Treatment Management Guide

LYNOZYFIC™ (linvoseltamab-gcpt) Injection 5mg | 200mg

A resource for dosing, administration, and adverse reaction management

INDICATION AND USAGE

LYNOZYFIC is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

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

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY, including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

- **Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving LYNOZYFIC. Initiate treatment with LYNOZYFIC step-up dosing to reduce the risk of CRS. Manage CRS, withhold LYNOZYFIC until CRS resolves, and modify the next dose or permanently discontinue based on severity.**
- **Neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), including serious or life-threatening reactions, can occur in patients receiving LYNOZYFIC. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS during treatment. Manage neurologic toxicity, including ICANS, withhold LYNOZYFIC until neurologic toxicity, including ICANS resolves, and modify the next dose or permanently discontinue based on severity.**
- **Because of the risk of CRS and neurologic toxicity, including ICANS, LYNOZYFIC is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LYNOZYFIC REMS.**

Introduction

LYNOZYFIC is a BCMAxCD3 bispecific antibody for eligible patients with R/R multiple myeloma after at least 4 prior lines of treatment[1]

This guide provides an overview of the dosing and adverse reactions observed with LYNOZYFIC, as well as strategies for addressing adverse reactions. The guide contains information on:

- The LYNOZYFIC dosing schedule, including step-up dosing and pretreatment medications.
- Administration of LYNOZYFIC as an IV infusion.
- Identification and management of cytokine release syndrome and neurologic toxicity, including ICANS.
- Identification and management of other adverse reactions that may occur with LYNOZYFIC.
- Counseling patients on CRS and neurologic toxicity, including ICANS.
- The LYNOZYFIC REMS program.

It's important that you read through the entire Treatment Management Guide and full Prescribing Information before you administer LYNOZYFIC to your patients.

Medical inquiries

Healthcare professionals, patients, or caregivers may request specific product information, report an adverse reaction, or report a product complaint for a Regeneron product to our Medical Information Department.

Please call **1-844-REGN-MID (1-844-734-6643)** for further information.

Learn more at **LYNOZYFIChcp.com**.

BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IV, intravenous; R/R, relapsed/refractory.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions

Cytokine Release Syndrome (CRS): LYNOZYFIC can cause CRS, which can be serious or life-threatening. In LINKER-MM1, CRS occurred in 46% (54/117) of patients who received LYNOZYFIC at the recommended dose, with Grade 1 CRS occurring in 35% (41/117) of patients, Grade 2 in 10% (12/117), and Grade 3 in 0.9% (1/117).

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

LYNOZYFIC dosing schedule

LYNOZYFIC is administered by IV infusion with 2 step-up doses, followed by weekly treatment for 12 doses and every-2-week treatment for 5 doses. After at least 17 full doses, patients can switch to every-4-week treatment if they achieve ≥VGPR at or after Week 24, or continue at every 2 weeks for responses <VGPR. Continue treatment until disease progression or unacceptable toxicity.[1]

Dosing schedule[1]

QW dosing*					Q2W dosing for all patients*†	Q4W dosing for eligible patients*‡
Day 1 Step-up dose 1	**Day 8** Step-up dose 2	**Day 15** Full dose 1	**Week 4** Full dose 2	**Weeks 5-13**	**At Week 14**§	**At Week 24 or after**‖
5 mg	**25 mg**	**200 mg**	**200 mg**	**200 mg**	**200 mg**	**200 mg**
24-hour hospitalization post-infusion	**24-hour hospitalization** post-infusion					

4-hr infusion | **1-hr** infusion if tolerated¶ | **30-min** infusion if tolerated¶

‡For patients with ≥VGPR at or after Week 24 and ≥17 full doses. For <VGPR, continue with Q2W dosing.

*Weekly doses should be at least 5 days apart. Biweekly doses should be at least 10 days apart. Every-4-week doses should be at least 24 days apart.

†Q2W dosing for all patients receiving treatment.

§Dose is at Week 14 and every 2 weeks thereafter.

‖Dose is at Week 24 or after and every 4 weeks thereafter.

¶For patients who experienced CRS with the previous dose of LYNOZYFIC, the duration of infusion should be maintained at the duration of the previous infusion; reduce the duration of infusion sequentially in subsequent doses in patients who do not experience CRS (eg, 4 hours, 1 hour, then 30 minutes).

Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week; VGPR, very good partial response.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Cytokine Release Syndrome (CRS) (cont'd): Thirty-eight percent (45/117) of patients had CRS following step-up dose 1, including 1 patient who experienced Grade 3 CRS; 8% (9/117) had an initial CRS event following a subsequent dose. Seventeen percent (19/113) of patients developed CRS after step-up dose 2, 10% (11/111) developed CRS after the first full 200-mg dose of LYNOZYFIC, and 3.6% (4/110) developed CRS after the second full dose. Recurrent CRS occurred in 20% (23/117) of patients. The median time to onset of CRS from the end of infusion was 11 (range: -1 to 184) hours after the most recent dose, with a median duration of 15 (range: 1 to 76) hours.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Important monitoring instructions[1]

LYNOZYFIC should be administered by a healthcare provider with immediate access to emergency equipment and appropriate medical support to manage severe reactions such as CRS, IRR, and neurologic toxicity, including ICANS.

