

Generic name: Loncastuximab tesirine-lpyl (pronounced (LON kas TUX i mab TES ir een), often referred to as Lonca

Trade name(s): Zynlonta® by ADC Therapeutics SA

Drug type: Loncastuximab is an advanced anti-cancer therapy that is classified as an antibody-drug conjugate (ADC) or immunoconjugate. In certain B cell lymphomas, including Waldenstrom's macroglobulinemia (WM), this drug works by binding to the CD19 protein found on the surface of B cells and immature plasma cells, including cancerous cells. It directly delivers a toxic drug *inside* the cancer cell to destroy it while limiting damage to healthy tissues.

Fast facts about loncastuximab

- **Antibody-drug conjugate:** An antibody-drug conjugate (ADC) is an advanced cancer treatment that acts like a biological guided missile by pairing a targeted antibody against cancer cells with a powerful cell-killing chemotherapy drug. Unlike traditional chemotherapy, which kills both cancerous and healthy rapidly dividing cells, loncastuximab delivers its potent cancer-killing toxin directly *inside* cells that have the designated marker that is being targeted on the cell. This minimizes broad exposure to healthy surrounding tissues and limits chemotherapy side effects.
- **Potential benefit:** The potential benefits of loncastuximab center around its ability to provide a powerful, highly targeted treatment option for adult patients with difficult-to-treat B cell lymphomas while resulting in limited effects to healthy tissues. It is primarily used after two or more traditional therapies have failed. It is a finite, six-month treatment plan rather than continuous therapy, so it offers a distinct quality-of-life advantage if it is successful.
- **Dosage:**
In clinical trials evaluating loncastuximab for WM, the treatment is administered as an in-hospital or clinic therapy spanning multiple cycles (usually over six months), injected into a vein (intravenously) at specific intervals determined by the study protocol. The dosing schedule typically involves an initial phase followed by adjusted doses in subsequent cycles to manage side effects while sustaining treatment effectiveness.
- **Clinical trials:** Loncastuximab is not FDA-approved for the treatment of WM. However, it is being evaluated in patients with relapsed or refractory WM through ongoing clinical trials.
- **Side effects:** The primary side effects and toxicities monitored in WM patients include:
 - Low blood counts
 - Fluid retention

- Skin changes
- Liver enzyme elevations
- Fatigue
- Mild nausea or diarrhea

Beyond the fast facts about loncastuximab

What conditions are treated by loncastuximab?

Loncastuximab is approved by the US Food and Drug Administration (FDA) and the European Commission (EC) to treat adults 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. Relapsed means that the disease returned after remission from prior therapy, while refractory means that the disease did not respond to treatment. These indications achieved accelerated FDA approval based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Without specific approval for treating WM, loncastuximab prescribed for WM patients is given “off label,” signifying the drug is being used for an unapproved indication or in an unapproved age group, dosage, or route of administration. This ability to prescribe drugs for uses beyond officially approved indications is common in medicine. The National Comprehensive Cancer Network (NCCN) guidelines include loncastuximab as a useful therapy for relapsed or refractory WM patients in certain circumstances. This drug may be useful after treatment with a Bruton’s tyrosine kinase inhibitor (BTKi) and rituximab-based regimens and may be appropriate for high-risk disease.

How does loncastuximab work?

Normal, healthy cells divide and grow in a precise, orderly way. Cancer cells, however, no longer have the normal mechanisms in place that control and limit cell division, resulting in rapid and uncontrollable growth. Oncologists use ADCs for refractory disease, when cancer spreads (metastasizes), or for relapsed disease. Because the medicine goes straight to the target, doctors can use stronger, more effective drugs with less overall side effects (toxicity) than traditional chemotherapy.

The following explains how the components of this medication work together:

- **The antibody:** A lab-made protein or monoclonal antibody that locates and binds to specific proteins. In loncastuximab, the monoclonal antibody is humanized IgG1 and the target is CD19, a protein abundant on the surface of B and immature plasma lymphoma cells.

- **The payload:** A very powerful cancer-killing toxic drug attached to the antibody. In loncastuximab, this drug is SG3199, which is a highly potent pyrrolobenzodiazepine (PBD) dimer cytotoxin (cell killer).
- **The linker and release:** The linker is a chemical bond that holds the antibody and the drug together while traveling through the bloodstream. Once the antibody binds to the CD19 protein, the cell internalizes the PBD drug, releasing the payload to destroy the targeted cell from the inside.

Although it cannot cure WM, emerging data from clinical trials of loncastuximab show clear clinical activity in patients.

What is the primary clinical trial evaluating loncastuximab for WM?

Since WM is currently not curable, the goal of loncastuximab therapy is to reduce the disease enough to provide symptom relief and reduce the risk of organ damage. In an ongoing clinical trial, loncastuximab therapy has been generally well-tolerated and effective.

