

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

<sup>a</sup> 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.<sup>1</sup>

### 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)  $\geq 35$  kg/m<sup>2</sup>, 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

- 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<sup>®</sup> (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  $\geq 3$  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),  $\leq 2.5$  times upper limit of normal (ULN), total bilirubin  $\leq 1.5$  times ULN, and creatinine clearance  $\geq 60$  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  $\geq 2\%$  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  $\geq 2\%$  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  $\geq 4\%$  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  $\geq 5\%$  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 (%)
<b><i>General Disorders and Administration Site Conditions</i></b>		
Fatigue <sup>b</sup>	38	1 <sup>a</sup>
Edema <sup>c</sup>	28	3 <sup>a</sup>
<b><i>Skin and Subcutaneous Tissue Disorders</i></b>		
Rash <sup>d</sup>	30	2 <sup>a</sup>
Pruritus	12	0
Photosensitivity reaction	10	2 <sup>a</sup>
<b><i>Gastrointestinal Disorders</i></b>		
Nausea	23	0
Diarrhea	17	2 <sup>a</sup>
Abdominal pain <sup>e</sup>	14	3
Vomiting	13	0
Constipation	12	0
<b><i>Musculoskeletal and Connective Tissue Disorders</i></b>		
Musculoskeletal pain <sup>f</sup>	23	1 <sup>a</sup>
<b><i>Metabolism and Nutrition Disorders</i></b>		
Decreased appetite	15	0
<b><i>Respiratory Disorders</i></b>		
Dyspnea <sup>g</sup>	13	1 <sup>a</sup>
Pleural effusion	10	2 <sup>a</sup>
<b><i>Infection</i></b>		
Upper respiratory tract infection <sup>h</sup>	10	<1 <sup>a</sup>

<sup>a</sup> No Grade 4 adverse reactions occurred

<sup>b</sup> Fatigue includes fatigue, asthenia, and lethargy

<sup>c</sup> Edema includes edema, face edema, generalized edema, peripheral edema, ascites, fluid overload, peripheral swelling, swelling, and swelling face

<sup>d</sup> 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

<sup>e</sup> Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower, and abdominal pain upper

<sup>f</sup> 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

<sup>g</sup> Dyspnea includes dyspnea, and dyspnea exertional

<sup>h</sup> 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<sup>a</sup> (5%), sepsis<sup>b</sup> (2%)
- Skin and subcutaneous disorders: Hyperpigmentation (4%)
- General disorders: Infusion site extravasation (<1%)

<sup>a</sup> Pneumonia includes pneumonia and lung infection

<sup>b</sup> 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 ( $\geq 10\%$ ) That Worsened from Baseline in Patients with Relapsed or Refractory DLBCL Who Received ZYNLONTA in LOTIS-2**

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

<sup>a</sup> 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

<sup>b</sup> 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.

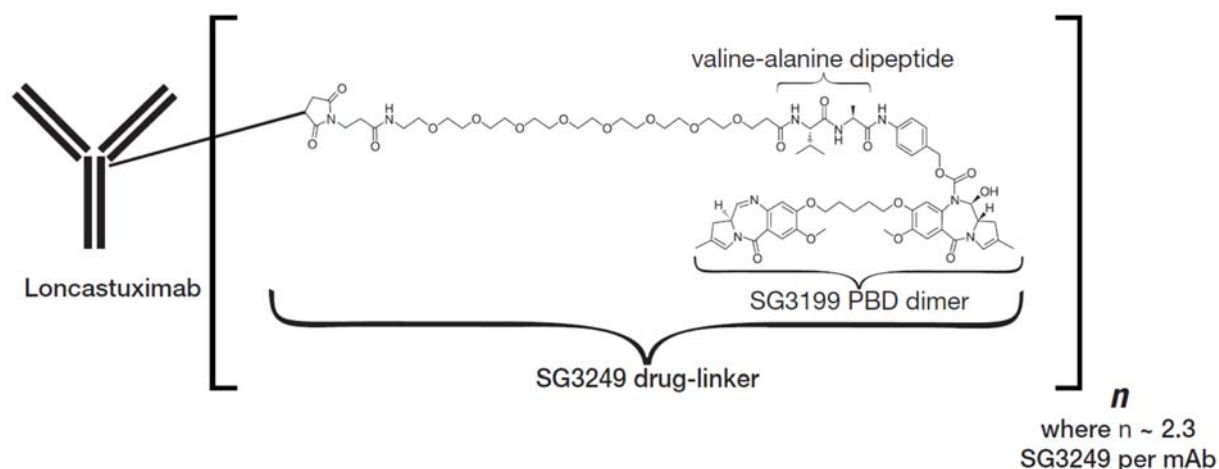
## 8.6 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin  $\leq$  upper limit of normal [ULN] and aspartate aminotransferase (AST)  $>$  ULN or total bilirubin  $>$  1 to  $1.5 \times$  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  $>$   $1.5 \times$  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  $\geq 2$  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<sup>a</sup>**

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

<sup>a</sup> 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  $\leq$  ULN and AST  $>$  ULN, or total bilirubin  $>1$  to  $1.5 \times$  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  $\leq 3 \times$  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.

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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 in monkeys. 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 DLBCL not otherwise specified (NOS) in 88% (including 20% with DLBCL arising from low-grade lymphoma) and high-grade B-cell lymphoma in 7%. 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**

<b>Efficacy Parameter</b>	<b>ZYNLONTA N = 145</b>
<b>Overall response rate by IRC<sup>a</sup>, (95% CI)</b>	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)
<b>Duration of overall response<sup>b</sup></b>	<b>N = 70</b>

Median (95% CI), months	10.3 (6.9, NE)
CI = confidence interval, NE = not estimable <sup>a</sup> IRC = independent review committee using Lugano 2014 criteria <sup>b</sup> Of 70 patients with objective response, 25 (36%) were censored prior to 3 months. Twenty-six percent of responders had a duration of response $\geq$ 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.<sup>1</sup>

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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