# Summary Report of Benefit-Risk Assessment

## ZYNLONTA FOR INJECTION 10MG/VIAL

## NEW DRUG APPLICATION

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|---|---|
| **Active Ingredient(s)** | Loncastuximab tesirine |
| **Product Registrant** | Orient Europharma Pte Ltd |
| **Product Registration Number** | SIN17098P |
| **Application Route** | Abridged evaluation |
| **Date of Approval** | 25 September 2024 |

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## A INTRODUCTION

Zynlonta is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

The active substance, loncastuximab tesirine, is an antibody-drug conjugate (ADC) targeting CD19. The monoclonal IgG1 kappa antibody component binds to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. The small molecule component is a pyrrolobenzodiazepine (PBD) dimer cytotoxic alkylating agent (designated as SG3199), which is attached to the linker, tesirine. Upon binding to CD19, loncastuximab tesirine is internalised followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell death.

Zynlonta is available as lyophilised powder for infusion containing 10 mg/vial of loncastuximab tesirine. Other ingredients in the vial are L-histidine, L-histidine monohydrochloride, polysorbate 20 and sucrose.

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## B ASSESSMENT OF PRODUCT QUALITY

The drug substance, loncastuximab tesirine, and drug product, Zynlonta for Injection 10 mg/vial are manufactured at BSP Pharmaceuticals S.p.A, Italy.

**Drug substance:**

Loncastuximab tersirine is produced by chemical conjugation of loncastuximab monoclonal antibody and cytotoxic alkylating agent through a protease-cleavable linker. The monoclonal antibody is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line, and the small molecule components are produced by chemical synthesis.

Adequate controls have been presented for the raw materials, cell banks and drug substance intermediates. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits have been appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2(R2) guidelines with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is sterile 2 L polyethylene terephthalate copolyester, glycol modified (PETG) Thermo Scientific™ Nalgene™ Square bottles with high-density polyethylene (HDPE) closure. The stability data presented was adequate to support the storage of the drug substance at ≤ -60°C with a shelf life of 24 months.

**Drug product:**

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2(R2) guidelines with information on the reference standards used for identity, assay and impurities testing presented.

The container closure system is clear Type I glass vial with a 20 mm Teflon-coated rubber lyophilisation stopper and tamper-evident aluminum seal. The stability data submitted was adequate to support the approved shelf-life of 48 months when stored at 2-8°C.

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## C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of loncastuximab tesirine for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy was based primarily on one Phase II study (ADCT-402-201). This was an ongoing, multicentre, open-label, single-arm study of the efficacy and safety of loncastuximab tesirine in patients with relapsed or refractory DLBCL following at least two prior systemic treatment regimens.

The study included a screening period (of up to 28 days), a treatment period (cycles of 3 weeks) for up to 1 year or until progressive disease, unacceptable toxicity, or other discontinuation criteria, whichever occurred first, and a follow-up period for up to 3 years. Disease assessments were performed at baseline and 6 and 12 weeks from Day 1 of Cycle 1, then every 9 weeks during the treatment period, and at end of treatment. Loncastuximab tesirine was administered as an intravenous infusion over 30 minutes on Day 1 of each cycle (every 3 weeks [Q3W]) at a dose of 150 µg/kg for 2 cycles and then 75 µg/kg for subsequent cycles. Premedication with dexamethasone (4 mg orally twice daily) was administered the day before loncastuximab tesirine administration (where possible), the day of loncastuximab tesirine administration (given at least 2 hours prior to administration when not given the day before; otherwise, any time prior to administration), and the day after loncastuximab tesirine administration.

The primary efficacy endpoint was overall response rate (ORR), defined as the proportion of patients who achieved either complete response (CR) or partial response (PR) as best overall response assessed by an independent central review (ICR) according to the 2014 Lugano criteria[1]. Other efficacy endpoints included duration of response (DOR), CR rate, time to response (TTR), progression-free survival (PFS), relapse-free survival (RFS) and overall survival (OS). The endpoints were standard and considered to be appropriate.

[1] The Lugano criteria is the gold standard for lymphoma staging, evaluation, and response assessments, and is based on the positron emission tomography–computed tomography (PET-CT) scan.

A sample size of 140 patients was required to provide more than 99% power that the ORR by central review for patients treated with loncastuximab tesirine was significantly greater than 20% based on the response rates reported for patients with relapsed or refractory DLBCL in the second-line salvage therapy setting. A total of 145 patients were enrolled and received at least one dose of loncastuximab tesirine, hence the sample size was reasonably adequate to estimate the effect size as measured based on ORR. The median age of the patients was 66 years (range: 23 to 94). 59% of the patients were male, and 94% had an ECOG performance status of 0 to 1. The majority of the patients (90%) were White. 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 (HGBCL) in 7% of the patients. The median number of prior therapies was 3 (range: 2 to 7) and 63% of the patients had refractory disease, 17% had prior stem cell transplant (SCT), and 9% had prior chimeric antigen receptor (CAR) T-cell therapy.

