Adverse Reactions Timing and Management from the LOTIS-2 Clinical Trial

Zynlonta®
loncastuximab tesirine-lpyl
for injection, for intravenous use • 10mg

INDICATION AND USAGE

ZYNLONTA® is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNINGS AND PRECAUTIONS

Effusion and Edema: Monitor for the development of pleural effusion, pericardial effusion, ascites, peripheral edema, and general edema. Consider diagnostic imaging when symptoms develop or worsen.

Myelosuppression: Monitor blood cell counts. Withhold, reduce, or discontinue ZYNLONTA® based on severity.

Infections: Monitor for infection and treat promptly.

Cutaneous Reactions: Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Dermatologic consultation should be considered.

Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.

Learn more at zynlontahcp.com

Please see additional Important Safety Information on pages 12 – 13 and accompanying full Prescribing Information

EFFUSION & EDEMA

Zynlonta® loncastuximab tesirine-lpyl for injection, for intravenous use • 10mg

PATIENTS WITH EVENTS IN THE LOTIS-2 (N=145) CLINICAL TRIAL[1,a]

		Incidence	Onset (median)	Duration[c] (median)
EFFUSION	Any Grade	11.0% (n = 16)	51.5 Days Range: 3 – 203	19.5 Days Range: 4 – 252
	Grade ≥ 3	2.8% (n = 4)	118 Days Range: 17 – 277	20.5 Days Range: 6 – 82
EDEMA[b]	Any Grade	27.6% (n = 40)	40 Days Range: 1 – 277	50.5 Days Range: 2 – 407
	Grade ≥ 3	3.4% (n = 5)	106 Days Range: 9 – 183	5 Days Range: 3 – 112

DOSE MANAGEMENT IN THE LOTIS-2 CLINICAL TRIAL[1,a]

	Delayed	Reduced	Withdrawn
EFFUSION (Any Grade)	1.4% (n = 2)	0% (n = 0)	2.8% (n = 4)
EDEMA[b] (Any Grade)	5.5% (n = 8)	0.7% (n = 1)	2.8% (n = 4)

[a] Post-hoc analysis.

[b] Edema includes edema, face edema, generalized edema, peripheral edema, ascites, fluid overload, peripheral swelling, swelling, and swelling face.

[c] Missing end dates were imputed using the date of new anticancer therapy (NAT; for patients who received NAT) or end of study (EOS) or data cutoff date for patients who did not receive NAT for the calculation of the duration of adverse events. Partial end dates were imputed using the last month or day of a month bounded by EOS.

ADVERSE REACTION MANAGEMENT IN THE ZYNLONTA® PRESCRIBING INFORMATION

PREMEDICATION

Dexamethasone premedication should be administered to reduce the incidence and severity of PBD-related adverse reactions such as effusion/edema and liver-function test abnormalities.[2,3]

PATIENT ADVISEMENT

Advise patients to contact their healthcare provider if they experienced shortness of breath, or difficult, labored breathing.[2]

RECOMMENDED DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS IN THE ZYNLONTA® PRESCRIBING INFORMATION

PLEURAL EFFUSION

For Grade 2 or higher pleural effusions (symptomatic, intervention indicated [e.g., diuretics or therapeutic thoracentesis]), withhold ZYNLONTA® until the toxicity resolves to ≤ Grade 1 (asymptomatic, clinical or diagnostic observation only; intervention not indicated). [2,5]

PERICARDIAL EFFUSION

For Grade 2 or higher pericardial effusions (asymptomatic effusion size small to moderate), withhold ZYNLONTA® until the toxicity resolves to ≤ Grade 1.[2,5]

EDEMA

For Grade 2 or higher edema (edema interfering with ADLs; oral therapy initiated), withhold ZYNLONTA® until the toxicity resolves to ≤ Grade 1 (noted on exam; 1+ pitting edema).[2,5]

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.[2]

ADVERSE REACTION MANAGEMENT IN THE LOTIS-2 CLINICAL TRIAL

MANAGEMENT

For patients with weight gain greater than 1 kg from Cycle 1 Day 1 and/or new or worsening edema or pleural effusion in LOTIS-2, spironolactone at standard doses (titrated as clinically indicated) was administered. Additional diuretic support was added for further increase in weight, edema, or pleural effusion.[4]

PATIENT ADVISEMENT

Patients were advised to monitor their weight on a daily basis, at around the same time (preferably in the morning), and to notify their healthcare provider if they gained >1 kg (2.2 pounds) over baseline.[4]

ADL, activities of daily living; PBD, pyrrolobenzodiazepine.

