Up Close with Linvoseltamab

This section provides an overview of linvoseltamab-gcpt (LYNOZYFIC™).

- Indications
- Dosing and Administration
- CRS
- Neurotoxicity (including ICANS)
- Other Toxicities
- REMS

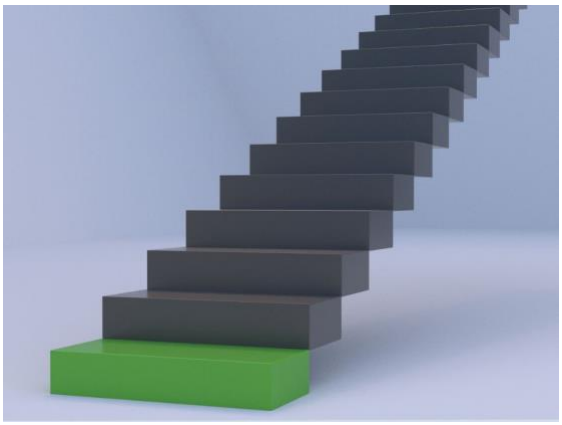
🏷️ Indications

Linvoseltamab is a **bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager** indicated for adult patients with:

- **Relapsed or refractory multiple myeloma** who have received **at least 4 prior lines of therapy**, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Note: This indication is approved under accelerated approval based on response rate and durability of response. Continued approval may be contingent upon verification of clinical benefit in confirmatory trials.

💊 Dosing and Administration



Linvoseltamab is administered **intravenously once weekly for 14 weeks**, followed by once every 2 weeks. In patients that have **achieved and maintained a very good partial response (VGPR) or better at or after Week 24 and received at least 17 doses of 200 mg,** linvoseltamab is then administered **every 4 weeks**. Treatment is continued until disease progression or unacceptable toxicity.

- **Step-up dosing schedule:** 2 step-up doses on Days 1 and 8, followed by the first treatment dose on Day 15 to reduce the incidence and severity of CRS.
    - Per the US Package Insert, **patients should be hospitalized for 24 hour**s after administration of the **first step-up dose**, and for **24 hours** after administration of the **second step-up dose**.
- After step-up dosing, linvoseltamab is administered as a **200-mg dose once weekly** starting at Week 3 through Week 13.
    - A minimum of 5 days should be maintained between weekly doses.
- After weekly dosing, linvoseltamab is administered as a **200-mg dose once every 2 weeks** starting at Week 14.
    - A minimum of 10 days should be maintained between weekly doses.

Linvoseltamab Dosing Schedule

Dosing Schedule	Day of Treatment	Linvoseltamab Dose / Route		Duration of Infusion
Step-up Dosing Schedule	1	Step-up dose 1	5 mg IV	4 hours
	8	Step-up dose 2	25 mg IV	
	15	First treatment dose	200 mg IV	
Weekly Dosing Schedule	One week after first treatment dose and weekly thereafter through week 13	Subsequent treatment doses	200 mg IV	1 hour for the second treatment dose, and 30 minutes for subsequent doses
Every 2 Week Dosing Schedule *Responders only, Week 24 onward*	Week 14 and every 2 weeks thereafter	Subsequent treatment doses	200 mg IV	30 minutes
Every 4 Week Dosing Schedule	Week 24 or after and every 4 weeks thereafter	Subsequent treatment doses	200 mg IV	30 minutes
IV, intravenously				

Recommendations for Restarting Therapy with Linvoseltamab After Dosage Delay		
Last Dose Administered	**Time Since the Last Dose Administered***	**Action for Next Dose**
Step-up dose 1 (5 mg)	2 weeks or less (≤ 14 days)	Administer 25 mg
	Greater than 2 weeks (> 14 days)	Restart step-up dosing from 5 mg
Step-up dose 2 (25 mg)	2 weeks or less (≤ 14 days)	Administer 200 mg
	Greater than 2 weeks and less than or equal to 4 weeks (15 days to ≤ 28 days)	Restart step-up dosing from 25 mg
	Greater than 4 weeks (> 28 days)	Restart step-up dosing from 5 mg
Any treatment dose (200 mg)	7 weeks or less (≤ 49 days)	Administer 200 mg
	Greater than 7 weeks (> 49 days)	Restart step-up dosing from 5 mg
*Consider benefit-risk of restarting linvoseltamab in patients who require a dose delay of more than 30 days.		

Recommended Pre-Treatment Medications

Administer the following pre-treatment medications **before each dose of linvoseltamab** in the **step-up dosing schedule**, which includes step-up dose 1, step-up dose 2, and the **first treatment dose**, the **second treatment dose**, and if indicated, subsequent treatment doses, to reduce the risk of CRS.