**Summary of key efficacy results**

| | **Loncastuximab tesirine (N=145)** |
|---|---|
| **Primary endpoint** | |
| ORR, n (%)<br>(95% CI) | 70 (48.3%)<br>(39.9, 56.7) |
| **Other endpoints** | |
| CR rate, n (%)<br>(95% CI) | 35 (24.1%)<br>(17.4, 31.9) |
| DOR<br>Median (months)<br>(95% CI) | <br>10.3<br>(6.9, NR) |
| TTR<br>Median (months)<br>(Min, max) | <br>1.3<br>(1.1, 8.1) |
| PFS<br>Median (months)<br>(95% CI) | <br>4.9<br>(2.9, 8.3) |
| RFS<br>Median (months)<br>(95% CI) | <br>13.4<br>(10.3, NR) |
| OS<br>Median (months)<br>(95% CI) | <br>9.9<br>(6.7, 11.5) |

NR: Not reached

As the study was single-arm and non-comparative, there was no statistical testing and the results were descriptively presented. It showed that the ORR was 48.3% (95% CI: 39.9, 56.7), with a CR rate of 24.1% (95% CI: 17.4, 31.9) and a PR rate of 24.1% (95% CI: 17.4, 31.9). A total of 9 patients were able to proceed to consolidation with SCT.

The median DOR was 10.3 months [95% CI: 6.9, not estimable (NR)] and TTR was 1.3 months (range: 1.1 to 8.1). The probability of maintaining response was 68.1% at 6 months, 63.8% at 9 months, and 38.3% at 12 months. The median PFS was 4.9 months (95% CI: 2.9, 8.3) and median OS was 9.9 months (95% CI: 6.7, 11.5). Among patients with CR, the median RFS (defined as the time from CR to disease progression or death) was 13.4 months (95% CI: 10.3, NR).

Overall, the ORR of 48.3% and CR of 24.1% observed with loncastuximab tesirine were considered clinically meaningful and generally within the range of that observed with other drug therapies (ORR ranging from approximately 29% to 63% and CR ranging from approximately

13% to 50% for polatuzumab vedotin plus bendamustine and rituximab, selinexor and glofitamab) which have been approved for DLBCL in similar disease setting based on single-arm studies with similar sample sizes.

## D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of loncastuximab tesirine was based primarily on pooled safety data from 215 patients with relapsed or refractory DLBCL who received loncastuximab tesirine monotherapy at the proposed dose of 150 µg/kg. A total of 145 patients were from the pivotal study ADCT-402-201 and the remaining patients were from study ADCT-402-101, which was a Phase I, open-label, dose-escalation and expansion study to evaluate the safety and tolerability of loncastuximab tesirine as monotherapy in patients with relapsed or refractory non-Hodgkin lymphoma, including DLBCL.

For study ADCT-402-201, the median exposure was 3 cycles or 45 days. The relative dose intensity was greater than 90% in 94% of patients. The exposure was considered sufficient to evaluate the short-term safety profile of loncastuximab tesirine. However, the data was limited in patients (34%) who received at least 5 or more cycles.

**Overview of safety profile**

| TEAE | Study ADCT-402-201 (N=145) | Study ADCT-402-101 (N=70) | Total (N=215) |
|---|---|---|---|
| Any TEAE | 143 (98.6%) | 69 (98.6%) | 212 (98.6%) |
| Treatment-related TEAE | 117 (80.7%) | 58 (82.9%) | 175 (81.4%) |
| Grade ≥3 TEAE | 105 (72.4%) | 53 (75.7%) | 158 (73.5%) |
| Treatment-related Grade ≥3 TEAE | 74 (51.0%) | 35 (50.0%) | 109 (50.7%) |
| Serious TEAE | 57 (39.3%) | 30 (42.9%) | 87 (40.5%) |
| Discontinuations due to TEAE | 34 (23.4%) | 8 (11.4%) | 42 (19.5%) |
| Deaths due to TEAE | 8 (5.5%) | 11 (15.7%) | 19 (8.8%) |

Almost all the subjects (98.6%) experienced a treatment emergent adverse event (TEAE). The most common TEAEs (≥20%) included gamma-glutamyltransferase (GGT) increased (34.9%), neutropenia (34.4%), fatigue (30.2%), anaemia (28.8%), thrombocytopenia (28.4%), nausea (26.5%), oedema peripheral (23.3%), cough (20.9%), and rash (20.0%). A total of 73.5% of the patients had a Grade 3 or higher TEAE. The most common Grade 3 or higher TEAEs included neutropenia (23.7%), GGT increased (16.7%), thrombocytopenia (15.8%), and anaemia (11.6%).

A total of 40.5% of the patients experienced a serious TEAE (SAE) leading to hospitalisation or death. The SAEs which occurred at an incidence of ≥2% included febrile neutropenia (3.3%), hypercalcaemia (2.8%), and pyrexia (2.3%). Treatment-related SAEs occurred in 14.0% of the patients. The incidence of deaths was 8.8% and the causes of death included sepsis or septic shock, pneumonia, lung infection, small intestinal perforation, abdominal compartment syndrome, gastrointestinal haemorrhage, acute kidney injury, haemoptysis, and subdural haematoma (secondary to a fall). The deaths were mostly due to disease progression and were not considered to be related to the study drug by the investigator except for one case of lung infection with a fatal outcome.

