTE: This is NOT a comprehensive list of all agents that should be reviewed)**
Brand (generic) Product
Actimmune (interferon gamma-1b) injection
Adstiladrin (Nadofaragene Firadenovec-vncg) intravesical instillation
Aldurazyme (laronidase) IV infusion
Alferon N (interferon alfa-n3) injection
Aliqopa (copanlisib) injection
Anktiva (Nogapendekin Alfa Inbakicept) intravesical instillation
Aphexda (Motixafortide) SQ injection
Apokyn (apomorphine) injection
Arzerra (ofatumumab) injection
Asparlas (Calaspargase Pegol-mknl) IV infusion
Azedra (Iobenguane I-131) IV injection and infusion
Bavencio (avelumab) injection
Besponsa (inotuzumab ozogamicin) injection
Bizengri (Zenocutuzumab) IV infusion
Brineura (cerliponase Alfa) intraventricular infusion
Chenodal (chenodial) tablet
Cuprimine (penicillamine) capsule
Cuvrior (trientine tetrahydrochloride) tablet
Defitelio (defibrotide sodium) injection
Depen (penicillamine) tablet
Egaten (triclabendazole) tablet
Elahere (Mirvetuximab Soravtansine-gynx) IV infusion
Elaprase (idursulfase) injection
Elzonris (Tagraxofusp) IV infusion
Endari (L-glutamine) oral powder
Erwinaze (Asparaginase Erwinia chrysanthemi) injection
Fintepla (fenfluramine) oral solution
Fyarro (sirolimus albumin-bound nanoparticles) IV infusion
Hepzato (melphalan) kit
Korsuva (difelikefalin acetate) IV infusion

iDose TR (travoporost) intracameral implant
Imdelltra (Tarlatamab) IV infusion
Imfinzi (durvalumab) IV infusion
Imjudo (Tremelimumab-actl) IV infusion
Imlygic (talimogene laherparepvec) injection
Impavido (miltefosine) capsule
Inbrija (levodopa) inhalation capsule
Infugem (gemcitabine) IV infusion
Intron A (interferon alfa-2b) injection
Istodax (romidepsin) powder for injection
Jelmyto (mitomycin) intravesical gel
Kanuma (sebelipase alfa) injection
Libtayo (Cemiplimab-rwlc) IV infusion
Loqtorzi (Toripalimab-tpzi) IV infusion
Lumoxiti (Moxetumomab Pasudotox-Tdfk) IV infusion
Lunsumio (Mosunetuzumab-axgb) IV infusion
Lutathera (Lutetium Dotatate Lu-177) IV infusion
Macrilen (macimorelin) for oral solution
Mepsevii (vestronidase alfa-vjbk) injection
Metastron (Strontium 89 Chloride) IV injection
Mylotarg (gemtuzumab ozogamicin) injection
Naglazyme (galsulfase) injection
Nourianz (istradefylline) tablet
Omisirge (omidubicel-onlv) kit
Onapgo (apomorphine) SQ infusion
Pedmark (sodium thiosulfate) IV infusion
Pegasys (peginterferon alfa-2a) injection
PegIntron (peginterferon alfa-2b) injection
Photrexa (riboflavin 5’-phosphate ophthalmic solution) 0.146% for topical ophthalmic use
Photrexa Viscous (riboflavin 5’-phosphate in 20% dextran ophthalmic solution) 0.146% for topical ophthalmic use
Pluvicto (lutetium Lu 177 vipivotide tetraxetan) IV injection
Quadramet (Samarium 153 Lexidronam) IV injection
Quzyttir (cetirizine hydrochloride) injection for IV infusion
Rebyota (Fecal Microbiota, Live-jslm) rectal suspension
RegeneCyte (HPC, Cord Blood) IV infusion
Romidepsin solution for injection
Rylaze (Asparaginase Erwinia chrysanthemi (recombinant)-rywn)
Rytelo (Imetelstat) IV infusion
Sinuva (mometasone furoate) sinus implant
Syprine (trientine) capsule
Targretin (bexarotene) gel
Tecentriq (Atezolizumab) injection

