Discussing ZYNLONTA With Your Patients

A conversation guide to help support patients and caregivers throughout treatment with ZYNLONTA.

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).

SELECT IMPORTANT SAFETY INFORMATION

ZYNLONTA® can cause serious adverse reactions including: effusion and edema, myelosuppression, fatal and serious infections, cutaneous reactions, and embryo-fetal toxicity.

Please see additional Important Safety Information throughout and on pages 20-21, and accompanying full Prescribing Information.

Learn more at www.zynlontahcp.com

Discussing ZYNLONTA with your patients

Getting into the mindset of people who may be in a vulnerable place

When people are prescribed ZYNLONTA, they have already been treated with 2 or more therapies for their DLBCL. These therapies either did not work or stopped working for them. At this stage in their experience, they might have difficult feelings and questions, such as:

"I feel really let down. Other treatments were working, but then the cancer came back. Even if this works at first, why should I think it will keep working?"

"I'm not feeling hopeful. If other therapies haven't worked, why would this be any different?"

These patients have relapsed or were refractory to curative options and may have lost hope.

Share with patients and caregivers the ZYNLONTA Patient Brochure

Goals for people with r/r DLBCL	How ZYNLONTA may help
Get to the root of the problem	Uses a **"find, bind, and release"** approach to target cancer cells: It first finds and binds to the cancer cells, then **releases** cancer-killing therapy
Try something different from traditional chemotherapy	Specifically targets DLBCL cancer cells, and is different from traditional chemotherapy
Try something that may work no matter what therapies they had before, or what their future therapy options may be	Was effective for many people who had past relapsed or refractory (r/r) DLBCL therapies. In the clinical trial that led to ZYNLONTA approval for use: • ZYNLONTA worked for about half of people with r/r DLBCL, including patients who had 2-7 prior therapies • 68 (of 145) patients received other anti-cancer therapy after ZYNLONTA

Throughout this guide, you'll find content designed to help support people with DLBCL and their caregivers.

It was developed based on what was heard from real people living with DLBCL.

Discussing ZYNLONTA with your patients

Who ZYNLONTA is for

ZYNLONTA was specifically studied in adults who needed their next DLBCL therapy option after trying 2 or more past therapies

ZYNLONTA is for people living with…

Relapsed DLBCL:
The cancer came back after past therapies worked

OR

Refractory DLBCL:
Therapy/therapies have not worked or no longer work

Share with patients and caregivers the ZYNLONTA study results

Please see Indication and Important Safety Information throughout and on pages 20-21, and accompanying full Prescribing Information.

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Table of contents

Throughout this guide, you will also find QR codes directing you and/or your patients to additional resources.

About ZYNLONTA

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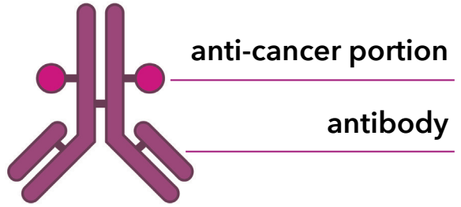
How ZYNLONTA works

An explanation of how ZYNLONTA works can help patients prior to their infusion.

ZYNLONTA

- specifically targets diffuse large B-cell lymphoma (DLBCL) cancer cells
- is different than traditional chemotherapy
- uses a "find, bind, and release" approach to target cancer cells. The antibody finds and binds to a specific area of the cancer cell called CD19, then releases cancer-killing therapy



Share with patients and caregivers information about how ZYNLONTA targets cancer

Questions to ask for meaningful conversations with your patient and their caregiver:

- Do you have any questions about how ZYNLONTA is different from past treatments?
- Do you know how targeted therapy, like ZYNLONTA, works differently from traditional chemotherapy?
- How can I help make both of you more comfortable?

Please see Indication and Important Safety Information throughout and on pages 20-21, and accompanying full Prescribing Information.

