ZYNLONTA® (loncastuximab tesirine-lpyl) – Maximum Dose and Final Vial Concentration

Summary

- ZYNLONTA is supplied as a lyophilized powder in a 10 mg single-dose vial for reconstitution and further dilution.[6]
    - The overfill amount of ZYNLONTA is approximately 0.3 mL after reconstitution. This was done to ensure that approximately 2 mL of drug at a concentration of 5 mg/mL could be extracted from the vial.[5]
- ZYNLONTA should be administered as an intravenous (IV) infusion over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer IV infusion as follows:[6]
    - 0.15 mg/kg every 3 weeks for 2 cycles, followed by 0.075 mg/kg every 3 weeks for subsequent cycles.[6]
    - For patients with a body mass index (BMI) ≥35 kg/m^2, calculate the dose based on an adjusted body weight (ABW). More than one vial may be needed.[6]
- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study which evaluated the safety and tolerability of ZYNLONTA monotherapy in 183 adult patients with relapsed or refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL).[3]
    - In Part 1 of the study, the maximum dose administered was 200 µg/kg (0.2 mg/kg). The maximum tolerated dose (MTD) was not reached, although an accumulation of adverse events was apparent at the 200 µg/kg (0.2 mg/kg) dose.
    - 10-mL, single-use glass vials of loncastuximab tesirine (frozen liquid formulation) were used in the study.[4]
- LOTIS-2 was a pivotal, Phase 2, multicenter, open-label, single-arm study that evaluated the efficacy and safety of ZYNLONTA monotherapy in adult patients with R/R diffuse large B-cell lymphoma (DLBCL) following ≥2 lines of prior systemic therapy.[2]
    - Patients received ZYNLONTA at a dose of 150 µg/kg (0.15 mg/kg) every 3 weeks (Q3W) for the first 2 cycles, followed by 75 µg/kg (0.075 mg/kg) Q3W for subsequent cycles.
    - ZYNLONTA was provided as a frozen liquid formulation (in 10 mL glass vials) or as a refrigerated, lyophilized, white to off-white powder in 8 mL glass vials (10 mg of ZYNLONTA per vial).
        - The lyophilized powder of ZYNLONTA was reconstituted with 2.2 mL of Sterile Water for Injection to deliver 2 mL. The final concentration of reconstituted ZYNLONTA was 5 mg/mL.
    - The amount of product to be diluted was dependent on the dose level, weight, and body mass index (BMI) of the patient. [1]
    - Patients with a BMI of ≥ 35 kg/m^2 had their dose calculated based on ABW. The ABW formula used in LOTIS-2 is provided in the **Overview: Maximum Concentration** section of this letter.
- ADC Therapeutics does not recommend dosage, administration, reconstitution or dilution of ZYNLONTA outside of what is recommended in the Prescribing Information.
- See the **Relevant Prescribing Information** section for further information regarding dosage, administration, reconstitution, and dilution of ZYNLONTA.

Background

- LOTIS-1 was a Phase 1, open-label, single-arm, multicenter study which evaluated the safety and tolerability of ZYNLONTA monotherapy in 183 adult patients with relapsed or refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL).[3]
- LOTIS-2 was a pivotal, Phase 2, multicenter, open-label, single-arm study that evaluated the efficacy and safety of ZYNLONTA monotherapy in adult patients with R/R diffuse large B-cell lymphoma (DLBCL) following ≥2 lines of prior systemic therapy.[2]

Clinical Data

Maximum Dose

- ZYNLONTA should be administered as an intravenous (IV) infusion over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer IV infusion as follows:[6]
    - 0.15 mg/kg every 3 weeks for 2 cycles, followed by 0.075 mg/kg every 3 weeks for subsequent cycles.
- The recommended dosing of ZYNLONTA was based on data from the dose finding Phase 1 (LOTIS-1) study and the subsequent dosing of LOTIS-2, which was 150 µg/kg (0.15 mg/kg) every 3 weeks (Q3W) for the first two cycles, followed by 75 µg/kg (0.075 mg/kg) Q3W for subsequent cycles.[3]
    - Overall, 183 patients received ZYNLONTA during Part 1 and Part 2 of LOTIS-1.
        - In Part 1, 88 patients received loncastuximab tesirine at doses of 15–200 µg/kg Q3W (15, 30, or 60 µg/kg; n=4 in each group, 90 µg/kg: n=5; 120 µg/kg: n=16; 150 µg/kg: n=19; 200 µg/kg: n=36).
        - Dose-limiting toxicities (all hematologic) were reported in 4 patients, and the maximum tolerated dose (MTD) was not reached, although an accumulation of adverse events was apparent at the 200 µg/kg (0.2 mg/kg) dose.
    - In LOTIS-2, patients received ZYNLONTA at a dose of 150 µg/kg (0.15 mg/kg) every 3 weeks (Q3W) for the first 2 cycles, followed by 75 µg/kg (0.075 mg/kg) Q3W for subsequent cycles.[2]
        - The initial 150 µg/kg (0.15 mg/kg) dose of ZYNLONTA was selected based on anti-tumor activity and increased rates of hematologic and hepatic adverse events at the 200 µg/kg (0.2 mg/kg) dose seen in LOTIS-1.