Tecentriq Hybreza (atezolizumab and hyaluronidase-tqjs) SQ injection
Tevimbra (tislelizumab-jsgr) IV infusion
Tivdak (tisotumab-tftv) IV infusion
Unloxcyt (Cosibelimab) IV infusion
Vistogard (uridine triacetate) oral granules
Vowst (fecal microbiota spores, live-brpk) capsule
Vyloy (Zolbetuximab) IV infusion
Vyxeos (daunorubicin; cytarabine) liposome injection
Xermelo (telotristat ethyl) tablet
Xiaflex (collagenase clostridium histolyticum) injection
Xipere (triamcinolone) suprachoroidal/intraocular injectable suspension
Xuriden (uridine triacetate) oral granules
Yondelis (trabectedin) injection
Zepzelca (lurbinectedin) IV infusion
Zevalin (ibritumomab tiuxetan) injection
Ziihera (Zanidatamab) IV infusion
Zilretta (triamcinolone) intra-articular injection
Zynyz (retifanlimab-dlwr) injection

Table 2

Designated compendia	
Compendium	**Covered Uses †**
AHFS-DI	Narrative text is supportive
NCCN Drugs and Biologics Compendium	Category Levels 1 and 2A
Thomson Micromedex DrugDex	Meets requirements for BOTH of the following: • Strength of recommendation: Class I (Recommended) or IIa (Recommended, In Most Cases) • Efficacy: Class I (Effective) or IIa (Evidence Favors Efficacy)
Clinical Pharmacology	Narrative text is supportive
† If covered use criteria are not met, the request should be denied. AHFS-DI, American Hospital Formulary Service Drug Information; NCCN, National Comprehensive Cancer Network. For additional information regarding designated compendia, please refer to the “Definitions” section.	

BILLING/CODING INFORMATION:

FDA-approved drugs may be reported using the appropriate alphanumeric HCPCS Level II code.

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Off-label/unlabeled use: use of a drug for an indication other than those stated in the FDA-approved labeling.

Table 3

Thomson Micromedex DrugDex Recommendation Ratings: 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 4

Thomson Micromedex DrugDex Recommendation Ratings: 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

Table 5

NCCN Categories of Evidence Consensus	
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 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

RELATED GUIDELINES:

None

OTHER:

2016 Florida Statutes:

Title XXXVII	**Chapter 627**	**SECTION 4239**
INSURANCE	**INSURANCE RATES AND CONTRACTS**	**Coverage for use of drugs in treatment of cancer.**

627.4239 Coverage for use of drugs in treatment of cancer.—

(1) DEFINITIONS.—As used in this section, the term:

(a) "Medical literature" means scientific studies published in a United States peer-reviewed national professional journal.

[1](b) "Standard reference compendium" means authoritative compendia identified by the Secretary of the United States Department of Health and Human Services and recognized by the federal Centers for Medicare and Medicaid Services.

(2) COVERAGE FOR TREATMENT OF CANCER.—

(a) An insurer may not exclude coverage in any individual or group insurance policy issued, amended, delivered, or renewed in this state which covers the treatment of cancer for any drug prescribed for the treatment of cancer on the ground that the drug is not approved by the United States Food and Drug Administration for a particular indication, if that drug is recognized for treatment of that indication in a standard reference compendium or recommended in the medical literature.

(b) Coverage for a drug required by this section also includes the medically necessary services associated with the administration of the drug.