How ZYNLONTA is given

Your patient will probably want to know how, how often, and for how long they need to receive ZYNLONTA. Some key points to discuss with your patient include:

- It is recommended that your patient be prescribed the steroid dexamethasone 4 mg (orally or via IV) twice daily for 3 days, beginning the day before infusion (unless contraindicated)
  - This helps minimize the chance of side effects associated with the anti-cancer portion, including effusion, edema, and liver function test abnormalities
  - For more information about dexamethasone, **see pages 10-11**
- Your team will decide how many ZYNLONTA infusions your patient needs

Dosing schedule

ZYNLONTA is given through an intravenous (IV) infusion

It takes about 30 minutes

It is given every 3 weeks

Download the ZYNLONTA Dosing & Administration Guide

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Effusion and Edema

Serious effusion and edema occurred in patients treated with ZYNLONTA®. Monitor patients for new or worsening edema or effusions. Withhold ZYNLONTA® for Grade 2 or greater edema or effusion until the toxicity resolves.

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First infusion: Preparing your patient and their caregiver

Before your patient receives their infusion, it can be helpful to determine their overall comfort level, listen to their concerns, and answer any questions they might have. Some key areas to touch on include:

Sorting out logistics

- Set expectations about premedication, total infusion time, and appointment scheduling
- Ensure transportation to and from the infusion clinic has been planned

Ensuring comfort on infusion day

- Make suggestions for what to do during the infusion, with considerations for both your patient and their caregiver. For example:
  - Your patient might want to bring something to read or make a playlist to listen to
  - Caregivers might want to run local errands or take some time to walk in a nearby park
- Suggest they bring any comfort items (like a back pillow or blanket)
- Let your patient know what clothing is best to wear for IV infusion administration

Informing on potential side effects

- Discuss potential side effects and general tips to help them before, during, and after the infusion

Brief them on which side effects are most serious **(refer to page 19 for additional information about possible side effects)**, and when to call the office or go to the ER

- Reinforce the importance of wearing sunblock and avoiding direct and artificial sunlight throughout treatment

Please see Indication and Important Safety Information throughout and on pages 20-21, and accompanying full Prescribing Information.

Questions to ask for meaningful conversations with your patient and their caregiver:

- How do you feel about your new treatment plan?
- When you're feeling up to it, what do you want to do on a day-to-day basis?
- What goals would you like to reach during time off treatment?
- Are there any special events you're looking forward to?
- Who do you most enjoy spending time with?

Share with patients and caregivers frequently asked questions about ZYNLONTA

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Myelosuppression

Treatment with ZYNLONTA® can cause serious or severe myelosuppression, including neutropenia, thrombocytopenia, and anemia. Monitor complete blood counts throughout treatment. Cytopenias may require interruption, dose reduction, or discontinuation of ZYNLONTA®.

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About premedication

Some patients may be prescribed the steroid dexamethasone 4 mg (orally or via IV) to lower the chance of side effects. Be sure to bring this up while helping your patient prepare.

If given orally, please ensure they understand the steroid needs to be taken:

2 times a day

for 3 days

starting the day before infusion(s)

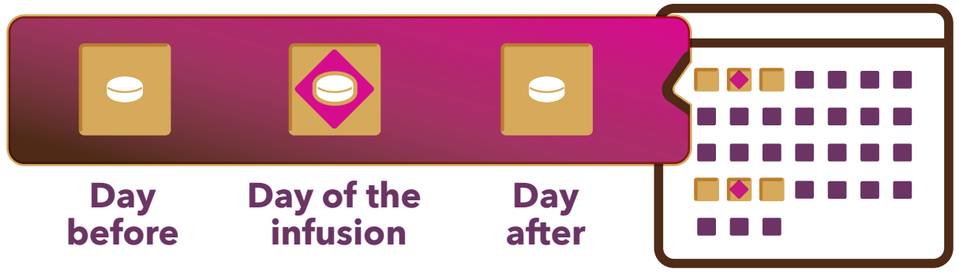
Tips for your patient:

Suggest they and/or their caregiver set a reminder on their phone about their therapy/therapies. This way, they can plan around their schedule.

Dexamethasone may cause insomnia, so suggest patients take it early in the morning.

Be sure your patient understands their infusion day schedule, including dexamethasone if it has been prescribed.

Full premedication and infusion schedule



Dexamethasone 4 mg (oral or IV) twice daily for 3 days, beginning the day before infusion (unless contraindicated).