- acetaminophen (or equivalent) 650 mg to 1000 mg orally 30-60 minutes prior to infusion
- diphenhydramine (or equivalent) 25 mg orally or intravenously 30-60 minutes prior to infusion
- dexamethasone (or equivalent) intravenously 1-3 hours prior to infusion
    - 40 mg dexamethasone (or equivalent) before step-up dose 1, step-up dose 2, and the first full treatment dose
    - Once a treatment dose of linvoseltamab is tolerated without CRS and/or infusion-related reactions (IRR) with 40 mg dexamethasone (or equivalent), administer 10 mg dexamethasone (or equivalent) prior to the subsequent linvoseltamab treatment dose

⚠ CRS

What is it? Cytokine release syndrome (CRS) is a systemic inflammatory response that can occur when the immune system is activated and releases large amounts of cytokines—proteins that help regulate immune responses.

- **Signs and symptoms:** pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia.
    - CRS is frequently graded using the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria.

Why it matters. CRS occurred in **46%** of patients who received linvoseltamab at the recommended dosage, in the clinical trial, LINKER-MM1.

- **Most CRS events** were reported in the **step-up dosing schedule**, either at **step-up dose 1 (38%)**, **step-up dose 2 (17%)**, or the **initial treatment dose (10%**) and were **primarily Grade 1 (35%)**.
    - CRS did **recur in approximately 20% patients** regardless of their dosing schedule.
- The **median time to onset** of CRS from the end of infusion was **11 hours** (range: -1 to 184) post-administration. The **median duration** of CRS was **15 hours** (range: 1 to 76).
- Care teams should monitor for signs/symptoms of CRS and **withhold or permanently discontinue linvoseltamab based on severity**.

The bottom line. CRS was primarily low grade, predictable, and manageable.

🧠 Neurotoxicity (including ICANS)

What is it? Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is characterized by various neurological symptoms resulting from the activation of the immune system and the resultant inflammatory processes.

- **Signs and symptoms:** encephalopathy, headaches, seizures, aphasia, motor deficits, ataxia, and tremor.
- ICANS is frequently graded using the ASTCT consensus criteria.

Why it matters. Neurological toxicity, including ICANS, occurred in **54% of patients** in LINKER-MM1, and **Grade 3 or 4 neurological toxicity** was reported in **8% of patients**. The most common neurological toxicities included: ICANS, depressed level of consciousness, encephalopathy, and toxic encephalopathy.

- **ICANS** specifically, was reported in **8% of patients** and **reoccurred in 1 patient**.
    - **Most ICANS events** were reported in the **step-up dosing schedule**, at step-up dose 1 (5%), however two patients reported ICANS during step-up dose 2 (1.8%). Following the introduction of the treatment dose as part of the weekly dosing schedule, 1 patient reported ICANS.
        - The most commonly reported clinical signs and symptoms of ICANS included confusion, depressed level of consciousness, and lethargy.
    - The **median time to onset** of ICANS across all doses was **1 day** (range: 1 to 4) post-administration. The **median duration** of ICANS was **2 days** (range: 1 to 11).
    - The onset of ICANS may be experienced concurrently with CRS, in the absence of CRS, or even following the resolution of CRS.
- Care teams should monitor for signs/symptoms of neurological toxicity/ICANS.
    - **Patients should be discouraged from driving or operating heavy machinery** that may be considered potentially dangerous **during the step-up dosing schedule and 48 hours following completion of the step-up schedule** the in event of any new onset of neurological toxicity occurs or until symptoms resolve.
    - Additionally, care teams should **consider withholding or permanently discontinuing linvoseltamab based on severity**.

The bottom line. ICANS events were less common compared to CRS but resolved relatively quickly over a few days.

🚨 Other Toxicities

Linvoseltamab may cause other adverse reactions such as **infections, neutropenia, hepatotoxicity,** and **embryo-fetal toxicity.**

Why it matters. In addition to the risks of CRS and neurotoxicity (including ICANS), care teams need to be on the lookout for other **linvoseltamab**-associated toxicities.

Infections. Linvoseltamab may cause serious and fatal infections.

- **Serious infections**, including opportunistic infections, occurred in **42% of patients**, with **Grade 3 or 4 infections in 38%**, and **fatal infections in 4%**.
    - The most common serious infections reported were pneumonia and sepsis.

The bottom line. Care teams should **monitor patients for signs of infection and immunoglobulin levels before and during treatment**; treat appropriately.