MYELOSUPPRESSION

Zynlonta® loncastuximab tesirine-lpyl for injection, for intravenous use • 10mg

PATIENTS WITH EVENTS IN THE LOTIS-2 (N=145) CLINICAL TRIAL[1,a]

		Incidence[b]	Onset[b] (median)	Duration[b,c] (median)
NEUTROPENIA	Any Grade	53.8% (n = 78)	22 Days Range: 1 – 232	22 Days Range: 1 – 133
	Grade ≥ 3	29.7% (n = 43)	36 Days Range: 6 – 232	10 Days Range: 1 – 110
THROMBOCYTOPENIA	Any Grade	66.2% (n = 96)	15 Days Range: 1 – 281	31.5 Days Range: 5 – 368
	Grade ≥ 3	17.9% (n = 26)	29 Days Range: 9 – 281	23 Days Range: 1 – 195
ANEMIA	Any Grade	93.8% (n = 136)	17 Days Range: 1 – 84	42 Days Range: 2 – 525
	Grade ≥ 3	11.0% (n = 16)	22 Days Range: 6 – 92	4 Days Range: 1 – 103

DOSE MANAGEMENT IN THE LOTIS-2 CLINICAL TRIAL[1,a]

	Delayed[b]	Reduced[b]	Withdrawn[b]
NEUTROPENIA (Any Grade)	12.4% (n = 18)	0% (n = 0)	0.7% (n = 1)
THROMBOCYTOPENIA (Any Grade)	9.0% (n = 13)	0.7% (n = 1)	1.4% (n = 2)
ANEMIA (Any Grade)	2.8% (n = 4)	0% (n = 0)	0% (n = 0)

[a] Post-hoc analysis.

[b] Incidence of hematologic abnormalities were based on laboratory reporting, while dose modifications, time to onset, and duration were based on adverse event reporting.

[c] Missing end dates were imputed using the date of new anticancer therapy (NAT; for patients who received NAT) or end of study (EOS) or data cutoff date for patients who did not receive NAT for the calculation of the duration of adverse events. Partial end dates were imputed using the last month or day of a month bounded by EOS.

ADVERSE REACTION MANAGEMENT IN THE ZYNLONTA® PRESCRIBING INFORMATION

PREMEDICATION

Consider prophylactic granulocyte colony-stimulating factor administration as applicable.[2]

PATIENT ADVISEMENT

Advise patients to contact their healthcare provider for a fever of 38°C (100.4°F) or greater or signs or symptoms of bruising or bleeding.[2]

Advise patients of the need for periodic monitoring of blood counts.[2]

RECOMMENDED DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS IN THE ZYNLONTA® PRESCRIBING INFORMATION

NEUTROPENIA

For Grade 3 or higher neutropenia (ANC less than 1 x 10^9/L), withhold ZYNLONTA® until ANC returns to 1 x 10^9/L or higher.[2,5]

THROMBOCYTOPENIA

For Grade 3 or higher thrombocytopenia (platelet count less than 50,000/mcL), withhold ZYNLONTA® until platelet count returns to 50,000/mcL or higher.[2,5]

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.[2]

ADVERSE REACTION MANAGEMENT IN THE LOTIS-2 CLINICAL TRIAL

MANAGEMENT

In LOTIS-2, patients were eligible for treatment with ZYNLONTA® if baseline ANC ≥ 1 × 10^9/L (without growth factors for at least 72 hours) and baseline platelet count ≥ 50,000/mcL (without transfusion in the prior 7 days).[4]

Growth factors for neutropenia were administered to 29.0% (n = 42) of patients at the discretion of the investigator and aligned with protocols at the clinical site.[1]

- Growth factors for neutropenia were administered prophylactically to 13.8% (n = 20) of patients and as treatment to 22.8% (n = 33) of patients.[1]

ANC, absolute neutrophil count.