If dexamethasone administration does not begin the day before ZYNLONTA, dexamethasone should begin at least 2 hours prior to administration of ZYNLONTA.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Infections

Fatal and serious infections, including opportunistic infections, occurred in patients treated with ZYNLONTA®. The most frequent Grade ≥3 infections included sepsis and pneumonia.

Cutaneous Reactions

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

Please see Indication and Important Safety Information throughout and on pages 20-21, and accompanying full Prescribing Information.

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Frequently asked questions

Below are some frequently asked questions and their answers. Feel free to cover any of the topics below while counseling your patient and their caregivers before the first infusion.

Patients and caregivers may ask…

How long does the infusion take?

The infusion of ZYNLONTA takes about 30 minutes.

How should we prepare for an infusion?

Before every ZYNLONTA treatment, you might need to give them a prescription steroid. Your team will determine if this is appropriate.

Please refer to pages 8-9 for additional information about infusion preparation.

What if we miss a treatment?

If they miss a ZYNLONTA treatment, be sure to let them know to alert you immediately to discuss options.

How soon can we expect results?

About 50% of patients saw a response in 1.3 months. Some patients took longer to respond: the range of time to response was between 1.1 months and 8.1 months.[a]

Of patients who saw a response, half had all signs of the cancer go away (a complete response), while the other half had some of the cancer lessen (a partial response).

[a]In a clinical trial, 145 patients with DLBCL that has come back (relapsed) or did not respond to previous treatment (refractory) were treated with ZYNLONTA to see how well it worked. The median time that it took for half of people to respond was 1.3 months. It took the other half longer to respond, up to 8.1 months.

How often will blood tests be done?

During treatment with ZYNLONTA, their blood count should be monitored and other laboratory tests should be run through blood samples. Let them know how often this testing will be required.

They should also be monitored for infusion site reactions, infections, and skin reactions. CT scans may be needed to monitor the DLBCL.

Can I keep going with my daily routine while on treatment?

This may depend on their routine and how they're doing with treatment.

What side effects might I experience?

ZYNLONTA may cause serious side effects, including fluid retention, low blood cell counts, infections, and skin reactions. **See page 19 for more information.**

If I have a serious side effect, what should I do?

If your patient is concerned about or experiences any serious side effects, they should reach out to you and their doctor's office, or call 911 in case of an emergency.

You may need to stop or delay treatment. You might also need to change their dose of ZYNLONTA.

Share with patients and caregivers the ZYNLONTA website

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Supporting caregivers

People with DLBCL might feel worried, stressed, and anxious about their treatment. The people who care for them may have similar feelings.

Before, during, and after treatment: what caregivers should know

Before

- How to get to and from the treatment location, including information about parking and any available transportation services
- What to expect in each infusion session
- Whether the person they care for will need to stop eating at a certain time before any part of their treatment
- What they can do beforehand to make the infusion time smoother for the person they care for

During

- The expected total length of each visit, how much time they should block off, and how often they will need to visit
- Whether they need to stay on site or if they can leave and come back
- If there is a waiting area, or any local places to run errands or have some quiet time

After

- How taxing the treatment could be
- What the mood of the person receiving treatment may be like upon returning home
- How attentive they should be
- How active the person they care for can be
- How much independence or space the person they care for should have

Throughout treatment: what caregivers should keep in mind

Which symptoms they should look out for, and the best ways to help manage them

- **Refer to page 19** for more information about possible side effects

Who to call during an emergency

- Direct them to call 911 in an emergency. And for less-immediate questions or concerns, consider providing them with your extension so they can speak with you directly

How to make sure their own needs are being met

- For example, suggest they take the time to recognize when they are feeling stressed or weary/hopeless
- Offer ideas to help them be at their best, such as meditating, exercising, getting good rest, seeing their friends, and taking some time for themselves
- Recommend support groups you know other caregivers rely on to help with their particular situation

Share with caregivers more information about supporting a person with DLBCL

Ongoing treatment: Preparing your patient and their caregiver

Remind the patient and caregiver of:

- Timing for premedication, ZYNLONTA 30-minute infusion, and expected total length of appointment
- Potential side effects and general tips to help them before, during, and after the infusion
- Potential serious side effects, and when to call their doctor's office or visit the ER
- The expected dose reduction after 2 cycles. Some patients check their notes and records in their healthcare portal, so preparing them for a change in dose can help avoid misunderstandings before they occur
- When the caregiver can come back to pick up the patient (if applicable)
- Their next appointment
- Activities they can do during infusion and comfort items they can bring (blankets, back pillows, etc)
- Support and advocacy groups that may be able to help them

Most of all, you want to ensure your patient is comfortable in their infusion chair. If they seem anxious, suggest taking their mind off of it by engaging in an enjoyable activity. If they seem scared during or after treatment, ensure they have company to help them feel more secure.

For more information, download the Adverse Reaction Management Guide

Please see Indication and Important Safety Information throughout and on pages 20-21, and accompanying full Prescribing Information.

Dose delays or modifications

Discuss with your patient that if they experience severe side effects, their treatment may need to be adjusted:

Their dose may be changed

Their treatment may be delayed or stopped

While side effects can be worrisome for someone living with DLBCL, you can help put them at ease:

- Let them know they will be monitored closely for any signs of side effects during treatment
- Be sure they have information about potential side effects that may occur after treatment
- Instruct them to report any symptoms, and provide the best contact information for your office (eg, phone number with your extension)

Share with patients and caregivers information about ZYNLONTA infusions

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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 and male patients with female partners of the potential risk to a fetus.

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Help your patient and their caregiver take advantage of time between treatments

After undergoing 2 or more other therapies, it can be important for people living with DLBCL to be able to do what they want with their time.

Discussing what is important to your patient and their caregiver can be meaningful and affect their outlook on therapy, and can help motivate them to make the most of the 3 weeks between treatments. Recommending patient advocacy groups can help them find further resources and support.

Questions to ask for meaningful conversations with your patient and their caregiver:

- How are you feeling about your treatment plan so far?
- How has it been getting to your appointments?
- How have you been doing with your goals?
- How was that special event you were looking forward to?
- Have you been able to spend time with [the person or people they mentioned before]?

Please see Indication and Important Safety Information throughout and on pages 20-21, and accompanying full Prescribing Information.

Potential side effects

The time between appointments is crucial. Be sure your patient and their caregiver know about these potential side effects and what to do if they occur.

They should contact you or their doctor's office if they experience any of the following:

Fluid retention

If your patient experiences new or worsening swelling, weight gain, shortness of breath, or difficult, labored breathing—they should contact you or their doctor's office.
(See section 5.1 of Prescribing Information)

Low blood cell counts

A fever of 100.4°F (38°C) or greater or signs or symptoms of bruising or bleeding can sometimes happen. This is why their blood count is frequently tested.
(See section 5.2 of Prescribing Information)

Infections

They should contact you or their doctor's office if any sign of potential infection such as fever, chills, weakness, and/or difficulty breathing develops or worsens.
(See section 5.3 of Prescribing Information)

Skin reactions

Patients may experience sensitivity to sunlight, skin rash, peeling, redness, or irritation.

Advise your patient to minimize or avoid exposure to direct natural or artificial sunlight, including sunlight exposure through glass windows.
(See section 5.4 of Prescribing Information)

Share with patients and caregivers information about side effects

Important Safety Information

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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).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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%.

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.

Please see accompanying full Prescribing Information.

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.

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Savings, support, and resources with ADVANCING Patient Support

Personalized support means your patient can reach their goals. Whether they need help paying for their treatments or understanding their insurance coverage, ADVANCING Patient Support is here for them.

ADVANCING Patient Support
Personalized assistance from ADC Therapeutics

Enroll your patient in ADVANCING Patient Support so they can reach out to a dedicated case manager who will get to know them.

Download the enrollment form

[a] For commercially insured patients, 18 years of age and older with coverage for ZYNLONTA. Patients are not eligible if they participate in any federal or state healthcare program with prescription drug coverage, such as Medicaid, Medicare, Medicare Part D or Medicare Advantage plan, VA, DOD, or TRICARE. Excludes patients who are uninsured or full cash-paying. Maximum benefit per patient, per calendar year (1/1-12/31) is $25,000. Additional eligibility requirements and other restrictions apply. Visit **ADVANCINGPatientSupport.com/copay-terms-conditions**.