Dosing in Patients with High Body Mass Index (≥ 35 kg/m)[6]

- For patients with a body mass index (BMI) ≥35 kg/m^2, calculate the dose of ZYNLONTA based on an adjusted body weight (ABW) as follows:

$$\text{ABW in kg} = 35\ \text{kg/m}^2 \times (\text{height in meters})^2$$

- More than one vial may be needed to achieve the calculated dose.
- Convert the calculated dose (mg) to volume using 5 mg/mL, which is the concentration of ZYNLONTA after reconstitution.

Maximum Vial Concentration[6]

- In LOTIS-1, 10-mL, single-use glass vials of loncastuximab tesirine (frozen liquid formulation) were used.[4]
    - Vials were inspected prior to use. The appropriate quantity of loncastuximab was removed from the vial with a syringe and diluted into a 50 mL IV bag containing 5% dextrose in water.

The amount of the product to be diluted was dependent on the dose level and body mass of the patient.

- Once loncastuximab was transferred, the bag was mixed to ensure homogeneity of the dosing solution. The contents of the IV bag were then administered to the patient with a dosing pump per institutional guidelines for IV fluid.

- In LOTIS-2, patients received ZYNLONTA at a dose of 150 µg/kg (0.15 mg/kg) every 3 weeks (Q3W) for the first 2 cycles, followed by 75 µg/kg (0.075 mg/kg) Q3W for subsequent cycles [2]
  - Loncastuximab tesirine was provided as a frozen liquid formulation (10 mL glass vials) or as a refrigerated, lyophilized, white to off-white powder in 8 mL glass vials (10 mg of ZYNLONTA per vial).[5]
    - The lyophilized powder of ZYNLONTA was reconstituted with 2.2 mL of Sterile Water for Injection to deliver 2 mL.[5]
      - The final concentration of reconstituted ZYNLONTA was 5 mg/mL.
  - The amount of product to be diluted was dependent on the dose level, weight, and body mass index (BMI) of the patient. [5]
  - Patients with a BMI of ≥ 35 kg/m^2 had their dose calculated based on an actual body weight (ABW) as follows:[5]

    ABW in kg=35 kg/m^2 × (height in meters)^2

    Dose to administer (mg)=dosage (µg/kg) × ABW/1000

- ZYNLONTA is supplied as a lyophilized powder in a 10 mg single-dose vial for reconstitution and further dilution.**Error! Bookmark not defined.**
  - The overfill amount of ZYNLONTA is approximately 0.3 mL after reconstitution. This was done to ensure that approximately 2 mL of drug at a concentration of 5 mg/ml could be extracted from the vial.[6]
- Reconstitute each ZYNLONTA vial using 2.2 mL of Sterile Water for Injection, USP with the stream directed toward the inside wall of the vial.[6]
- The final concentration of reconstituted ZYNLONTA, prior to dilution, should be 5 mg/mL.[6]
- Add the calculated dose volume of ZYNLONTA solution into a 50 mL infusion bag of **5% Dextrose Injection, USP**.[6]

Alternative Dosing and Administration of ZYNLONTA

- ADC Therapeutics does not recommend dosage, administration, reconstitution or dilution of ZYNLONTA outside of what is recommended in the Prescribing Information.
- See the **Relevant Prescribing Information** section for further information regarding dosage or administration, including reconstitution and dilution of ZYNLONTA.

Literature Search

- A PubMed biomedical literature search conducted on March 28, 2025, yielded no further relevant data regarding ZYNLONTA's maximum dose and final vial concentration.

Relevant Prescribing Information

Section 2: Dosage and Administration[6]

Section 2.1 Recommended Dosage[6]

- ZYNLONTA as an intravenous infusion administered over 30 minutes on Day 1 of each cycle (every 3 weeks). Administer intravenous infusion as follows:
    - 0.15 mg/kg every 3 weeks for 2 cycles.
    - 0.075 mg/kg every 3 weeks for subsequent cycles.