24-hour hospitalization[1]

Due to the risk of CRS and neurologic toxicity, including ICANS, patients should be hospitalized for 24 hours after administration of the first and second step-up dose.

IRR, infusion-related reaction.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Cytokine Release Syndrome (CRS) (cont'd): Clinical signs and symptoms of CRS included, but were not limited to pyrexia, chills, hypoxia, tachycardia, and hypotension. Administer pretreatment medications and initiate therapy according to LYNOZYFIC step-up dosing to reduce the incidence and severity of CRS. Monitor patients for signs and symptoms of CRS after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Recommended pretreatment medications[1]

Administer pretreatment medications to reduce the risk of CRS and/or IRR[1]

Dose	Pretreatment medications	Administration relative to LYNOZYFIC infusion
Step-up dose 1, step-up dose 2, the first full treatment dose, the second full treatment dose	Acetaminophen (or equivalent) 650 mg to 1,000 mg orally	30 to 60 minutes prior to infusion
	Diphenhydramine (or equivalent) 25 mg orally or IV	30 to 60 minutes prior to infusion
	Dexamethasone (or equivalent) intravenously • 40 mg dexamethasone (or equivalent) before step-up dose 1, step-up dose 2, and the first full treatment dose • Once a full treatment dose of LYNOZYFIC is tolerated without CRS and/or IRR with 40 mg dexamethasone (or equivalent), administer 10 mg dexamethasone (or equivalent) prior to the subsequent LYNOZYFIC treatment dose	1 to 3 hours prior to infusion
Subsequent doses	Pretreatment medications may be discontinued once a treatment dose of LYNOZYFIC is tolerated without CRS and/or IRR following pretreatment with 10 mg dexamethasone (or equivalent), acetaminophen (or equivalent), and diphenhydramine (or equivalent) as described.	

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Cytokine Release Syndrome (CRS) (cont'd): At the first sign of CRS, immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care; withhold LYNOZYFIC until CRS resolves and modify the next dose or permanently discontinue LYNOZYFIC based on severity.

Infusion Related Reactions

Infusion-related reactions (IRR) may be clinically indistinguishable from manifestations of CRS. In the patients who were treated with the recommended step-up dosing regimen and pretreatment medications, the rate of IRR was 9% [11/117 including Grade 2 IRR (4.3%) and Grade 3 IRR (1.7%)]. For IRR, interrupt or slow the rate of infusion or permanently discontinue LYNOZYFIC based on severity of reaction.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Restarting LYNOZYFIC therapy

Recommendations for restarting therapy with LYNOZYFIC after a dose delay[1]

Last dose administered	Time since the last dose administered	**Action for next dose** (For CRS/IRR or neurologic toxicity, including or excluding ICANS, refer to the dose modification tables on pages 12 and 15)
5 mg	14 days or less	Administer 25 mg
	Greater than 14 days	Restart step-up dosing from 5 mg
25 mg	14 days or less	Administer 200 mg
	Greater than 14 days and less than or equal to 28 days	Restart step-up dosing from 25 mg
	Greater than 28 days	Restart step-up dosing from 5 mg
200 mg	49 days or less	Administer 200 mg
	Greater than 49 days	Restart step-up dosing from 5 mg
NOTE: Administer pretreatment medications as per page 5. Consider benefit-risk of restarting LYNOZYFIC in patients who require a dose delay of more than 30 days.		

- Dosage interruptions or delays of LYNOZYFIC due to adverse reactions occurred in 74% of patients

Refer to pages 9-17 and 22-23 for recommendations about management of CRS, ICANS, and other adverse reactions.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Neurologic Toxicity, including Immune Effector Cell Associated Neurotoxicity Syndrome: LYNOZYFIC can cause serious or life-threatening neurologic toxicity, including ICANS. In LINKER-MM1, neurologic toxicity occurred in 54% of patients, with Grade 3 or 4 neurologic toxicity occurring in 8%, at the recommended dose. Neurologic toxicities included ICANS, depressed level of consciousness, encephalopathy, and toxic encephalopathy. ICANS occurred in 8% of patients who received LYNOZYFIC with the recommended dosing regimen, including Grade 3 events in 2.6%. Most patients experienced ICANS following step-up dose 1 (5%). Two patients (1.8%) experienced initial ICANS following step-up dose 2 and one patient developed the first occurrence of ICANS following a subsequent full dose of LYNOZYFIC. Recurrent ICANS occurred in one patient. The median time to onset of ICANS was 1 (range: 1 to 4) day after the most recent dose with a median duration of 2 (range: 1 to 11) days. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Preparation for infusion

Administer LYNOZYFIC as an IV infusion only[1]