Please see Indication and Important Safety Information throughout and on pages 20-21, and accompanying full Prescribing Information.

This personalized program gives them a range of support:

Financial assistance

They can find out if they qualify for:

$0 Copay: If they're commercially insured and eligible, ADVANCING Patient Support can help your office enroll them in the copay program. Once they're signed up, they may pay as little as $0 per treatment[a]

Coverage of therapy costs: If they are uninsured or underinsured, ADVANCING Patient Support can help them find out if they qualify for the Patient Assistance Program

Help understanding insurance

Their case manager can help them understand:

Coverage: Whether ZYNLONTA is covered under their health plan

Cost: What the cost may be for their therapy

Requirements: What, if any, approvals or additional information they need before receiving therapy

Learn more about ADVANCING Patient Support

About this discussion guide

This guide is designed to help you have meaningful conversations about ZYNLONTA with patients and their caregivers. It covers treatment experience topics, such as:

- How to prepare for their first infusion
- Things to bring with them on infusion day
- Side effects to watch for after their treatment

Find more ZYNLONTA resources for you, your patients, and their caregivers

Reference: ZYNLONTA [package insert]. Murray Hill, NJ: ADC Therapeutics SA; 2022.

www.zynlontahcp.com

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.

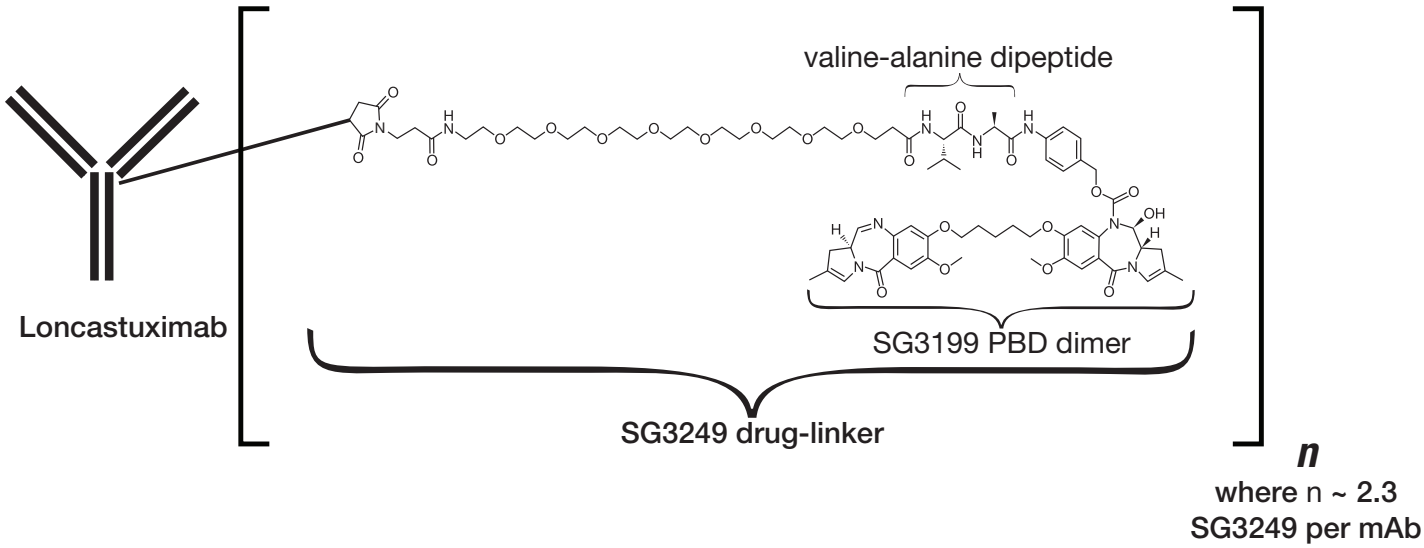
8.6 Hepatic Impairment

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.

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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

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