INFECTIONS

Zynlonta® loncastuximab tesirine-lpyl for injection, for intravenous use • 10mg

PATIENTS WITH EVENTS IN THE LOTIS-2 (N=145) CLINICAL TRIAL[1,a]

		Incidence	Onset (median)	Duration[c] (median)
INFECTIONS[b]	Any Grade	33.1% (n = 48)	30 Days Range: 1 – 197	20 Days Range: 2 – 436
	Grade ≥ 3	9.0% (n = 13)	36 Days Range: 3 – 168	10 Days Range: 2 – 64

DOSE MANAGEMENT IN THE LOTIS-2 CLINICAL TRIAL[1,a]

	Delayed	Reduced	Withdrawn
INFECTIONS[b] (Any Grade)	7.6% (n = 11)	0.7% (n = 1)	1.4% (n = 2)

[a] Post-hoc analysis.

[b] Infections, including upper respiratory tract infections (i.e., upper respiratory tract infection, upper respiratory tract congestion, nasopharyngitis, rhinitis, rhinovirus infection, and sinusitis).

[c] Missing end dates were imputed using the date of new anticancer therapy (NAT; for patients who received NAT) or end of study (EOS) or data cutoff date for patients who did not receive NAT for the calculation of the duration of adverse events. Partial end dates were imputed using the last month or day of a month bounded by EOS.

ADVERSE REACTION MANAGEMENT IN THE ZYNLONTA® PRESCRIBING INFORMATION

PATIENT ADVISEMENT

Advise patients to contact their healthcare provider for signs or symptoms of infection, including fever, chills, weakness and/or difficulty breathing.[2]

RECOMMENDED DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS IN THE ZYNLONTA® PRESCRIBING INFORMATION

INFECTION

For Grade 3 or higher infection, withhold ZYNLONTA® until the infection resolves to ≤ Grade 1.[2]

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.[2]

CUTANEOUS REACTIONS

Zynlonta® loncastuximab tesirine-lpyl for injection, for intravenous use • 10mg

PATIENTS WITH EVENTS IN THE LOTIS-2 (N=145) CLINICAL TRIAL[1,a]

		Incidence	Onset (median)	Duration[c] (median)
PHOTOSENSITIVITY CUTANEOUS REACTION[b]	Any Grade	10.3% (n = 15)	37 Days Range: 13 – 150	119 Days Range: 35 – 288
	Grade ≥ 3	2.1% (n = 3)	35 Days Range: 32 – 101	38 Days Range: 12 – 200
NON-PHOTOSENSITIVITY CUTANEOUS REACTION[b]	Any Grade	30.3% (n = 44)	30 Days Range: 1 – 104	85.5 Days Range: 1 – 360
	Grade ≥ 3	2.1% (n = 3)	56 Days Range: 8 – 89	7 Days Range: 2 – 10

DOSE MANAGEMENT IN THE LOTIS-2 CLINICAL TRIAL[1,a]

	Delayed	Reduced	Withdrawn
PHOTOSENSITIVITY CUTANEOUS REACTION[b] (Any Grade)	2.8% (n = 4)	0% (n = 0)	0.7% (n = 1)
NON-PHOTOSENSITIVITY CUTANEOUS REACTION[b] (Any Grade)	4.8% (n = 7)	0% (n = 0)	0% (n = 0)

[a] Post-hoc analysis.

[b] Cutaneous reactions include rash (i.e., 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), pruritus, and photosensitivity reaction.

[c] Missing end dates were imputed using the date of new anticancer therapy (NAT; for patients who received NAT) or end of study (EOS) or data cutoff date for patients who did not receive NAT for the calculation of the duration of adverse events. Partial end dates were imputed using the last month or day of a month bounded by EOS.

ADVERSE REACTION MANAGEMENT IN THE ZYNLONTA® PRESCRIBING INFORMATION

PATIENT ADVISEMENT

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.[2]

If a skin reaction or rash develops, dermatologic consultation should be considered.[2]

RECOMMENDED DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS IN THE ZYNLONTA® PRESCRIBING INFORMATION

PHOTOSENSITIVITY

For Grade 3 or higher photosensitivity (erythema covering > 30% BSA and erythema with blistering, oral corticosteroid therapy indicated, pain control indicated), withhold ZYNLONTA® until the toxicity resolves to ≤ Grade 1 (painless erythema and erythema covering < 10% BSA).[2,5]