LYNOZYFIC is a clear to slightly opalescent, colorless to pale yellow solution, available as[1]:

5 mg/2.5 mL (2 mg/mL)
single-dose vial

200 mg/10 mL (20 mg/mL)
single-dose vial

LYNOZYFIC volumes for addition to the infusion bag[1]

LYNOZYFIC dose	LYNOZYFIC vial strength	Volume of LYNOZYFIC to be added to the infusion bag	0.9% Sodium Chloride Injection infusion bag (PVC or PO) volume
2.5 mg*	5 mg/2.5 mL	1.25 mL	50 mL
5 mg	5 mg/2.5 mL	2.5 mL	50 mL or 100 mL
25 mg	5 mg/2.5 mL	12.5 mL	50 mL or 100 mL
200 mg	200 mg/10 mL	10 mL	50 mL or 100 mL

*Modified dose due to adverse reaction. For instructions on when to use the modified dose, refer to pages 12, 15, and 22-23.

Use aseptic technique to prepare LYNOZYFIC. Each vial is intended for one time use only. Do not shake[1]

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. LYNOZYFIC is a clear to slightly opalescent, colorless to pale yellow solution. Discard the vial if the solution is cloudy, discolored, or contains particulate matter
- Withdraw the desired dose from the vial of LYNOZYFIC and transfer into an IV infusion bag (polyvinyl chloride [PVC] or polyolefin [PO]) of 0.9% Sodium Chloride Injection, according to the table on the upper right of this page. Discard any unused portion left in the vial
- Mix diluted solution by gentle inversion. Do not shake the solution

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Neurologic Toxicity, including Immune Effector Cell Associated Neurotoxicity Syndrome (cont'd): The most common clinical signs and symptoms of ICANS are confusion, depressed level of consciousness, and lethargy.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Storage and administration guidance

Storage of infusion solution[1]

Use diluted LYNOZYFIC immediately. If not used immediately, store the solution:

- at room temperature up to 25°C (77°F) for no more than 8 hours from preparation to the start of the infusion

or

- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 48 hours from preparation to the start of the infusion

Do not freeze.

Do not shake.

Administration

LYNOZYFIC should be administered by a healthcare provider with immediate access to emergency equipment and appropriate medical support to manage severe reactions such as CRS, IRR, and neurologic toxicity, including ICANS.

1

Administer only as an IV infusion after dilution in 0.9% Sodium Chloride Injection. Refer to the dosing schedule on page 3 for duration of infusion.

2

Connect the prepared IV infusion bag containing the final LYNOZYFIC solution to IV tubing constructed of PVC, polyethylene (PE)-lined PVC, or polyurethane (PU). Use of a 0.2-micron to 5-micron polyethersulfone (PES) filter is required.

3

Prime with LYNOZYFIC to the end of the IV tubing.

4

Do not mix LYNOZYFIC with other drugs or concurrently administer other drugs through the same intravenous line.

5

Upon completion of LYNOZYFIC infusion, flush the infusion line with an adequate volume of sterile 0.9% Sodium Chloride Injection to ensure that the entire contents of the infusion bag are administered.

6

Total infusion time should include flushing of the infusion line.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Neurologic Toxicity, including Immune Effector Cell Associated Neurotoxicity Syndrome (cont'd): Monitor patients for signs and symptoms of neurologic toxicity, including ICANS during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate the patient; provide supportive therapy and consider further management per current practice guidelines.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

CRS and ICANS identification

What is CRS?

Cytokine release syndrome (CRS) is a clinically significant inflammatory syndrome that can be associated with the administration of T-cell–engaging therapies, including bispecific antibodies. When targeted and activated by LYNOZYFIC, T cells can release pro-inflammatory cytokines, initiating a cytokine release cascade that can result in the pathogenic inflammation referred to as cytokine release syndrome.[2,3]

LYNOZYFIC has a Boxed WARNING for CRS, which may be serious or life-threatening.[1] See pages 11-12 for recommendations on managing CRS.

Identifying CRS

Clinical signs and symptoms of CRS in LINKER-MM1 included, but were not limited to[1]:

- Pyrexia
- Chills
- Hypoxia
- Tachycardia
- Hypotension

Infusion-related reactions (IRR) may be clinically indistinguishable from manifestations of CRS.[1]

What is ICANS?

Immune effector cell-associated neurotoxicity syndrome (ICANS), a type of neurotoxicity, is a disorder associated with immune effector therapy, including T-cell–engaging therapies such as bispecific antibodies. While the exact disease mechanism is not well understood, pro-inflammatory cytokines likely play a role, and ICANS may be preceded by CRS. Neurotoxicity causes a range of neurological symptoms and may be monitored by the Immune Effector Cell-Associated Encephalopathy (ICE) assessment.[4]

In LINKER-MM1, in addition to ICANS, neurologic toxicities included depressed level of consciousness, encephalopathy, and toxic encephalopathy.