The AEs of special interest reported with locastuximab tersirine included GGT increased (34.9%), oedema peripheral (23.3%), rash (20.0%), blood alkaline phosphatase increased (19.1%), alanine aminotransaminase (ALT) increased (16.3%), aspartate aminotransferase

(AST) increased (15.8%), pleural effusion (13.0%), and pruritus (11.2%). The AEs of special interest have been adequately described as warnings and precautions in the package insert.

The safety profile of loncastuximab tesirine was similar to that of other ADCs, characterised by high incidences of toxicities such as neutropenia, anaemia, thrombocytopenia, liver enzyme abnormalities and oedema. Given the significant toxicities associated with the treatment, mitigation measures including dose modifications and delays, close monitoring and supportive care including the administration of premedication have been incorporated in the package insert to guide clinicians in appropriate patient management.

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## E ASSESSMENT OF BENEFIT-RISK PROFILE

Patients with relapsed or refractory DLBCL after 2 or more regimens have poor prognosis and there is currently no standard treatment. Current available data have shown that patients receiving salvage therapies (platinum, etoposide, and/or cytarabine-based combination regimens with rituximab) typically have limited treatment outcomes, with an ORR of 26% (CR rate 7%) to subsequent lines of therapy. The median survival for these patients is approximately 6 months. Although newer therapies such as polatuzumab vedotin with bendamustine-rituximab, selinexor, and glofitamab as well as CAR-T such as axicabtagene ciloleucel and tisagenlecleucel are available, there remains a need for more treatment options in view that not all patients have access to CAR-T and may have varying degree of tolerance to the different toxicity profiles of the currently available drugs.

While study ADCT-402-201 has limitations with respect to its single-arm and non-comparative design, the sample size of 145 patients was reasonably sufficient to provide adequate precision for the expected ORR range in patients with relapsed or refractory DLBCL after at least 2 prior systemic regimens. Loncastuximab tesirine demonstrated promising results with an ORR of 48.3% (95% CI: 39.9, 56.7), of which 24.1% of patients achieving a CR. The ORR was supported by a reasonably long median DOR of 10.3 months (95% CI: 6.9, NR). The median TTR was 1.3 months (range: 1.1 to 8.1), RFS was 13.4 months (95% CI: 10.3, NR), PFS was 4.9 months (95% CI: 2.9, 8.3) and OS was 9.9 months (95% CI: 6.7, 11.5).

As 71% of patients had received an intensive salvage regimen, SCT, or CAR-T therapy, the observed ORR of 48% with associated durability for loncastuximab tesirine was considered clinically meaningful as compared with currently approved therapies in the target patient population who have poor prognosis and limited treatment options. In addition, a total of 9 patients were able to proceed to consolidation with SCT.

Treatment with loncastuximab tesirine is associated with significant toxicities and high incidences of Grade ≥3 TEAEs, including neutropenia, GGT increased, thrombocytopenia, and anaemia. The AEs of special interest included GGT increased, oedema peripheral, pleural effusion, rash, blood alkaline phosphatase increased, AST/ALT increased and pruritus. These AEs have been adequately described in the package insert, and mitigation strategies such as dose modifications and treatment delays as well as recommendations for monitoring and premedication have been included to guide clinicians in managing patients and optimise the benefit-risk balance through careful monitoring and timely interventions.

Considering the poor prognosis and limited effective treatment options in patients with relapsed or refractory DLBCL after two or more lines of systemic therapy, and that mitigation strategies are in place to manage the risks associated with loncastuximab tesirine, the benefits of

loncastuximab tesirine were considered to outweigh the risks. Data from the ongoing Phase III confirmatory study ADCT-402-311 evaluating loncastuximab tesirine in combination with rituximab versus immunochemotherapy in patients with relapsed or refractory DLBCL would be required to confirm the efficacy and safety profile of Zynlonta.

## F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Zynlonta for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy was deemed favourable and approval of the product registration was granted on 25 September 2024. The approval of this application is subject to the submission of the final study report of the ongoing Phase III study ADCT-402-311 to confirm the clinical benefit and favourable overall risk-benefit profile.

## APPROVED PACKAGE INSERT AT REGISTRATION

**FULL PRESCRIBING INFORMATION**
ZYNLONTA FOR INJECTION 10MG/VIAL

## 1 INDICATIONS AND USAGE

ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

This indication is approved based on overall response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

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.

### 2.2 Recommended Premedication

Unless contraindicated, administer dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day before administering ZYNLONTA. If dexamethasone administration does not begin the day before ZYNLONTA, dexamethasone should begin at least 2 hours prior to administration of ZYNLONTA.