The primary clinical trial evaluating loncastuximab for WM is an ongoing, prospective, multicenter Phase 2 clinical trial. Because loncastuximab is an antibody-drug conjugate targeting CD19 (a protein highly expressed on B cells and plasma cells involved in WM), researchers are investigating it as a targeted approach for advanced cases. This is a single-arm, open-label study designed to evaluate how safe and effective loncastuximab is for managing relapsed or refractory WM. The trial is led by the Dana-Farber Cancer Institute and runs in collaboration with major medical networks, including the Mayo Clinic and the Fred Hutchinson Cancer Center. Symptomatic patients with WM who already received at least two prior treatments were enrolled. Crucially, these previous treatments must have included a standard anti-CD20 antibody (like rituximab) and a BTK inhibitor (like ibrutinib, zanubrutinib, or acalabrutinib).

Patients with WM typically have a good prognosis with a long-life expectancy, but when a patient has high-risk disease, such as a mutation in *CXCR4* or *TP53*, their disease is more likely to be resistant to therapies and have a shorter response time after therapy. Between 30% and 40% of patients have a *CXCR4* mutation, and approximately 10% of patients have a *TP53* alteration, although the number of patients with *TP53* alterations increases significantly in patients who have been previously treated. This study included a high proportion of patients with high-risk disease and will evaluate the efficacy of loncastuximab in this cohort.

Patients on this trial received six cycles of intravenous loncastuximab tesirine monotherapy over the course of six months in a hospital or clinic setting. Preliminary data from the trial reported on 14 patients who completed this study who were between the ages of 53 and 81 and were heavily treated, with a median of four prior therapies. Of these patients, 12 had disease with the *MYD88* mutation, eight with *CXCR4* mutation, and eight with *TP53* alteration. The researchers reported

71% of patients experienced a complete response or very good partial response. Notably, all patients with *TP53* alteration responded to treatment, and 89% of patients with *TP53* alteration had a complete response or very good partial response.

Recent clinical updates indicate that this therapy has been driving deep remissions in heavily pretreated patients who otherwise ran out of standard care options. Additional follow-up is needed to assess the durability of the response after therapy completion.

What are the side effects of loncastuximab?

- The drug is generally well-tolerated, especially because the clinical trial protocol uses a finite, 6-cycle "step-down" approach (lowering the dose after cycle 2) to proactively limit toxicity. The primary side effects and toxicities monitored in WM patients include:
 - Hematologic toxicity (low blood counts) Because the pyrrolobenzodiazepine (PBD) toxin payload affects bone marrow cells, changes in blood count levels are a primary focus.
 - Neutropenia: A drop in neutrophils, a type of white blood cell, which temporarily increases a patient's risk of infections.
 - Thrombocytopenia: Lower platelet counts, which can lead to easier bruising or mild bleeding.
 - Anemia: Decreased red blood cells, which can trigger fatigue, weakness, or shortness of breath.
 - Fluid retention (edema and effusion) PBD payloads are known to cause fluid leaks into body tissues.
 - Peripheral edema: Mild to moderate swelling in the lower legs, ankles, or hands.
 - Pleural/pericardial effusion: Fluid gathering around the lungs or heart. Patients are monitored for development of cough or shortness of breath. The trial protocol mandates premedication with the steroid dexamethasone around each infusion specifically to suppress this fluid buildup.
 - Cutaneous reactions (skin changes)
 - Photosensitivity: The skin becomes highly sensitive to ultraviolet light, even through glass windows. Patients with WM are advised to strictly avoid direct sun exposure, wear protective clothing, and use broad-spectrum sunscreen.
 - Skin rashes: Dry, itchy rashes, or rashes that feature flat, discolored areas of skin (macules) and elevated lesions (papules).
 - Liver enzyme elevations
 - The liver metabolizes the toxin component of the drug, which can lead to temporary elevations in liver function tests, such as gamma-glutamyl transferase (GGT) and transaminases. Routine laboratory panels are monitored before every monthly dose to ensure the liver recovers.

- Constitutional and gastrointestinal symptoms
 - Fatigue: A general feeling of low energy or sluggishness, primarily occurring in the days immediately following the 30-minute infusion.
 - Mild nausea or diarrhea: This is typically manageable with standard dietary adjustments or supportive over-the-counter medications.

Most people will not have all these side effects. If you experience any side effects, tell your healthcare provider. There are medications and strategies that can help lessen their severity.

When should a healthcare provider be contacted right away?

Even though it is rare, some people may have serious side effects when taking loncastuximab. Inform your doctor right away if you have any of the following signs or symptoms, as you may need immediate medical attention:

- Allergic reactions—skin rash, itching, hives, swelling of the face, lips, tongue, or throat.
- Bleeding—bloody or black, tar-like stools, vomiting blood or brown material that looks like coffee grounds, red or dark brown urine, small red or purple spots on skin, unusual bruising or bleeding. Your risk of severe bleeding may increase if you are also taking blood thinner medicine.
- Infection—fever, chills, cough, sore throat, wounds that don't heal, pain or trouble when passing urine, general feeling of discomfort or being unwell.
- Liver injury—right upper belly pain, loss of appetite, nausea, light-colored stool, dark yellow or brown urine, yellowing skin or eyes, unusual weakness or fatigue.
- Low red blood cell level—unusual weakness or fatigue, dizziness, headache, trouble breathing.
- Skin reactions on sun-exposed areas—severe sunburn or blisters.
- Swelling of the ankles, hands or feet, shortness of breath or trouble breathing, sudden weight gain.