LYNOZYFIC has a Boxed WARNING for neurologic toxicity, including ICANS, which may be serious or life-threatening.[1] See pages 14-15 for recommendations on managing ICANS and page 22 for recommendations on managing neurologic toxicity excluding ICANS.

Identifying ICANS

The most common clinical signs and symptoms of ICANS are[1]:

- Confusion
- Depressed level of consciousness
- Lethargy

IMPORTANT SAFETY INFORMATION (cont'd)

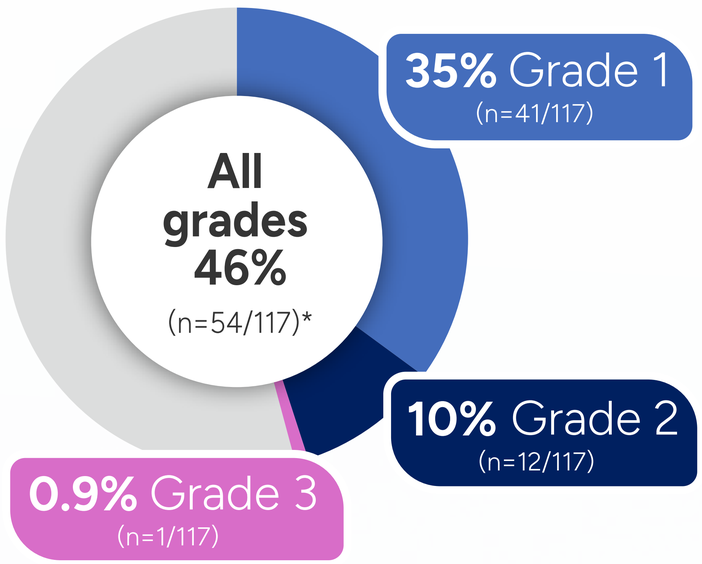
Warnings and Precautions (cont'd)

Neurologic Toxicity, including Immune Effector Cell Associated Neurotoxicity Syndrome (cont'd): Withhold LYNOZYFIC until ICANS resolves and modify the next dose or permanently discontinue LYNOZYFIC based on severity. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity, including ICANS occur at any time.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

CRS rates and onset in LINKER-MM1

Rates of CRS[1]



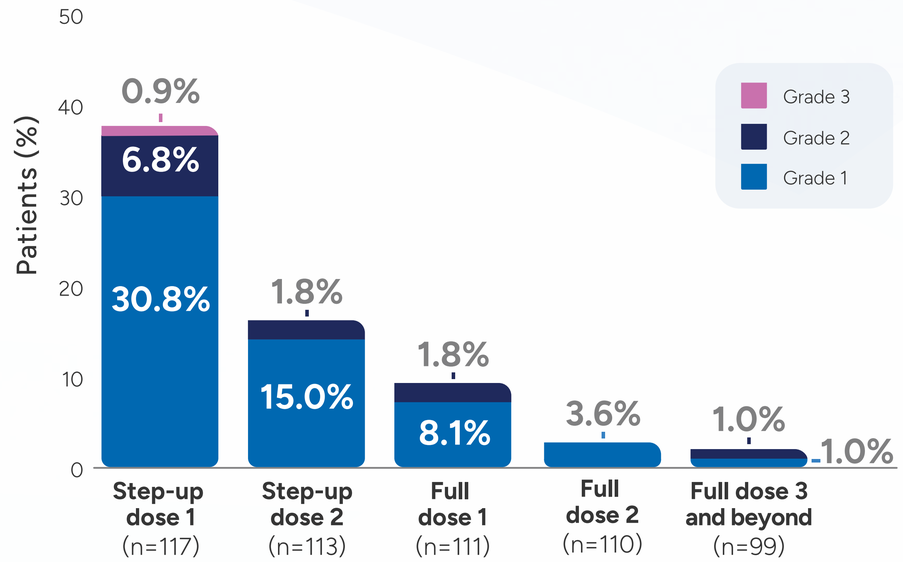
*There were no Grade 4 or 5 events of CRS.

Median time to CRS onset: 11 hours (range: -1 to 184)[1,5†]

- Median time to Grade 1: 12 hours (range: 0 to 184)
- Median time to ≥Grade 2: 6 hours (range: -1 to 105)[†]

- Median duration of CRS: 15 hours (range: 1 to 76)[1]

CRS by dose in LINKER-MM1[5]



CRS events usually occurred during the step-up dosing period.[1]

- 38% (45/117) of patients had a CRS event after step-up dose 1[1]
- 8% (9/117) had an initial CRS event following a subsequent dose[1]
- There was one Grade 3 event, which occurred following step-up dose 1[1]
- Recurrent CRS occurred in 20% (23/117) of patients[1]

[†]Negative numbers indicate CRS onset prior to the end of LYNOZYFIC administration.[6]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Neurologic Toxicity, including Immune Effector Cell Associated Neurotoxicity Syndrome (cont'd): Due to the potential for neurologic toxicity, including ICANS, patients receiving LYNOZYFIC are at risk of confusion and depressed consciousness. Advise patients to refrain from driving, or operating heavy or potentially dangerous machinery, for 48 hours after completion of each of the step-up doses and in the event of new onset of any neurological symptoms, until symptoms resolve.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

CRS identification and management

Recommendations for management of CRS[1]

At the first signs of CRS:

Immediately evaluate patients for hospitalization.