### 2.3 Dosage Modifications and Delays

Recommended Dosage Modifications for Adverse Reactions

| Adverse Reactions | Severity[a] | Dosage Modification |
|---|---|---|
| **Hematologic Adverse Reactions** | | |
| Neutropenia *[see Warnings and Precautions (5.2)]* | Absolute neutrophil count less than 1 x $10^9$/L | Withhold ZYNLONTA until neutrophil counts returns to 1 x $10^9$/L or higher |
| Thrombocytopenia *[see Warnings and Precautions (5.2)]* | Platelet count less than 50,000/mcL | Withhold ZYNLONTA until platelet count returns to 50,000/mcL or higher |
| **Nonhematologic Adverse Reactions** | | |
| Edema or Effusion *[see Warnings and Precautions (5.1)]* | Grade 2[a] or higher | Withhold ZYNLONTA until the toxicity resolves to Grade 1 or less |
| Other Adverse Reactions *[see Warnings and Precautions (5.3), (5.4), Adverse Reactions (6.1)]* | Grade 3[a] or higher | Withhold ZYNLONTA until the toxicity resolves to Grade 1 or less |

[a] National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

Recommendations for Dosage Delays
If dosing is delayed by more than 3 weeks due to toxicity related to ZYNLONTA,

reduce subsequent doses by 50%. If toxicity reoccurs following dose reduction, consider discontinuation.

Note: If toxicity requires dose reduction following the second dose of 0.15 mg/kg (Cycle 2), the patient should receive the dose of 0.075 mg/kg for Cycle 3.

## 2.4 Reconstitution and Administration Instructions

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.[1]

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:
  ABW in kg = 35 kg/m$^2$× (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

- 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

- 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

- 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.

## 3 DOSAGE FORMS AND STRENGTHS

For Injection: 10 mg of loncastuximab tesirine as a white to off-white lyophilized powder in a single-dose vial for reconstitution and further dilution.

## 4 CONTRAINDICATIONS

None

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Effusion and Edema

Serious effusion and edema occurred in patients treated with ZYNLONTA. Grade 3 edema occurred in 3% (primarily peripheral edema or ascites) and Grade 3 pleural effusion occurred in 3% and Grade 3 or 4 pericardial effusion occurred in 1% *[see Adverse Reactions (6.1)]*.

Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA for Grade 2 or greater edema or effusion until the toxicity resolves. Consider diagnostic imaging in patients who develop symptoms of pleural effusion or pericardial effusion, such as new or worsened dyspnea, chest pain, and/or ascites such as swelling in the abdomen and bloating. Institute appropriate medical management for edema or effusions *[see Dosage and Administration (2.3)]*.

### 5.2 Myelosuppression

Treatment with ZYNLONTA can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 neutropenia occurred in 32%, thrombocytopenia in 20%, and anemia in 12% of patients. Grade 4 neutropenia occurred in 21% and thrombocytopenia in 7% of patients. Febrile neutropenia occurred in 3% *[see Adverse Reactions (6.1)]*.

Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA. Consider prophylactic granulocyte colony-stimulating factor administration as applicable *[see Dosage and Administration (2.3)]*.

### 5.3 Infections

Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA. Grade 3 or higher infections occurred in 10% of patients, with fatal infections occurring in 2%. The most frequent Grade ≥3 infections included sepsis and pneumonia *[see Adverse Reactions (6.1)]*.

Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA until infection has resolved *[see Dosage and Administration (2.3)]*.

### 5.4 Cutaneous Reactions

Serious cutaneous reactions occurred in patients treated with ZYNLONTA. Grade 3 cutaneous reactions occurred in 4% and included photosensitivity reaction, rash (including exfoliative and maculo-papular), and erythema *[see Adverse Reactions (6.1)]*.

Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA for severe (Grade 3) cutaneous reactions until resolution *[see Dosage and Administration (2.3)]*. Advise patients to minimize or avoid exposure to direct natural or artificial sunlight including exposure through glass windows. Instruct patients to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products. If a skin reaction or rash develops, dermatologic consultation should be considered *[see Nonclinical Toxicology (13)]*.

### 5.5 Embryo-Fetal Toxicity

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman because it contains a genotoxic compound (SG3199) and affects actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 10 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZYNLONTA, and for 7 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

## 6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

Effusion and Edema *[see Warnings and Precautions (5.1)]*
Myelosuppression *[see Warnings and Precautions (5.2)]*
Infections *[see Warnings and Precautions (5.3)]*
Cutaneous Reactions *[see Warnings and Precautions (5.4)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ZYNLONTA as a single agent at an initial dose of 0.15 mg/kg in 215 patients with DLBCL in studies ADCT-402-201 (LOTIS-2) and ADCT-402-101, which includes 145 patients from LOTIS-2 treated with 0.15 mg/kg x 2 cycles followed by 0.075 mg/kg for subsequent cycles. Among 215 patients who received ZYNLONTA, the median number of cycles was 3 (range 1 to 15) with 58% receiving three or more cycles and 30% receiving five or more cycles.

In this pooled safety population of 215 patients, the most common (>20%) adverse reactions, including laboratory abnormalities, were thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain.

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

*LOTIS-2*

The safety of ZYNLONTA was evaluated in LOTIS-2, an open-label, single-arm clinical trial that enrolled 145 patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including high-grade B-cell lymphoma, after at least two prior systemic therapies *[see Clinical Studies (14.1)]*. 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. Patients received ZYNLONTA 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. Among the 145 patients, the median number of cycles received was 3, with 34% receiving 5 or more cycles.