RASH (MACULOPAPULAR)

For Grade 3 or higher rash (macules/papules covering > 30% BSA with moderate or severe symptoms, limiting self care ADL), withhold ZYNLONTA® until the toxicity resolves to ≤ Grade 1 (macules/papules covering < 10% BSA with or without symptoms).[2,5]

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.[2]

ADVERSE REACTION MANAGEMENT IN THE LOTIS-2 CLINICAL TRIAL

PATIENT ADVISEMENT

Skin rash was reported in the Phase 1 study (ADCT-402-101) in areas at risk for sun exposure. It was therefore recommended that precautions were taken to avoid prolonged exposure of skin to sunlight.[4]

ADL, activities of daily living; BSA, body surface area.

GAMMA-GLUTAMYLTRANSFERASE (GGT) ELEVATION

Zynlonta® loncastuximab tesirine-lpyl for injection, for intravenous use • 10mg

PATIENTS WITH EVENTS IN THE LOTIS-2 (N=145) CLINICAL TRIAL[1,a]

		Incidence[b]	Onset[b] (median)	Duration[b,c] (median)
GGT ELEVATION	Any Grade	72.4% (n = 105)	36 Days Range: 1 – 245	70 Days Range: 6 – 526
	Grade ≥ 3	22.1% (n = 32)	54.5 Days Range: 8 – 136	49 Days Range: 3 – 335

DOSE MANAGEMENT IN THE LOTIS-2 CLINICAL TRIAL[1]

	Delayed[b]	Reduced[b]	Withdrawn[b]
GGT ELEVATION (Any Grade)	20.7% (n = 30)	4.1% (n = 6)	10.3% (n = 15)

[a] Post-hoc analysis.

[b] Incidence of liver enzyme abnormalities were based on laboratory reporting, while dose modifications, time to onset, and duration were based on adverse event reporting.

[c] Missing end dates were imputed using the date of new anticancer therapy (NAT; for patients who received NAT) or end of study (EOS) or data cutoff date for patients who did not receive NAT for the calculation of the duration of adverse events. Partial end dates were imputed using the last month or day of a month bounded by EOS.

ADVERSE REACTION MANAGEMENT IN THE ZYNLONTA® PRESCRIBING INFORMATION

PREMEDICATION

Dexamethasone premedication should be administered to reduce the incidence and severity of PBD-related adverse reactions such as edema/effusion and liver-function test abnormalities.[2,3]

RECOMMENDED DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS IN THE ZYNLONTA® PRESCRIBING INFORMATION

GGT ELEVATION

For Grade 3 or higher GGT elevation (> 5.0 - 20.0 x ULN if baseline was normal; 5.0 - 20.0 x baseline if baseline was abnormal), withhold ZYNLONTA® until the toxicity resolves to ≤ Grade 1 (> ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal).[2,5]

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.[2]

PBD, pyrrolobenzodiazepine; ULN, upper limit of normal.

IMPORTANT SAFETY INFORMATION

Zynlonta® loncastuximab tesirine-lpyl
for injection, for intravenous use • 10mg

EFFUSION & 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%.

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.

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%.

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.

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.

Monitor for any new or worsening signs or symptoms consistent with infection. For Grade 3 or 4 infection, withhold ZYNLONTA® until infection has resolved.

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.

Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Withhold ZYNLONTA® for severe (Grade 3) cutaneous reactions until resolution. 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.

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.

ADVERSE REACTIONS

In a pooled safety population of 215 patients (Phase 1 and LOTIS-2), 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.

In LOTIS-2, 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.

DOSAGE MODIFICATIONS AND DELAYS

Recommended Dosage Modifications for Adverse Reactions

For any Grade 3 or greater nonhematologic toxicity, ZYNLONTA® should be held until the toxicity resolves to Grade 1 or less. For neutropenia: if absolute neutrophil count is <1 x 10^9/L, withhold ZYNLONTA® until the neutrophil count returns to 1 x 10^9/L or higher. For thrombocytopenia: if platelet count is <50,000/mcL, withhold ZYNLONTA® until the platelet count returns to 50,000/mcL or higher. For Grade 2 or greater edema or effusion, ZYNLONTA® should be held until the toxicity resolves to Grade 1 or less.