Evaluate for and treat other causes of fever, hypoxia, and hypotension.

Withhold LYNOZYFIC until CRS resolves and modify the next dose or permanently discontinue LYNOZYFIC based on severity.

Manage CRS according to the recommendations on this page, page 12, and per current practice guidelines.

Administer supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

LYNOZYFIC REMS: LYNOZYFIC is available only through a restricted program under a REMS called the LYNOZYFIC REMS because of the risks of CRS and neurologic toxicity, including ICANS.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

CRS identification and management (cont'd)

	Grade 1*	Grade 2*	Grade 3*	Grade 4*	Other*
Definition	• Fever ≥100.4°F (38°C)†	• Fever ≥100.4°F (38°C)† with: Hypotension responsive to fluids and not requiring vasopressors **and/or** hypoxia requiring low-flow oxygen‡ by nasal cannula or blow-by	• Fever ≥100.4°F (38°C)† with: Hypotension requiring a vasopressor (with or without vasopressin) **and/or** hypoxia requiring high-flow oxygen‡ by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Fever ≥100.4°F (38°C)† with: Hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** hypoxia requiring oxygen by positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	• AST/ALT >5x ULN associated with CRS ≤Grade 3
Management	• Withhold LYNOZYFIC until CRS resolves • Provide supportive care, which may include intensive care		• **First occurrence:** Withhold LYNOZYFIC until CRS resolves • **Recurrence:** Permanently discontinue LYNOZYFIC • Provide supportive care, which may include intensive care	• Permanently discontinue LYNOZYFIC • CRS should be managed per Grade 3 recommendations	• Withhold LYNOZYFIC until CRS resolves and AST/ALT are <3x ULN if baseline was normal or 1.5-3x baseline if baseline was abnormal • Provide supportive care, which may include intensive care, and monitor
Restarting LYNOZYFIC	• When CRS resolves, resume treatment with LYNOZYFIC§‖	• When CRS resolves, resume treatment with LYNOZYFIC§‖ ▪ Consider a decrease in infusion rate up to 50% (no more than 6 hours total) when resuming treatment. Increase rate on subsequent infusions if tolerated ▪ Monitor patients within proximity of a healthcare facility for 24 hours following this dose, and consider hospitalization	• When CRS resolves, resume treatment with LYNOZYFIC at reduced dose§¶ ▪ Decrease infusion rate up to 50% (≤6 hours total) ▪ Hospitalize for 24 hours after the administration for this dose • After resuming treatment, if administered dose is tolerated: ▪ Continue with next dose of the recommended dosing regimen ▪ If full dose is tolerated, infusion rate can be increased to the rate prior to the adverse reaction		• No change in dose is needed in patients without CRS symptoms with transaminase levels that are trending toward baseline within 7 days • If values do not trend toward baseline in 7 days, decrease the dose¶ • See infusion rate information by CRS grade

*Based on American Society for Transplantation and Cellular Therapy (ASTCT) criteria for grading CRS (2019).

†Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as steroids, antipyretics, or anticytokine therapy.

‡Low-flow oxygen defined as oxygen delivered at <6 L/minute: high-flow oxygen defined as oxygen delivered at ≥6 L/minute.

§Administer pretreatment medications prior to next dose.

‖Follow the recommendations on page 6 for restarting dosing.

¶If the last dose administered was 5 mg, administer 2.5 mg. If the last dose administered was 25 mg, restart step-up dosing from 5 mg. If the last dose administered was 200 mg, refer to page 6 for recommendations regarding restarting therapy based on time since the last dose.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BiPAP, bilateral positive airway pressure; CPAP, continuous positive airway pressure; ULN; upper limit of normal.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Infections: LYNOZYFIC can cause serious, life-threatening, or fatal infections. In patients who received LYNOZYFIC at the recommended dose in LINKER-MM1, serious infections, including opportunistic infections, occurred in 42% of patients, with Grade 3 or 4 infections in 38% and fatal infections in 4%.