(3) APPLICABILITY AND SCOPE.—This section may not be construed to:

(a) Alter any other law with regard to provisions limiting coverage for drugs that are not approved by the United States Food and Drug Administration.
(b) Require coverage for any drug if the United States Food and Drug Administration has determined that the use of the drug is contraindicated.
(c) Require coverage for a drug that is not otherwise approved for any indication by the United States Food and Drug Administration.
(d) Affect the determination as to whether particular levels, dosages, or usage of a medication associated with bone marrow transplant procedures are covered under an individual or group health insurance policy or health maintenance organization contract.
(e) Apply to specified disease or supplemental policies.
(4) Nothing in this section is intended, expressly or by implication, to create, impair, alter, limit, modify, enlarge, abrogate, prohibit, or withdraw any authority to provide reimbursement for drugs used in the treatment of any other disease or condition.
History.—s. 1, ch. 95-268; s. 1, ch. 2009-202; s. 72, ch. 2009-223.
[1]Note.—As amended by s. 72, ch. 2009-223. For a description of multiple acts in the same session affecting a statutory provision, see preface to the Florida Statutes, "Statutory Construction." Paragraph (1)(b) was also amended by s. 1, ch. 2009-202, and that version reads:
(b) "Standard reference compendium" means an authoritative compendium identified by the Secretary of the United States Department of Health and Human Services and recognized by the federal Centers for Medicare and Medicaid Services.

REFERENCES:

1. American Society of Clinical Oncology. Reimbursement for cancer treatment: coverage of off-label drug indications. J Clin Oncol 2006;24:3206-8.
2. American Society of Clinical Oncology. Recent Developments in Medicare Coverage of Off-Label Cancer Therapies. J Oncol Pract 2009;5(1):18-20
3. Cox JV. Off-Label. J Oncol Pract 2011:69.
4. Centers for Medicaid and Medicare Services Covered medical and other health services. Medicare Benefit Policy Manual.
5. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 9/4/18.
6. The 2018 Florida Statutes. Copyright© 1995 – 2018. The Florida Legislature. Florida Statute 627.4239. Available at http://www.leg.state.fl.us/statutes/index.cfm?App_mode=Display_Statute&Search_String=&URL=0600-0699/0627/Sections/0627.4239.html Accessed 9/4/18.
7. Drugs@FDA [Internet]. Silver Spring (MD): US Food and Drug Administration; 2018. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name/. Accessed 9/4/18.
8. DailyMed [Internet]. Bethesda (MD): National Library of Medicine; 2018. Available from: http://dailymed.nlm.nih.gov/dailymed/index.cfm/. Accessed 9/4/18.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/14/25.

GUIDELINE UPDATE INFORMATION:

11/15/01	MCG Reformatted and revised.
10/15/03	Reviewed; no changes in coverage statement.
10/15/05	Scheduled review; no changes in coverage statement.
08/15/07	Updated guideline number.
11/15/07	Review and revision to guideline; consisting of changing MCG name, MCG number, including all off-label drug use, reformatting guideline, updated Florida statute regarding cancer treatment, updated internet links and updated references.
11/15/08	Review and revision to guideline; consisting of updating references. Move to no longer review status.
01/15/10	Revision to guideline; consisting of modifying position statement language.
06/15/11	Revision to guideline, consisting of revising categories of coverage in the position statement for the NCCN Compendia.
11/15/11	Review and revision to guideline; consisting of updating Florida statute and references.
11/15/12	Review and revision to guideline; consisting of revising position statement to include orphan drugs and revising definition section; updating references
02/15/13	Revision to guideline; consisting of minor revision of position statement.
11/15/13	Review and revision to guideline; consisting of revising position statement, updating definitions, and Florida Statute.
11/15/14	Review and revision to guideline; consisting of reformatting the position statement and revising the position statement to strengthen Orphan Drug indication approval.
05/15/15	Revision of guideline; consisting of position statement, descripton, references.
10/01/15	Revision of guidelines; consisting of position statement, description, coding, definitions.
12/15/15	Review and revision of guidelines; consisting of position statement, references.
03/15/16	Revision of guideline; consisting of adding Yondelis, Imlygic, Kanuma,Vistogard to Position Statement.
05/15/16	Revison of guideline; consisting of updating program exceptions with current LCD L33915.
07/15/16	Revision of guideline; consisting of updating position statement.
09/15/16	Revision of guideline; consisting of adding Arzerra, Defitelio, Tecentriq, and Zevalin to Position Statement.
12/15/16	Review and revision of guidelines; consisting of position statement, references.
03/15/17	Revison of guideline; consisting of adding Elaprase, Myozyme, Naglazyme to Position Statement.
6/15/17	Revision of guideline; consisting of addming Bavencio and Xermelo to Position Statement.
09/15/17	Revision of guideline; consisting of adding Brineura, Endari, Imfinzi, and Apokyn to Position Statement.
11/15/17	Revision to guideline; consisting of adding Vyxeos, Besponsa, Mylotarg, and Aliqopa to Position Statement.
03/15/18	Revision to guideline; consisting of adding Macrilen, Mepsevii, Zilretta to Position Statement.
6/15/18	Revision to guideline; consisting of revising Position Statement and adding Pegvaliase to Position Statement.