Side effects that usually do not require medical attention (report these to your care team if they continue or are bothersome):

- Fatigue
- Muscle pain
- Nausea
- Skin rash

These are not all the side effects that can occur with loncastuximab. In general, it's always good practice to inform your healthcare provider if you experience any unusual symptoms. Some serious side effects may require changes in therapy, such as lowering the dose given, waiting longer between doses, or stopping the use of the drug. You may also report side effects to the FDA at 1-800-FDA-1088.

What are some self-care tips while taking loncastuximab?

The following are some things you need to do or know while taking this drug. Before starting treatment with loncastuximab, tell your doctor if you:

- Have any allergies to drugs, foods, or other substances (like latex for example).
- Have medical problems, especially kidney or liver disease.
- Are, or may be, pregnant. This drug may cause harm to an unborn baby. A pregnancy test will be done before you start loncastuximab to make sure you are not pregnant. You cannot breastfeed while taking this drug for one week after your last dose. Females who are able to become pregnant should use effective birth control (contraception) during treatment and for at least one week after the last dose of loncastuximab.
- Desire to father a child. Loncastuximab may impair fertility in some men; this may resolve after treatment, last several years, or be permanent. Discuss this with your doctor.
- Are taking medications that prevent or treat blood clots.
- Are taking any other medications or supplements. Some supplements (i.e. vitamin E) can increase the risk of bleeding. Loncastuximab may affect how other medications work, and other medications may affect the way this medication works. Give your health care provider a list of all the medicines, herbs, non-prescription drugs, or dietary supplements you use. Also tell them if you smoke, drink alcohol, or use illegal drugs. Some items may interact with your medicine.

While taking loncastuximab:

- This medication is injected into a vein. It is given by your care team in a hospital or clinic setting. Your healthcare team may change your dose or tell you stop taking this medication if you get severe side effects. Keep appointments for follow-up doses. It is important not to miss your dose. Call your care team if you are unable to keep an appointment.
- You may be at risk of infection so try to avoid crowds or people with infections, colds, or flu and wash your hands often.
- You may bleed more easily. Avoid contact sports or activities that could cause injury. Use an electric razor and a soft toothbrush to minimize bleeding.
- To reduce nausea, take anti-nausea medications as prescribed by your doctor and eat small, frequent meals. In general, drinking alcoholic beverages should be kept to a minimum or avoided completely.
- If you take aspirin or products containing aspirin, talk with your healthcare provider before making any changes to your medication. Loncastuximab may increase the risk of bleeding.
- If you or your partner may get pregnant, use birth control while taking this drug and for nine months after the last dose for women and six months after the last dose for men. Loncastuximab may cause harm to an unborn child.

- If you are going to need surgery or other medical procedures, tell your healthcare team that you are using this medication. You may need to discontinue this medication prior to the procedure.
- Tell your dentist and oral surgeon that you are taking loncastuximab before having dental work or surgery. Your healthcare team may recommend delaying or adjusting treatment around certain procedures. When possible, have a dental exam and address any dental problems before starting treatment. Continue to practice good oral hygiene and maintain regular dental follow-up.

How will I be monitored while taking loncastuximab?

You will be checked regularly by your doctor to monitor side effects and assess your response to therapy. Periodic blood work will be obtained to monitor your blood counts and evaluate the function of organs, such as your liver and kidneys.

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About the IWMMF

The International Waldenstrom's Macroglobulinemia Foundation (IWMMF) is a patient-founded and patient-driven, nonprofit 501(c)(3) organization (EIN: 54-1784426) that is dedicated to a simple but compelling vision, "a World without WM," and a mission to "support and educate everyone affected by Waldenstrom's macroglobulinemia (WM) to improve patient outcomes while advancing the search for a cure."

More information about Waldenstrom macroglobulinemia and the services and support offered by IWMMF, and its affiliate organizations, can be found on our website, www.iwmmf.com.

IWMMF relies on donations to continue its mission and we welcome your support. The Foundation's mailing address is 1449 S. Michigan Ave. STE 13329, Chicago, IL 60605. Contact IWMMF by phone at 941-927-4963 or by email at office@iwmmf.com.

The information presented here is intended for educational purposes only. It is not meant to be a substitute for professional medical advice. Patients should use the information provided in full consultation with, and under the care of a physician with experience in the treatment of WM. We discourage the use by a patient of any information contained herein without disclosure to his or her medical specialist.

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