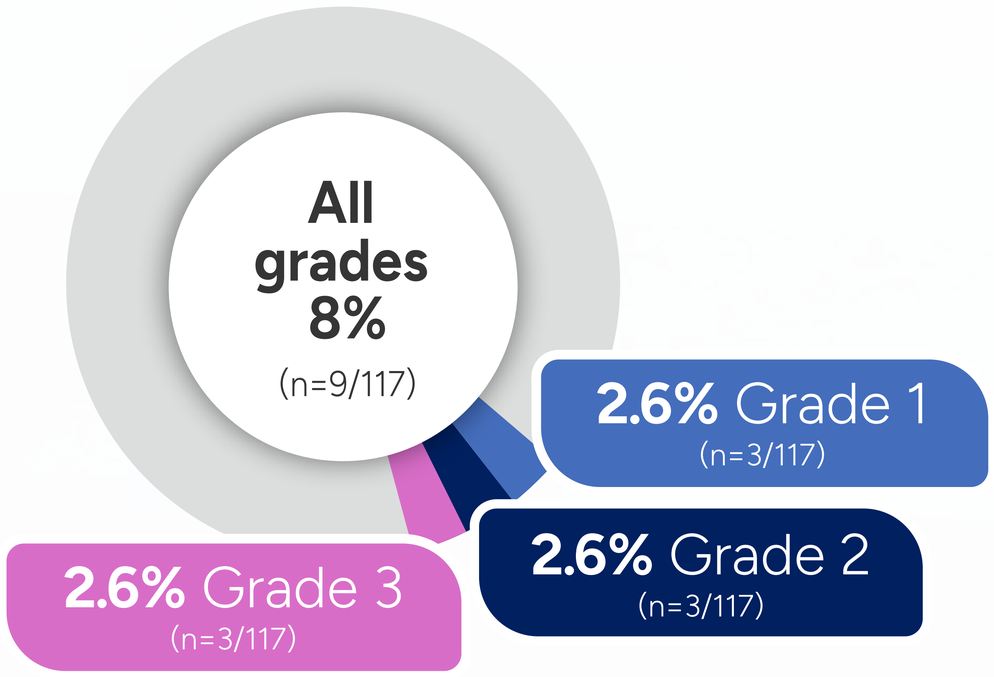
Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Rates of neurologic toxicity, including ICANS, in LINKER-MM1

Neurologic toxicity occurred in 54% of patients in LINKER-MM1[1]

- Neurologic toxicity that occurred in ≥5% of patients included headache* (22%), encephalopathy† (18%), sensory neuropathy‡ (13%), insomnia (13%), ICANS (8%), and dizziness (8%)[1,5]
- 8% of patients experienced Grade 3 or Grade 4 neurologic toxicity[1]

Rates of ICANS in LINKER-MM1[1,6]



ICANS events usually occurred during the step-up dosing period, with generally early time to onset and short time to resolution[1,5,6]

- Median time to ICANS onset: **1 day** (range: 1 to 4)
- Median duration of ICANS: **2 days** (range: 1 to 11)
- Timing of ICANS:
  - 5% (6/117) of patients experienced ICANS following the first step-up dose
  - 1.8% (2/113) experienced initial ICANS after step-up dose 2, and 1 patient developed ICANS following a subsequent full dose
  - Recurrent ICANS occurred in 1 patient
- The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS

*Headache includes headache and migraine.[5]
†Encephalopathy includes agitation, amnesia, cognitive disorder, confusional state, delirium, depressed level of consciousness, encephalopathy (including hyperammonemic and toxic encephalopathy), irritability, lethargy, memory impairment, mental status changes, somnolence, and excludes ICANS. The percentage of patients impacted by each individual adverse event included in encephalopathy ranged from 0.9% to 3.4%.[5]
‡Sensory neuropathy includes hypoesthesia, neuralgia, paresthesia, paresthesia oral, peripheral neuropathy, peripheral sensory neuropathy, and sciatica. The percentage of patients impacted by each individual adverse event included in sensory neuropathy ranged from 0.9% to 6.0%.[5]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Infections (cont'd): The most common serious infection reported (≥10%) were pneumonia and sepsis. Two cases of progressive multifocal leukoencephalopathy (PML) occurred in patients receiving LYNOZYFIC.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Identification and management of neurologic toxicity, including ICANS

The ICE scoring system is an important component of ICANS grading[7]

Five areas are evaluated:

Area for evaluation	Definition	Points
Orientation	Orientation to year, month, city, hospital	4 points (1 each)
Naming	Ability to name 3 objects	3 points (1 each)
Following commands	Ability to follow simple commands	1 point
Writing	Ability to write a standard sentence	1 point
Attention	Ability to count backwards from 100 by 10	1 point

Scoring:

10 POINTS	7-9 POINTS	3-6 POINTS	0-2 POINTS	0 POINTS
No impairment	Grade 1 ICANS	Grade 2 ICANS	Grade 3 ICANS	Due to patient being unarousable and unable to perform ICE assessment: Grade 4 ICANS

At the first signs of neurologic toxicity, including ICANS[1]:

- Immediately evaluate the patient and withhold LYNOZYFIC until ICANS resolves and modify the next dose or permanently discontinue LYNOZYFIC based on severity
- Consider consultation with a neurologist and other specialists
- Rule out other causes of neurologic symptoms
- Provide supportive therapy, which may include intensive care for severe or life-threatening ICANS
- Manage ICANS according to the recommendations on this page, page 15, and per current practice guidelines
- Manage neurologic adverse reactions (excluding ICANS) according to the recommendations on page 22