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 (C2D1), the patient should receive the dose of 0.075 mg/kg for Cycle 3.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to ADC Therapeutics at 1-855-690-0340.

REFERENCES

1. Data on File. ADC Therapeutics SA. 06Apr2020 data cutoff.
2. ZYNLONTA® [package insert]. Murray Hill, NJ. ADC Therapeutics SA; October 2022.
3. Caimi PF, et al. *Lancet Oncol*. 2021 Jun;22(6):790-800.
4. ADCT-402-201 Clinical Study Protocol. ADC Therapeutics SA.
5. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017. US Department of Health and Human Services.

Zynlonta®
loncastuximab tesirine-lpyl
for injection, for intravenous use • 10mg

ADVANCING Patient Support
Personalized assistance from ADC Therapeutics

Offers personalized assistance from ADC Therapeutics

Dedicated case managers can provide the access and reimbursement support and resources to help patients get started and stay on ZYNLONTA®.

Coverage Support

Financial Support[a]

Nursing Support

To get started and enroll your patient, visit **ADVANCINGPatientSupport.com** or contact one of our case managers at **1-855-690-0340** Monday-Friday (8AM-8PM ET)

[a]Eligibility restrictions apply.

zynlontahcp.com

THERAPEUTICS
Innovating Science. Inspiring Hope.

US-Comm-LTX-00162. October 2022

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYNLONTA safely and effectively.

See full prescribing information for ZYNLONTA.

ZYNLONTA® (loncastuximab tesirine-lpyl) for injection, for intravenous use

Initial U.S. Approval: 2021

----------INDICATIONS AND USAGE----------

ZYNLONTA is a CD19-directed antibody and alkylating agent conjugate indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma. (1)

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1)

---------- DOSAGE AND ADMINISTRATION----------

- ZYNLONTA is an intravenous infusion over 30 minutes on Day 1 of each cycle (every 3 weeks). The recommended dosage is:
  - 0.15 mg/kg every 3 weeks for 2 cycles.
  - 0.075 mg/kg every 3 weeks for subsequent cycles. (2.1)
- Premedicate with dexamethasone 4 mg orally or intravenously twice daily for 3 days beginning the day before ZYNLONTA. (2.2)
- See Full Prescribing Information for instructions on preparation and administration. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 10 mg of loncastuximab tesirine-lpyl as a lyophilized powder in a single-dose vial for reconstitution and further dilution. (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Effusion and Edema: Monitor for the development of pleural effusion, pericardial effusion, ascites, peripheral edema, and general edema. Consider diagnostic imaging when symptoms develop or worsen. (5.1)
- Myelosuppression: Monitor blood cell counts. Withhold, reduce, or discontinue ZYNLONTA based on severity. (5.2)
- Infections: Monitor for infection and treat promptly. (5.3)
- Cutaneous Reactions: Monitor patients for new or worsening cutaneous reactions, including photosensitivity reactions. Dermatologic consultation should be considered. (5.4)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Most common (≥20%) adverse reactions, including laboratory abnormalities, are thrombocytopenia, increased gamma-glutamyltransferase, neutropenia, anemia, hyperglycemia, transaminase elevation, fatigue, hypoalbuminemia, rash, edema, nausea, and musculoskeletal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ADC Therapeutics at 1-855-690-0340 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYNLONTA is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.

This indication is approved under accelerated approval based on overall response rate *[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 1×10^9/L	Withhold ZYNLONTA until neutrophil counts returns to 1×10^9/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-lpyl 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-lpyl. 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-lpyl 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.