9/15/18	Revision to guideline; consisting of removing Palyniq (Pegvaliase-Pqpz) and adding Braftovi, Mektovi, Impavido, Sinuva, Photrexa, Photrexa Viscous to Position Statement.
11/15/18	Review and revision to guideline; consisting of updating references.
12/15/18	Revision to guideline; consisting of adding to Position Statement.
1/15/19	Revision to guidline; consisting of removing Braftovi and Mektovi from position statement.
03/15/19	Revision to guideline; adding Revcovi, Elzonris, and Asparlas to Position Statement.
04/15/19	Revision to guideline; removal of Krystexxa from Position Statement (Krystexxa moved to separate policy).
06/15/19	Revision to guideline; adding Infugem to Position Statement.
09/15/19	Revision to guideline; adding Inbrija to Position Statement.
12/15/19	Review and revision to guideline; adding Egaten and FDA labeled dosing to Position statement.
02/15/20	Revision to guideline; adding Zilretta quantity limits to Position Statement.
03/15/20	Revision to guideline; adding Nourianz and Scenesse to Position Statement.
06/15/20	Revision to guideline; adding Istodax and Romidepsin to and removing Sylatron from Position Statement.
07/15/20	Revision to guideline; adding Jelmyto and Zepzelca to Position Statement.
12/15/20	Revison to guideline; adding Fintepla to Position Statement
01/15/21	Revision to guideline; adding Targretin (bexarotene) gel to Position Statement
11/15/21	Revision to guideline; added Korsuva, Rylaze, Erwinaze to table 1; removed Lumizyme from table 1.
03/15/21	Revision to guideline; added Fyarro and Tivdak to table 1.
06/15/22	Review and revision to guidelines; added Pluvicto to table 1.
12/15/22	Review and revision to guidelines; removed Scense from table 1.
04/01/23	Review and revision to guideline; added Elahere, Imjudo, Lunsumio, Pedmark, Rebyota, Xipere to table 1.
06/15/23	Review and revision to guideline; added Zynz to table 1.
09/15/23	Revision to guideline; added Vowst and Omisirge to table 1.
11/15/23	Revision to guideline; added Aphexda, Cuvrior, and Hepzato Kit to table 1.
03/15/24	Revision to guideline; added Adstiladrin and Loqtorzi to table 1.
04/15/24	Revision to guideline; updated position statement to require documentation from the medical record for Xiaflex.
06/15/24	Review and revision to guideline; added iDose TR, Tevimbra, and Quzyttir to table 1.
09/15/24	Revision to guideline; added Anktiva, Imdelltra, and Rytelo to table 1.
11/15/24	Revision to guideline; added Tecentriq Hybreza to table 1.
03/15/25	Revision to guideline; added Bizengri, RegeneCyte, Unloxcyt, Vyloy, and Ziihera to table 1
06/15/25	Revision to guideline; added Onapgo and Chenodal and removed Chemet from table 1