The median age was 66 years (range 23 to 94), 59% were male, and 94% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian.

Serious adverse reactions occurred in 28% of patients receiving ZYNLONTA. The most common serious adverse reactions that occurred in ≥2% receiving ZYNLONTA 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 of ZYNLONTA occurred in 19% of patients. Adverse reactions resulting in permanent discontinuation of ZYNLONTA in ≥2% were gamma-glutamyltransferase increased, edema, and effusion.

Dose reductions due to an adverse reaction of ZYNLONTA occurred in 8% of patients. Adverse reactions resulting in dose reduction of ZYNLONTA in ≥4% was gamma-glutamyltransferase increased.

Dosage interruptions due to an adverse reaction occurred in 49% of patients receiving ZYNLONTA. Adverse reactions leading to interruption of ZYNLONTA in ≥5% were gamma-glutamyltransferase increased, neutropenia, thrombocytopenia, and edema.

Table 1 summarizes the adverse reactions in LOTIS-2.

**Table 1: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory DLBCL who received ZYNLONTA in LOTIS-2**

| Adverse Reaction | ZYNLONTA (N=145) | |
|---|---|---|
| | All Grades (%) | Grades 3 or 4 (%) |
| ***General Disorders and Administration Site Conditions*** | | |
| Fatigue[b] | 38 | 1[a] |
| Edema[c] | 28 | 3[a] |
| ***Skin and Subcutaneous Tissue Disorders*** | | |
| Rash[d] | 30 | 2[a] |
| Pruritus | 12 | 0 |
| Photosensitivity reaction | 10 | 2[a] |
| ***Gastrointestinal Disorders*** | | |
| Nausea | 23 | 0 |
| Diarrhea | 17 | 2[a] |
| Abdominal pain[e] | 14 | 3 |
| Vomiting | 13 | 0 |
| Constipation | 12 | 0 |
| ***Musculoskeletal and Connective Tissue Disorders*** | | |
| Musculoskeletal pain[f] | 23 | 1[a] |
| ***Metabolism and Nutrition Disorders*** | | |
| Decreased appetite | 15 | 0 |
| ***Respiratory Disorders*** | | |
| Dyspnea[g] | 13 | 1[a] |
| Pleural effusion | 10 | 2[a] |
| ***Infection*** | | |
| Upper respiratory tract infection[h] | 10 | <1[a] |

[a] No Grade 4 adverse reactions occurred
[b] Fatigue includes fatigue, asthenia, and lethargy
[c] Edema includes edema, face edema, generalized edema, peripheral edema, ascites, fluid overload, peripheral swelling, swelling, and swelling face
[d] Rash includes rash, rash erythematous, rash maculopapular, rash pruritic, rash pustular, erythema, generalized erythema, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative generalized, and palmar-plantar erythrodysesthesia syndrome
[e] Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper
[f] Musculoskeletal pain includes musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, back pain, limb discomfort, myalgia, neck pain, non-cardiac chest pain, and pain in extremity
[g] Dyspnea includes dyspnea, and dyspnea exertional
[h] Upper respiratory tract infection includes upper respiratory tract infection, upper respiratory tract congestion, nasopharyngitis, rhinitis, rhinovirus infection, and sinusitis

Clinically relevant adverse reactions in <10% of patients (all grades) who received ZYNLONTA included:

- Blood and lymphatic system disorders: Febrile neutropenia (3%)
- Cardiac disorders: Pericardial effusion (3%)
- Infections: Pneumonia[a] (5%), sepsis[b] (2%)
- Skin and subcutaneous disorders: Hyperpigmentation (4%)
- General disorders: Infusion site extravasation (<1%)

[a] Pneumonia includes pneumonia and lung infection
[b] Sepsis includes sepsis, escherichia sepsis, and septic shock

*Selected Other Adverse Reactions*

- Inflammatory-related conditions were reported in 3% of patients in LOTIS-2, including pericarditis, pneumonitis, pleuritis, and dermatitis.

Table 2 summarizes the laboratory abnormalities in LOTIS-2.

**Table 2: Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients with Relapsed or Refractory DLBCL Who Received ZYNLONTA in LOTIS-2**

| Laboratory Abnormality | ZYNLONTA[a] | |
|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) |
| **Hematologic** | | |
| Platelets decreased | 58 | 17 |
| Neutrophils decreased | 52 | 30 |
| Hemoglobin decreased | 51 | 10[b] |
| **Chemistry** | | |
| GGT increased | 57 | 21 |
| Glucose increased | 48 | 8 |
| AST increased | 41 | <1[b] |
| Albumin decreased | 37 | <1[b] |
| ALT increased | 34 | 3 |

[a] The denominator used to calculate the rate varied from 143 to 145 based on the number of patients with a baseline value and at least one post-treatment value

[b] No Grade 4 adverse reactions occurred

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ZYNLONTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Skin and Subcutaneous Tissue Disorders:** telangiectasia, blister, rash vesicular

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

Risk Summary

Based on its mechanism of action, ZYNLONTA can cause embryo-fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (SG3199) and affects actively dividing cells *[see Clinical Pharmacology (12.1)* and *Nonclinical Toxicology (13.1)]*. There are no available data on the use of ZYNLONTA in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with ZYNLONTA. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

*Animal Data*

Animal reproductive or developmental toxicity studies were not conducted with loncastuximab tesirine. The cytotoxic component of ZYNLONTA, SG3199, crosslinks DNA, is genotoxic, and is toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.