Section 2.4 Reconstitution and Administration Instructions[6]

- Reconstitute and further dilute ZYNLONTA prior to intravenous infusion. Use appropriate aseptic technique.
- ZYNLONTA is a hazardous drug. Follow applicable special handling and disposal procedures.[7]

Dose calculation

- Calculate the total dose (mg) required based on the patient's weight and prescribed dose [see *Dosage and Administration (2.1*)].
    - For patients with a body mass index (BMI) ≥35 kg/m^2, calculate the dose based on an adjusted body weight (ABW) as follows:

      $$\text{ABW in kg} = 35\ \text{kg/m}^2 \times (\text{height in meters})^2$$

    - More than one vial may be needed to achieve the calculated dose.
    - Convert the calculated dose (mg) to volume using 5 mg/mL, which is the concentration of ZYNLONTA after reconstitution.

Reconstitution of lyophilized ZYNLONTA[6]

- Reconstitute each ZYNLONTA vial using 2.2 mL of Sterile Water for Injection, USP with the stream directed toward the inside wall of the vial to obtain a final concentration of 5 mg/mL.
- Swirl the vial gently until the powder is completely dissolved. *Do not shake. Do not expose to direct sunlight.*
- Inspect the reconstituted solution for particulate matter and discoloration. The solution should appear clear to slightly opalescent, colorless to slightly yellow. Do not use if the reconstituted solution is discolored, is cloudy, or contains visible particulates.
- Use reconstituted ZYNLONTA immediately. If not used immediately, store the reconstituted solution in the vial for up to 4 hours refrigerated at 2°C to 8°C (36°F to 46°F) or room temperature 20°C to 25°C (68°F to 77°F). *Do not freeze.*
- The product does not contain a preservative. Discard unused vial after reconstitution if the recommended storage time is exceeded.

Dilution in infusion bag[6]

- Withdraw the required volume of reconstituted solution from the ZYNLONTA vial using a sterile syringe. Discard any unused portion left in the vial.
- Add the calculated dose volume of ZYNLONTA solution into a 50 mL infusion bag of **5% Dextrose Injection, USP**.
- Gently mix the intravenous bag by slowly inverting the bag. *Do not shake*.

- If not used immediately, store the diluted ZYNLONTA infusion solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature 20°C to 25°C (68°F to 77°F) for up to 8 hours. Discard diluted infusion bag if storage time exceeds these limits. Do not freeze.
- No incompatibilities have been observed between ZYNLONTA and intravenous infusion bags with product-contacting materials of polyvinylchloride (PVC), polyolefin (PO), and PAB® (copolymer of ethylene and propylene).

Administration[6]

- Administer by intravenous infusion over 30 minutes using a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2-or 0.22-micron pore size) and catheter.
- Extravasation of ZYNLONTA has been associated with irritation, swelling, pain, and/or tissue damage, which may be severe [*see Adverse Reactions (6.1)*].
- Monitor the infusion site for possible subcutaneous infiltration during drug administration.
- Do not mix ZYNLONTA with or administer as an infusion with other drugs.

References

[1] Data on File, LOTIS-2 Clinical Study Report. ADC Therapeutics.

[2] Caimi PF, Ai WZ, Alderuccio JP, et al. Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase 2 LOTIS-2 study. Haematol. Published online August 31, 2023. doi: 110.3324/haematol.2023.283459

[3] Hamadani M, Radford J, Carlo-Stella C, et al. Final Results of a Phase 1 Study of Loncastuximab Tesirine in Relapsed/Refractory B-cell Non-Hodgkin lymphoma. *Blood*. 2021 May 13; 137(19):2634-2645. DOI: 10.1182/blood.2020007512.

[4] Data on File, LOTIS-1 Clinical Study Report. ADC Therapeutics.

[5] Data on File, Memo. ADC Therapeutics.

[6] ZYNLONTA® (loncastuximab tesirine-lpyl) FDA-approved Prescribing Information. October 2022.

[7] OSHA Hazardous Drugs. United States Department of Labor: Occupational Safety and Health Administration. http://www.osha.gov/SLTC/hazardousdrugs/index.htm. Accessed May 10, 2022.

ADC Therapeutics encourages all health care professionals to report any adverse events and product quality complaints to medical information at 855-690-0340. Please consult the ZYNLONTA Prescribing Information.