09-J4000-05

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Reviewed: 01/08/25

Revised: 02/15/25

Subject: Loncastuximab Tesirine-lpyl (Zynlonta®) IV Infusion

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Loncastuximab tesirine (Zynlonta) is an antibody-drug conjugate (ADC) targeting CD19 that was approved by the U.S. Food and Drug Administration (FDA) in May 2021 for "the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma". The indication was approved under accelerated approval based on overall response rate, and continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). Loncastuximab tesirine was previously granted orphan drug designation by the FDA in 2017 for the treatment of diffuse large B-cell lymphoma. Loncastuximab tesirine is a CD19-directed antibody and alkylating agent conjugate, consisting of a humanized IgG1 kappa monoclonal antibody conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxic alkylating agent. Upon binding to CD19, loncastuximab tesirine is internalized followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to DNA and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell death.

The safety and efficacy of loncastuximab tesirine leading to initial FDA approval was evaluated in LOTIS-2 (NCT03589469), an open-label, single-arm trial in 145 adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 prior systemic regimens. The trial required hepatic transaminases, including gamma-glutamyltransferase (GGT), ≤2.5 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and creatinine clearance ≥60 mL/min. The trial excluded patients with bulky disease and active central nervous system lymphoma. Patients received loncastuximab tesirine 0.15 mg/kg every 3 weeks for 2 cycles, then 0.075 mg/kg every 3 weeks for subsequent cycles and

received treatment until progressive disease, or unacceptable toxicity. Of the 145 patients enrolled, the median age was 66 years (range 23 to 94), 59% male, and 94% had an ECOG performance status of 0 to 1. A total of 90% were White, 3% were Black, and 2% were Asian. The diagnosis was DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low-grade lymphoma) and high-grade B-cell lymphoma in 8%. The median number of prior therapies was 3 (range 2 to 7), 63% with refractory disease, 17% with prior stem cell transplant, and 9% with prior chimeric antigen receptor (CAR) T-cell therapy.

Efficacy was established on the basis of overall response rate (ORR) as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria. The median follow-up time was 7.3 months (range 0.3 to 20.2). Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles. The ORR was 48.3% (95% CI; 39.9 to 56.7%) with a complete response rate of 24.1% (95% CI; 17.4 to 31.9%) and a partial response rate of 24.1% (95% CI; 17.4 to 31.9%). The median duration of overall response (n=70) was 10.3 months (95% CI; 6.9 to not estimable). The median time to response was 1.3 months (range 1.1 to 8.1). Serious adverse reactions occurred in 28% of patients receiving loncastuximab tesirine. The most common serious adverse reactions that occurred in ≥2% were febrile neutropenia, pneumonia, edema, pleural effusion, and sepsis. Fatal adverse reactions occurred in 1%, due to infection. Permanent treatment discontinuation due to an adverse reaction occurred in 19% of patients, dose reductions due to an adverse reaction occurred in 8% of patients, and dosage interruptions due to an adverse reaction occurred in 49% of patients. Gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema were the most common reason for these events.

National Comprehensive Cancer Network (NCCN) Guidelines for B-cell lymphomas list loncastuximab tesirine as a third-line, single-agent treatment option (category 2A) in various large B-cell lymphomas including diffuse large B-cell lymphoma (DLBCL), indolent lymphomas transformed to DLBCL, high-grade B-cell lymphomas, HIV-related DLBCL, primary effusion lymphoma, HHV8-positive DLBCL not otherwise specified, and Post-Transplant Lymphoproliferative Disorders.

POSITION STATEMENT:

Initiation of loncastuximab tesirine (Zynlonta) **meets the definition of medical necessity** when **EITHER** of the following criteria are met ("1" or "2"):

1. Member has a diagnosis of large B-cell lymphoma, and **ALL** of the following criteria are met ("a" to "d"):
    a. The member has been diagnosed with **ANY** of the following large B-cell lymphomas subtypes – *medical record documentation confirming the member's diagnosis must be submitted:*
        i. Diffuse large B-cell lymphoma (DLBCL) [including HIV-related DLBCL, indolent lymphoma (e.g., follicular and marginal zone lymphomas) transformed to DLBCL, and HHV8-positive DLBCL, not otherwise specified (NOS)]
        ii. High-grade B-cell lymphoma, with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma)
        iii. High-grade B-cell lymphoma, not otherwise specified (NOS)
        iv. Primary effusion lymphoma

v. Post-Transplant Lymphoproliferative Disorders (B-cell type)

b. Loncastuximab tesirine is being used as third line or subsequent therapy for members with partial response, no response, relapsed, progressive or refractory disease

c. Loncastuximab tesirine will be used as single-agent treatment (i.e., not used in combination with other chemotherapy or immunotherapy)

d. The dosage does not exceed 0.15 mg/kg every 3 weeks for 2 cycles, followed by 0.075 mg/kg every 3 weeks for subsequent cycles [for patients with a body mass index (BMI) ≥35 kg/m^2, calculate the dose based on an adjusted body weight (ABW) as follows: ABW in kg = 35 $kg/m^2 \times$ (height in meters)^2]

2. Member has another FDA-approved or NCCN-supported diagnosis, and **ALL** of the following criteria are met ("a", "b" and "c"):

   a. **EITHER** of the following ("i" or "ii"):

      i. 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)

      ii. Indication **AND** usage are recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

   b. Loncastuximab tesirine is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis

   c. The dosage of loncastuximab tesirine does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

Approval duration: 6 months

Continuation of loncastuximab tesirine (Zynlonta) **meets the definition of medical necessity** when **BOTH** of the following criteria are met ("1" and "2"):