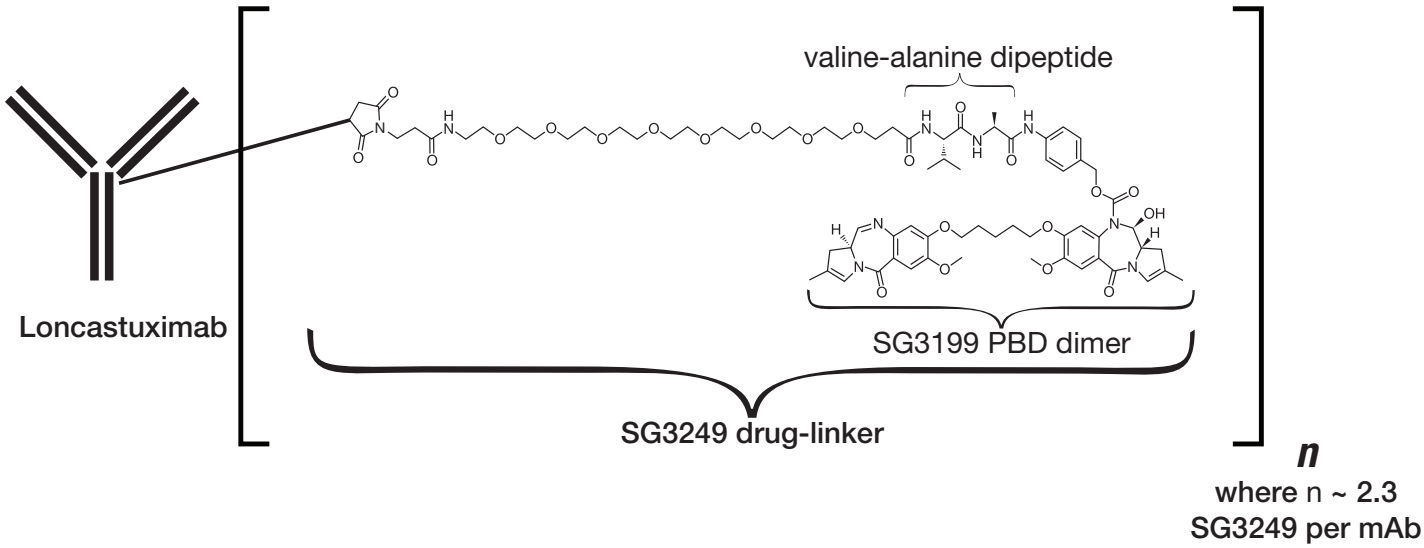
8.6 Hepatic Impairment

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-lpyl 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 tesirine-lpyl has an approximate molecular weight of 151 kDa. An average of 2.3 molecules of SG3249 are attached to each antibody molecule. Loncastuximab tesirine-lpyl 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-lpyl) 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-lpyl, 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-lpyl 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-lpyl 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-lpyl had anticancer activity in animal models of lymphoma.

12.2 Pharmacodynamics

Higher loncastuximab tesirine-lpyl 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-lpyl 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-lpyl does not cause large mean increases (i.e., >20 msec) in the QTc interval.

12.3 Pharmacokinetics

The exposure of loncastuximab tesirine-lpyl at the approved recommended dosage in Cycle 2 and at steady state is shown in Table 3. Loncastuximab tesirine-lpyl 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-lpyl 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-lpyl volume of distribution was 7.11 (26.6%) L.

Elimination

The mean (CV%) of loncastuximab tesirine-lpyl 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-lpyl was 20.8 (7.06) days at steady state.

Metabolism

The monoclonal antibody portion of loncastuximab tesirine-lpyl 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-lpyl 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-lpyl 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-lpyl 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-lpyl 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.

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-lpyl in other studies or to other products may be misleading.

In LOTIS-2, 0 of 134 patients tested positive for antibodies against loncastuximab tesirine-lpyl 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-lpyl 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-lpyl. Results from repeat-dose toxicity studies with intravenous administration of loncastuximab tesirine-lpyl in cynomolgus monkeys indicate the potential for impaired male reproductive function and fertility. Administration of loncastuximab tesirine-lpyl 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-lpyl 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

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 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ZYNLONTA (loncastuximab tesirine-lpyl) 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.

17 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:
ADC Therapeutics SA
Route de la Corniche 3B
1066 Epalinges, Switzerland
U.S. license No. 2166

Distributed by:
ADC Therapeutics America
Murray Hill, New Jersey 07974

For more information, go to www.ZYNLONTA.com or call 1-855-690-0340

PATIENT INFORMATION

ZYNLONTA® (zin lon' tah)
(loncastuximab tesirine-lpyl)
for injection, for intravenous use

What is ZYNLONTA?

ZYNLONTA is a prescription medicine used to treat adults with certain types of large B-cell lymphoma that has come back (relapsed) or that did not respond to previous treatment (refractory), who have already received two or more treatments for their cancer.

It is not known if ZYNLONTA is safe and effective in children.