ICE, immune effector cell-associated encephalopathy.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Infections (cont'd): Monitor patients for signs and symptoms of infection and immunoglobulin levels prior to and during treatment with LYNOZYFIC and treat appropriately. Administer prophylactic antimicrobials, antibiotics, antifungals, antivirals, vaccines, and subcutaneous or intravenous immunoglobulin (IVIG) according to guidelines, including prophylaxis for PJP and herpesviruses. Withhold LYNOZYFIC or consider permanent discontinuation of LYNOZYFIC based on severity of the infection.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Identification and management of neurologic toxicity, including ICANS (cont'd)

	Grade 1*	Grade 2*	Grade 3*		Grade 4*
Definition	ICE† score 7-9, or depressed level of consciousness‡: awakens spontaneously	ICE† score 3-6, or depressed level of consciousness‡: awakens to voice	ICE† score 0-2, or depressed level of consciousness‡: awakens only to tactile stimulus, or seizures, either: • any clinical seizure, focal or generalized, that resolves rapidly, or • nonconvulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local edema on neuroimaging		ICE† score 0, or depressed level of consciousness‡: either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures, either: • life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral edema, with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad
Management			1st occurrence	Recurrence	
Withhold LYNOZYFIC and resume once neurologic symptoms resolve or return to baseline§	✓	✓	✓		
Provide supportive therapy. Manage per current practice guidelines‖	✓	✓	✓	✓	✓
Consider non-sedating, anti-seizure medications for seizure prophylaxis	✓	✓	✓	✓	✓
Administer dexamethasone¶ 10 mg IV Q6h until resolution to ≤Grade 1, then taper		✓	✓	✓	✓
Consider neurology evaluation			✓	✓	✓
Permanently discontinue				✓	✓
Restarting LYNOZYFIC					
Special instructions for restarting LYNOZYFIC		Monitor patients within proximity of a healthcare facility for 24 hours following the next dose and consider hospitalization	Resume treatment at a reduced dose# and hospitalize for 24 hours after the dose**		

Management is determined by the most severe event, not attributable to any other cause.

*Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.

†If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital=4 points); Naming (name 3 objects, eg, point to clock, pen, button=3 points); Following Commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue"=1 point); Writing (ability to write a standard sentence=1 point); and Attention (count backwards from 100 by ten=1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS)=0 points.

‡Not attributable to any other cause.

§For Grades 1 and 2, follow the recommendations on page 6 for restarting dosing.

‖For Grades 3 and 4, supportive therapy may include intensive care.

¶All references to dexamethasone administration are dexamethasone or equivalent.

#If the last dose administered was 5 mg, administer 2.5 mg. If the last dose administered was 25 mg, restart step-up dosing from 5 mg. If the last dose administered was 200 mg, refer to page 6 for recommendations regarding restarting therapy based on time since the last dose.

**After resuming treatment, if the administered dose is tolerated, continue with the next dose of the recommended dosing regimen per the dosing schedule on page 3.

Q6h, every 6 hours.

Please see IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Infections

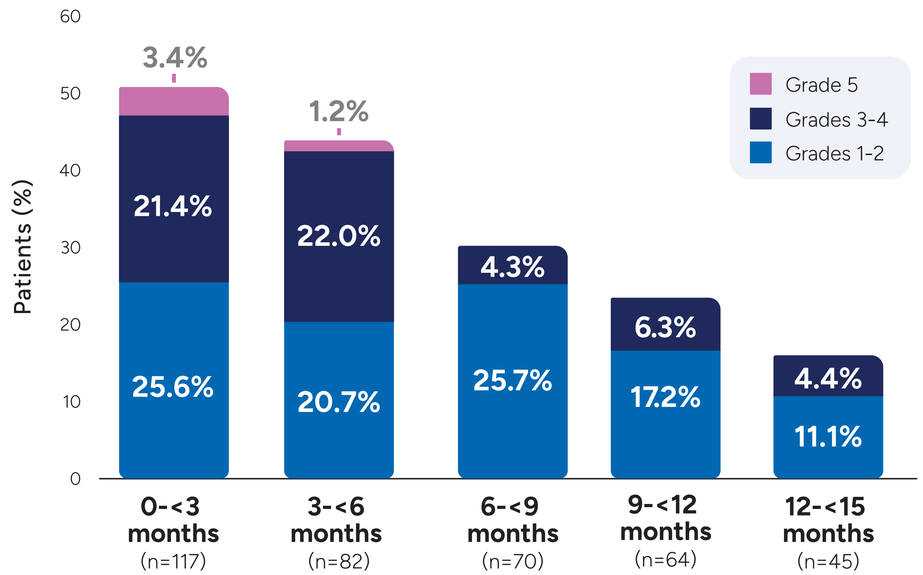
LYNOZYFIC can cause serious, life-threatening, or fatal infections.[1]

Most common infections
(≥10%; N=117)[1]