1. An authorization or reauthorization for loncastuximab tesirine has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of a large B-cell lymphoma, or other FDA-approved or NCCN-supported diagnosis; **OR** the member has previously met **ALL** indication-specific criteria.
2. **EITHER** of the following based on the member's diagnosis:

   a. Large B-cell lymphomas, and **ALL** of the following ("i", "ii", and "iii"):

      i. Loncastuximab tesirine will be used as single-agent treatment (i.e., not used in combination with other chemotherapy or immunotherapy)

      ii. The member has not had disease progression during treatment with loncastuximab tesirine

      iii. The dosage of loncastuximab tesirine does not exceed 0.075 mg/kg every 3 weeks [for patients with a body mass index (BMI) ≥35 kg/m^2, calculate the dose based on an adjusted body weight (ABW) as follows: ABW in kg = 35 $kg/m^2 \times$ (height in meters)^2]

b. Other FDA-approved or NCCN-supported diagnosis and **ALL** of the following ("i", "ii", and "iii"):

i. The dosage of loncastuximab tesirine does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guideline for the specific diagnosis

ii. Loncastuximab tesirine is used in a treatment regimen in accordance with the FDA-approved prescribing information or applicable NCCN guideline recommendation for the diagnosis

iii. The member has had a beneficial response to treatment with loncastuximab tesirine

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma
    - This indication is approved under accelerated approval based on overall response rate, and continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)
- The recommended dosage is 15 mg/kg an IV infusion administered over 30 minute every 3 weeks for 2 cycles followed by 0.075 mg/kg every 3 weeks for subsequent cycles
    - For patients with a body mass index (BMI) ≥35 kg/m^2, calculate the dose based on an adjusted body weight (ABW) as follows: ABW in kg = 35 kg/m^2 × (height in meters)^2
    - Unless contraindicated, administer dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day before administering loncastuximab. If dexamethasone administration does not begin the day before, dexamethasone should begin at least 2 hours prior to administration of loncastuximab.

Dose Adjustments

- Renal Impairment - Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.
- Hepatic Impairment - No dosage adjustment is necessary for mild hepatic impairment (total bilirubin level at or below the ULN and AST level greater the ULN OR total bilirubin level greater than 1 to 1.5 times the ULN and any AST level). Specific guidelines for dosage adjustments are not available for moderate or severe hepatic impairment (; it appears that no dosage adjustments are needed.
- Adverse Events
    - Neutropenia (absolute neutrophil count less than 1 × 10^9/L) - Withhold loncastuximab tesirine until neutrophil counts returns to 1 × 10^9/L or higher

- Thrombocytopenia (platelet count less than 50,000/mcL) - Withhold loncastuximab tesirine until platelet count returns to 50,000/mcL or higher
- Edema or Effusion (Grade 2 or higher) - Withhold loncastuximab tesirine until the toxicity resolves to Grade 1 or less
- Other Adverse Reactions (Grade 3 or higher) - Withhold loncastuximab tesirine until the toxicity resolves to Grade 1 or less
- If dosing is delayed by more than 3 weeks due to toxicity related to loncastuximab tesirine, reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation.

Drug Availability

- 10 mg preservative-free single-dose vial containing a white to off-white lyophilized powder for reconstitution and further dilution.
- Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not use beyond the expiration date shown on the carton. Do not freeze. Do not shake.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Effusion and Edema**: Monitor for the development of pleural effusion, pericardial effusion, ascites, peripheral edema, and general edema. Consider diagnostic imaging when symptoms develop or worsen.
- **Myelosuppression**: Monitor blood cell counts. Withhold, reduce, or discontinue loncastuximab tesirine based on severity.
- **Infections**: Monitor for infection and treat promptly.
- **Cutaneous Reactions**: Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Dermatologic consultation should be considered.
- **Embryo-Fetal Toxicity**: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.
- **Lactation**: Advise not to breastfeed.

BILLING/CODING INFORMATION:

HCPCS Coding

J9359	Injection, loncastuximab tesirine-lpyl, 0.075 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

B20	Human immunodeficiency virus [HIV] disease [for HIV-related B-cell lymphomas only and only used in combination with C83.30-C83.39, C83.80-C83.89, or C85.80-C85.89]
C83.30 – C83.39	Diffuse large B-cell lymphoma
C83.80 – C83.89	Other non-follicular lymphoma
C83.90 – C83.99	Non-follicular (diffuse) lymphoma, unspecified
C85.10 – C85.19	Unspecified B-cell lymphoma
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 - C85.89	Other specified types of non-Hodgkin lymphoma
D47.Z1	Post-transplant lymphoproliferative disorders

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

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021 Jun;22(6):790-800. Epub 2021 May 11.
2. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2024. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 12/26/24.
3. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 12/26/24.
4. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 12/26/24.
5. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. B-cell Lymphomas (Version 1.2025 – December 20, 2024) [cited 2024 Dec 26]. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
6. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2024 Dec 26]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.
7. Zynlonta (loncastuximab tesirine-lpyl intravenous injection) [package insert]. Murray Hill, NJ: ADC Therapeutics America. October 2022.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/08/25.

GUIDELINE UPDATE INFORMATION:

09/15/21	New Medical Coverage Guideline.
10/01/21	Revision: Addition of HCPCS code C9084.
02/15/22	Review and revision to guideline consisting of the position statement and references.
04/01/22	Revision: Addition of HCPCS code J9359 and deletion of codes C9084 and J9999.

02/15/23	Review and revision to guideline consisting of updates to the description, position statement, billing/coding, and references. AIDS-related B-cell lymphomas covered per NCCN recommendation.
02/15/24	Review and revision to guideline consisting of updates to the description, position statement, billing/coding, and references for the addition of Post-Transplant Lymphoproliferative Disorders and revised language of “AIDS-related” to “HIV-related” per NCCN recommendation.
02/15/25	Review and revision to guideline consisting of updating references.