## 8.2 Lactation

Risk Summary

There is no data on the presence of loncastuximab tesirine or SG3199 in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with ZYNLONTA and for 3 months after the last dose.

## 8.3 Females and Males of Reproductive Potential

ZYNLONTA can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating ZYNLONTA.

Contraception

*Females*

Advise women of reproductive potential to use effective contraception during treatment and for 10 months after the last dose.

*Males*

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during the treatment with ZYNLONTA and for 7 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

*Males*

Based on the results from animal studies, ZYNLONTA may impair fertility in males. The effects were not reversible in male cynomolgus monkeys during the 12-week drug-free period *[see Nonclinical Toxicology (13.1)]*.

### 8.4 Pediatric Use

Safety and effectiveness of ZYNLONTA in pediatric patients have not been established.

### 8.5 Geriatric Use

Of the 145 patients with large B-cell lymphoma who received ZYNLONTA in clinical trials, 55% were 65 years of age and older, while 14% were 75 years of age and older *[see Clinical Studies (14.1)]*. No overall differences in safety or effectiveness were observed between these patients and younger patients.

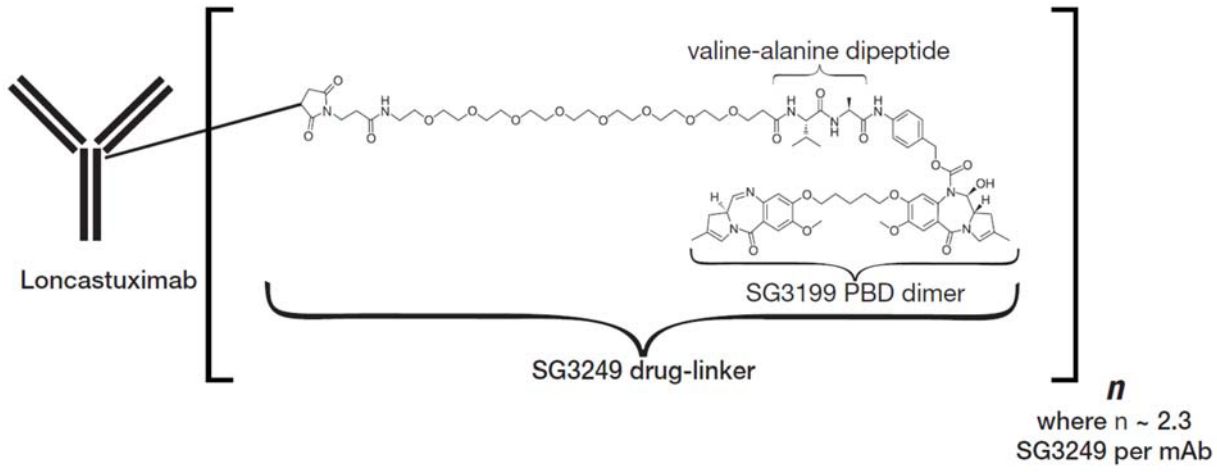
### 8.6 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN or total bilirubin > 1 to 1.5 × ULN and any AST). Monitor patients with mild hepatic impairment for potential increased incidence of adverse reactions and modify the ZYNLONTA dosage in the event of adverse reactions *[see Dosage and Administration (2.3)]*.

ZYNLONTA has not been studied in patients with moderate or severe hepatic impairment (total bilirubin > 1.5 × ULN and any AST) *[see Clinical Pharmacology (12.3)]*.

## 11 DESCRIPTION

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, through a protease-cleavable valine-alanine linker. SG3199 attached to the linker is designated as SG3249, also known as tesirine. Loncastuximab is produced in Chinese hamster ovary cells by recombinant DNA technology



Loncastuximab tesirine has an approximate molecular weight of 151 kDa. An average of 2.3 molecules of SG3249 are attached to each antibody molecule. Loncastuximab tesirine is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis.

ZYNLONTA (loncastuximab tesirine) for injection is supplied as a sterile, white to off- white, preservative-free, lyophilized powder, which has a cake-like appearance, for intravenous infusion after reconstitution and dilution. Each single-dose vial delivers 10 mg of loncastuximab tesirine, L-histidine (2.8 mg), L-histidine monohydrochloride (4.6 mg), polysorbate 20 (0.4 mg), and sucrose (119.8 mg). After reconstitution with 2.2 mL Sterile Water for Injection, USP, the final concentration is 5 mg/mL with a pH of approximately 6.0.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Loncastuximab tesirine is an antibody-drug conjugate (ADC) targeting CD19. The monoclonal IgG1 kappa antibody component binds to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. The small molecule component is SG3199, a PBD dimer and alkylating agent.