Before you receive ZYNLONTA, tell your healthcare provider about all of your medical conditions, including if you:

- have an active infection or have had one recently.
- have liver problems.
- are pregnant or plan to become pregnant. ZYNLONTA can harm your unborn baby.

  Females who can become pregnant:

  - Your healthcare provider may do a pregnancy test before starting treatment with ZYNLONTA.
  - You should use effective birth control (contraception) during treatment with ZYNLONTA and for 10 months after the last dose of ZYNLONTA. Talk to your healthcare provider about effective birth control. Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with ZYNLONTA.

  Males with female partners who can become pregnant:

  - You should use effective birth control (contraception) during treatment with ZYNLONTA and for 7 months after the last dose of ZYNLONTA.
- are breastfeeding or plan to breastfeed. It is not known if ZYNLONTA passes into breast milk. Do not breastfeed during treatment with ZYNLONTA and for 3 months after the last dose of ZYNLONTA.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get new medicine.

How will I receive ZYNLONTA?

- ZYNLONTA is given to you by your healthcare provider as an intravenous (IV) infusion into your vein over 30 minutes.
- ZYNLONTA is usually given every 3 weeks.
- Your healthcare provider may give you medicine before each infusion to decrease your chance of side effects.
- Your healthcare provider may stop your treatment, delay your treatment, or change your dose of ZYNLONTA if you have severe side effects.
- Your healthcare provider should do blood tests regularly to check for side effects of ZYNLONTA.
- Your healthcare provider will decide how many treatments you need.

What should I avoid while using ZYNLONTA?

Avoid or limit your exposure to sunlight, including sunlight through glass, such as buildings or vehicle windows and artificial sunlight such as sunlamps or tanning beds. Exposure to sunlight during treatment with ZYNLONTA can cause skin reaction or rash. Use sun protection measures such as sunscreen and wear loose-fitting clothes that cover your skin while out in sunlight.

What are the possible side effects of ZYNLONTA?

ZYNLONTA may cause serious side effects, including:

- **Fluid retention.** Your body may hold too much fluid during treatment with ZYNLONTA. This can be serious. Tell your healthcare provider if you develop new or worsening swelling or puffiness, weight gain, chest pain, shortness of breath, or trouble breathing.
- **Low blood cell counts** (platelets, red blood cells, and white blood cells). Low blood cell counts are common with ZYNLONTA but can also be serious or severe. Your healthcare provider will monitor your blood counts during treatment with ZYNLONTA. Tell your healthcare provider right away if you get a fever of 100.4°F (38°C) or above, or any bruising or bleeding.
- **Infections.** Serious infections, including infections that can cause death, have happened in people treated with ZYNLONTA. Tell your healthcare provider right away if you have new or worsening signs or symptoms of infection, including:
    - fever
    - chills
    - flu-like symptoms (cough, tiredness or weakness, and body aches)
    - headache
    - breathing problems
    - cuts or scrapes that are red, warm, swollen or painful
- **Skin Reactions.** Serious skin reactions have happened in people treated with ZYNLONTA. Tell your healthcare provider if you get new or worsening skin reactions, including sensitivity to sunlight, skin rash, peeling, redness or irritation. You may burn more easily or get severe sunburns. See **"What should I avoid while receiving ZYNLONTA?"**

The most common side effects of ZYNLONTA include:

- feeling tired or weak
- skin rash
- swelling
- nausea
- muscle or joint pain
- increase in blood sugar (hyperglycemia)
- changes in certain blood or laboratory tests

ZYNLONTA may cause fertility problems in males which may affect your ability to father children. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of ZYNLONTA. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ZYNLONTA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about ZYNLONTA that is written for healthcare professionals.

What are the ingredients in ZYNLONTA?

Active ingredient: loncastuximab tesirine-lpyl

Inactive ingredients: L-histidine, L-histidine monohydrochloride, polysorbate 20, and sucrose.

Manufactured by: ADC Therapeutics SA, Route de la Corniche 3B, 1066 Epalinges, Switzerland
U.S. license number 2166
Distributed by: ADC Therapeutics America, Murray Hill, New Jersey 07974

ZYNLONTA is a registered trademark of ADC Therapeutics SA

For more information, go to www.ZYNLONTA.com or call 1-855-690-0340

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: OCT 2022

US-Comm-LTX-00170 October 2022