- Withhold or discontinue linvoseltamab based on severity.
- Provide prophylactic antimicrobials, antibiotics, antifungals, antivirals, vaccines, and subcutaneous or intravenous immunoglobulin (IVIG) according to current practice guidelines. This should include prophylaxis for pneumocystis jirovecii pneumonia (PJP) and herpesviruses before starting linvoseltamab.

Neutropenia. Linvoseltamab may cause neutropenia and febrile neutropenia.

- In the LINKER-MM1 trial, **decreased neutrophils** occurred in **62% of patients**, with **Grade 3 or 4 decreased neutrophils in 47%**.
    - **Febrile neutropenia** occurred in **8% of patients**.

The bottom line. Care teams should monitor complete blood counts throughout treatment.

- **Withhold or discontinue linvoseltamab based on neutropenia severity**; consider prophylactic granulocyte colony-stimulating factor.

Hepatotoxicity. Linvoseltamab may cause hepatotoxicity.

- In the LINKER-MM1 trial, **elevated ALT** occurred in **46% of patients**, with **Grade 3 or 4 ALT elevation occurring in 6%**; **elevated AST** occurred in **61% of patients**, with **Grade 3 or 4 AST elevation occurring in 10%**.
    - **Grade 3 or 4 total bilirubin** elevations occurred in **1.7% of patients.**
    - Liver enzyme elevation can occur with or without concurrent CRS.

The bottom line. Care teams should monitor liver enzymes and bilirubin throughout treatment as clinically indicated.

- **Withhold or consider permanent discontinuation** of linvoseltamab **based on severity**.

Embryo-Fetal Toxicity. Linvoseltamab may cause fetal harm when administered to a pregnant woman.

- Advise **females of reproductive potential** to use effective contraception **during treatment and for 3 months after** the last dose.
- Verify pregnancy status before initiating linvoseltamab.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed during treatment and for 3 months after the last dose.
- **Geriatric Use:**
    - In LINKER-MM1, 36% were 65 years of age or older, and 26% were 75 years of age or older.
    - No overall differences in safety or effectiveness were observed in patients 65 years of age and older, including patients 75 years of age and older, compared to younger patients.
- **Pediatric Use:** At this time, no safety and effectiveness data has been established in pediatric patients.

REMS

Linvoseltamab has a **Risk Evaluation and Mitigation Strategy (REMS)** to mitigate the risk of CRS and neurologic toxicity, including ICANS.

Why it matters. Prescribers, pharmacies, and healthcare settings have specific requirements per the LYNOZYFIC REMS to treat patients with linvoseltamab.

Notable requirements of the LYNOZYFIC REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Prescribers must counsel patients receiving linvoseltamab about the risk of CRS and neurologic toxicity, including ICANS, and provide patients with LYNOZYFIC Patient Wallet Card.
- Pharmacies and healthcare settings that dispense linvoseltamab must be certified with the LYNOZYFIC REMS program and must verify prescribers are certified through the LYNOZYFIC REMS program.
- Wholesalers and distributors must only distribute linvoseltamab to certified pharmacies or healthcare settings.

Steps for a prescriber to become certified:

1. Review the prescribing information, prescriber training program, and adverse reaction management guide.
2. Successfully complete the knowledge assessment and submit it to the REMS
3. Complete the prescriber enrollment form and submit it to the REMS
4. Before treatment initiation (first step-up dose), counsel patients and/or their caregivers using the patient wallet card. Complete and provide patients or their caregivers with the patient wallet card.

Steps for pharmacies and healthcare settings to become certified:

1. Designate an Authorized Representative (AR) for the pharmacy and healthcare setting
    a. The AR can be a pharmacist, pharmacy technician, registered nurse, or any responsible individual assigned by the pharmacy or healthcare setting.
2. AR must review the Pharmacy and Healthcare Setting Training Program slides.
3. AR must complete the Pharmacy and Healthcare Setting Enrollment Form and submit it to the REMS
4. Train all relevant staff involved in dispensing linvoseltamab on the REMS requirements using the Pharmacy and Healthcare Setting Training Program slides.
    a. Before dispensing, obtain authorization to dispense each prescription by contacting the REMS to verify the prescriber is certified.

Go deeper. For more information on the LYNOZYFIC REMS program, click here.

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References

1. LYNOZYFIC™ (linvoseltamab-gcpt) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2025.
2. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758.
3. ©Regeneron Pharmaceuticals Inc. LYNOZYFIC™ Risk Evaluation and Mitigation Strategy (REMS). https://lynozyficrems.com/#Main. Accessed August 2025.
4. Bumma N, Richter J, Jagannath S, et al. Linvoseltamab for Treatment of Relapsed/Refractory Multiple Myeloma. J Clin Oncol. 2024;42(22):2702-2712. doi:10.1200/JCO.24.01008.