Upon binding to CD19, loncastuximab tesirine is internalized followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell death. Loncastuximab tesirine had anticancer activity in animal models of lymphoma.

### 12.2 Pharmacodynamics

Higher loncastuximab tesirine exposure in Cycle 1 was associated with higher incidence of some Grade ≥2 adverse reactions, including skin and nail reactions, liver function test abnormalities and increased gamma-glutamyltransferase. Lower loncastuximab tesirine

exposure in Cycle 1 was associated with lower efficacy over the dose range of 0.015-0.2 mg/kg (0.1 to 1.33 times the maximum recommended dose).

Cardiac Electrophysiology

At the maximum recommended therapeutic dose of 0.15 mg/kg during Cycle 1 and Cycle 2, loncastuximab tesirine does not cause large mean increases (i.e., >20 msec) in the QTc interval.

### 12.3 Pharmacokinetics

The exposure of loncastuximab tesirine at the approved recommended dosage in Cycle 2 and at steady state is shown in Table 3. Loncastuximab tesirine steady state $C_{max}$ was 28.2% lower than the $C_{max}$ after the first dose. The time to reach steady state was 105 days.

**Table 3: Loncastuximab Tesirine Exposure Parameters[a]**

| Time | $C_{max}$ (ng/mL) | $AUC_{tau}$ (ng • day/mL) |
|---|---|---|
| **Cycle 2** | 2,911 (35.3%) | 21,665 (54.1%) |
| **Steady state** | 1,776 (32.1%) | 16,882 (38.2%) |

$C_{max}$ = Maximum observed serum concentration; $AUC_{tau}$ = Area under curve over the dosing interval

[a] Data presented as mean and coefficient of variation (CV %)

Distribution
The mean (CV%) of loncastuximab tesirine volume of distribution was 7.11 (26.6%) L.

Elimination
The mean (CV%) of loncastuximab tesirine clearance decreased with time from 0.499 L/day (89.3%) after a single dose to 0.275 L/day (38.2%) at steady state. The mean (standard deviation) half-life of loncastuximab tesirine was 20.8 (7.06) days at steady state.

*Metabolism*
The monoclonal antibody portion of loncastuximab tesirine is expected to be metabolized into small peptides by catabolic pathways. The small molecule cytotoxin, SG3199, is metabolized by CYP3A4/5 in vitro.

*Excretion*
The major excretion pathways of SG3199 have not been studied in humans. SG3199 is expected to be minimally renally excreted.

Specific Populations
No clinically significant differences in the pharmacokinetics of loncastuximab tesirine were observed based on age (20-94 years), sex, race (White vs. Black), body weight (42.1 to 160.5 kg), ECOG status (0 to 2) or mild to moderate renal impairment (CLcr 30 to <90 mL/min using the Cockcroft-Gault equation).

The effect of severe renal impairment (CLcr 15 to 29 mL/min), and end-stage renal disease with or without hemodialysis on loncastuximab tesirine pharmacokinetics is unknown.

*Patients with Hepatic Impairment*
Mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin >1 to 1.5 × ULN and any AST) may increase the exposure of unconjugated SG3199, however there was no clinically significant effect on loncastuximab tesirine pharmacokinetics. The effect of moderate (total bilirubin >1.5 to ≤3 × ULN and any AST) or severe (total bilirubin >3 ULN and any AST) hepatic impairment on loncastuximab tesirine pharmacokinetics is unknown.

Drug Interaction Studies

*In Vitro Studies*

*Cytochrome P450 (CYP) Enzymes:* SG3199 does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 at clinically relevant unconjugated SG3199 concentrations.

*Transporter Systems:* SG3199 is a substrate of P-glycoprotein (P-gp), but not a substrate of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP)1B1, or organic cation transporter (OCT)1.

SG3199 does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, OCT2, OCT1, multi-antimicrobial extrusion protein (MATE)1, MATE2-K, or bile salt export pump (BSEP) at clinically relevant unconjugated SG3199 concentrations.

clinically significant effect on loncastuximab tesirine pharmacokinetics. The effect of moderate (total bilirubin >1.5 to ≤3 × ULN and any AST) or severe (total bilirubin >3 ULN and any AST) hepatic impairment on loncastuximab tesirine pharmacokinetics is unknown.

Drug Interaction Studies

*In Vitro Studies*

*Cytochrome P450 (CYP) Enzymes:* SG3199 does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 at clinically relevant unconjugated SG3199 concentrations.

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### 12.6 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies to loncastuximab tesirine in other studies or to other products may be misleading.

In LOTIS-2, 0 of 134 patients tested positive for antibodies against loncastuximab tesirine after treatment. The potential effect of anti-drug antibodies to ZYNLONTA on pharmacokinetics, efficacy, or safety is unknown.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with loncastuximab tesirine or SG3199.

SG3199 was genotoxic in an in vitro micronucleus test and a chromosome aberration assay using human lymphocytes through a clastogenic mechanism. These results are consistent with the pharmacological effect of SG3199 as a covalent DNA crosslinking agent. Results of a bacterial reverse mutation assay (Ames test) were inconclusive due to cytotoxicity.

Fertility studies have not been conducted with loncastuximab tesirine. Results from repeat- dose toxicity studies with intravenous administration of loncastuximab tesirine in cynomolgus monkeys indicate the potential for impaired male reproductive function and fertility. Administration of loncastuximab tesirine to cynomolgus monkeys every 3 weeks at 0.6 mg/kg for a total of 2 doses, or every 3 weeks at 0.3 mg/kg for 13 weeks resulted in adverse findings that included decreased weight and/or size of the testes and epididymis, atrophy of the seminiferous tubules, germ cell degeneration, and/or reduced sperm content. The dose of 0.3 mg/kg in animals results in an exposure (AUC) that is approximately 3 times the exposure at the maximum recommended human dose [MRHD] of 0.15 mg/kg. Findings were not reversible at the end of the 12-week recovery period following 4 or 13 weeks of dosing.

### 13.2 Animal Toxicology and/or Pharmacology

Inflammatory-mediated toxicities associated with PBDs have been observed at low incidence in animals. In repeat-dose toxicity studies in cynomolgus monkeys, administration of loncastuximab tesirine was associated with potential inflammatory mediated-toxicities, including in the lungs and kidneys. Renal toxicity including increased kidney weights and nephropathy with variable inflammation and fibrosis that was reversible was observed inmonkeys. Black skin spots potentially related to phototoxicity were observed and were still present after the 12-week treatment-free period.

## 14 CLINICAL STUDIES

### 14.1 Relapsed or Refractory Diffuse Large B-cell Lymphoma

The efficacy of ZYNLONTA 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 excluded patients with bulky disease and active central nervous system lymphoma. Patients received ZYNLONTA 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. Race was reported in 97% of patients; of these patients, 90% were White, 3% were Black, and 2% were Asian. The diagnosis was DLBCLnot otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low-grade lymphoma) and high-grade B-cell lymphoma in7%. 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 (Table 4). The median follow- up time was 7.3 months (range 0.3 to 20.2).

**Table 4 Efficacy Results in Patients with Relapsed or Refractory DLBCL**

| **Efficacy Parameter** | **ZYNLONTA N = 145** |
|---|---|
| **Overall response rate by IRC**[a]**,** (95% CI) | 48.3% (39.9, 56.7) |
| Complete response rate (95% CI) | 24.1% (17.4, 31.9) |
| Partial response rate (95% CI) | 24.1% (17.4, 31.9) |
| **Duration of overall response**[b] | **N = 70** |

| | |
|---|---|
| Median (95% CI), months | 10.3 (6.9, NE) |

CI = confidence interval, NE = not estimable
[a] IRC = independent review committee using Lugano 2014 criteria
[b] Of 70 patients with objective response, 25 (36%) were censored prior to 3 months. Twenty-six percent of responders had a duration of response ≥6 months

The median time to response was 1.3 months (range 1.1 to 8.1).

## 15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

## 16 NATURE AND CONTENTS OF THE CONTAINER

10 mg vial (Type 1 glass) coated rubber lyophilization stopper and tamper-evident aluminium sealed with an attached plastic button (overseal).

Pack sizes of 1 vial.

## 17 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ZYNLONTA (loncastuximab tesirine) for injection is a sterile, preservative-free, white to off-white lyophilized powder, which has a cake-like appearance, supplied in a single-dose vial for reconstitution and further dilution. Each carton (NDC 79952-110-01) contains one 10 mg single-dose vial.

Storage and Handling

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.

Special Handling

ZYNLONTA is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Any unused drug product or waste material should be disposed in accordance with local requirements.

## 18 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Effusion and Edema: Advise patients to contact their healthcare provider if they experience swelling, weight gain, shortness of breath, or difficult, labored breathing *[see Warnings and Precautions (5.1)]*.
- Myelosuppression: Advise patients to immediately contact their healthcare provider for a fever of 100.4°F (38°C) or greater, or signs or symptoms of bruising or bleeding. Advise patients of the need for periodic monitoring of blood counts *[see Warnings and Precautions (5.2)]*.
- Infections: Advise patients to contact their healthcare provider for signs or symptoms of infection, including fever, chills, weakness and/or difficulty breathing *[see Warnings and Precautions (5.3)]*.
- Cutaneous Reactions: Advise patients that skin reaction or rash can occur. Patients should be directed to minimize or avoid exposure to direct natural or artificial sunlight, including sunlight

exposure through glass windows. Patients should be instructed to protect skin from exposure to sunlight by wearing sun-protective clothing and/or the use of sunscreen products *[see Warnings and Precautions (5.4)]*.

- Embryo-Fetal Toxicity:
  - Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with ZYNLONTA *[see Use in Specific Populations (8.1)]*.
  - Advise women of reproductive potential to use effective contraception during treatment with ZYNLONTA and for 10 months after the last dose.
  - Advise male patients with female partners of reproductive potential, to use effective contraception during treatment with ZYNLONTA and for 7 months after the last dose *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.1), (8.3)]*.
- Lactation: Advise women not to breastfeed during treatment with ZYNLONTA and for 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

**Manufactured by**:

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