Adverse reaction	All grades (%)	Grades 3-4 (%)
Infections and infestations		
Upper respiratory tract infection*	35	6‖
Pneumonia†‡	28	21
COVID-19§	17	5
Urinary tract infections*	16	8‖
Sepsis	10	6

- Serious infections, including opportunistic infections, occurred in 42% of patients[1]
  - The most common serious infections reported (≥10%) were pneumonia and sepsis
- Grade 3 or 4 infections occurred in 38% of patients[1]
- Fatal infections occurred in 4% of patients[1]
- 2 cases of PML occurred in patients receiving LYNOZYFIC[1]

Observed rate of infections over time with LYNOZYFIC
(median follow-up: 11.1 months)[5]



Limitations: This analysis was not powered for statistical significance. Small patient numbers and lack of multiplicity adjustments can be limitations. No firm conclusions can be made.

*Includes other related terms.
†Includes fatal outcome.
‡Pneumonia includes atypical pneumonia, COVID-19 pneumonia, PJP, pneumonia, pneumonia cytomegaloviral, pneumonia fungal, pneumonia influenzal, and pneumonia viral.
§The LINKER-MM1 trial was initiated in 2019, prior to the development of the COVID-19 vaccines and management protocols.[6]
‖Only Grade 3 adverse reactions occurred.
PJP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Neutropenia: LYNOZYFIC can cause neutropenia and febrile neutropenia. In patients who received LYNOZYFIC at the recommended dose in LINKER-MM1, decreased neutrophil count occurred in 62% of patients with Grade 3 or 4 decreased neutrophil count in 47%. Febrile neutropenia occurred in 8% of patients.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Infections management[1]

- Monitor patients for signs and symptoms of infection and immunoglobulin levels prior to and during treatment with LYNOZYFIC and treat appropriately
- Administer prophylactic antimicrobials, antibiotics, antifungals, antivirals, vaccines, and subcutaneous or intravenous immunoglobulin (IVIG) according to guidelines, including prophylaxis for PJP and herpesviruses
- Withhold LYNOZYFIC in patients with active Grade 2-3 infection until the infection improves to Grade 1 or less
  - For Grade 4, consider permanent discontinuation of LYNOZYFIC
- Manage infections according to the recommendations on page 23 and per current practice guidelines

Please see additional warnings and precautions on neutropenia, hepatotoxicity, and embryo-fetal toxicity in the LYNOZYFIC Prescribing Information.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Neutropenia (cont'd): Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local guidelines. Monitor patients with neutropenia for signs of infection. Withhold LYNOZYFIC based on severity.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

LYNOZYFIC safety profile

LYNOZYFIC was evaluated in patients with relapsed or refractory multiple myeloma in an open-label, multicenter, multicohort, Phase 1/2 study: LINKER-MM1 (NCT03761108)[1,5]

- **Serious adverse reactions** occurred in 74% of patients who received LYNOZYFIC. Serious adverse reactions that occurred in >5% of patients included CRS (27%), pneumonia (13%), COVID-19 (7%), and acute kidney injury (5%)[1]
- **Fatal adverse reactions** occurred in 7% of patients and included sepsis (3.4%), chronic kidney disease (0.9%), pneumonia (0.9%), tumor lysis syndrome (0.9%), and encephalopathy (0.9%)[1]

Interruptions and discontinuations[1]

Permanent discontinuation of LYNOZYFIC due to adverse reactions occurred in 16% of patients. Adverse reactions leading to discontinuation that occurred in at least 2 patients included:

- Sepsis
- Pneumonia
- Encephalopathy

Dose interruptions or delays of LYNOZYFIC due to adverse reactions occurred in 74% of patients. Adverse reactions that required a dosage interruption or delay in >10% of patients included:

- Neutropenia (29%)
- Upper respiratory tract infection (18%)
- Pneumonia (15%)
- COVID-19 infection (11%)

The **most common adverse reactions** (≥20%) were musculoskeletal pain, CRS, cough, upper respiratory tract infection, diarrhea, fatigue, pneumonia, nausea, headache, and dyspnea.[1]

The **most common Grade 3 to 4 laboratory abnormalities** (≥30%) were decreased lymphocyte count, decreased neutrophil count, decreased hemoglobin, and decreased white blood cell count.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Hepatotoxicity: LYNOZYFIC can cause hepatotoxicity. In LINKER-MM1, 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% of patients who received the recommended dose. Grade 3 or 4 total bilirubin elevations occurred in 1.7% of patients. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold LYNOZYFIC or consider permanent discontinuation of LYNOZYFIC based on severity.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

LYNOZYFIC safety profile (cont'd)

Adverse reactions occurring in ≥10% of patients receiving LYNOZYFIC (N=117)[1]

Adverse reaction	All grades (%)	Grade 3-4 (%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	53	3.4†
Immune system disorders		
Cytokine release syndrome	46	0.9†
Hypogammaglobulinemia	13	0.9†
Respiratory, thoracic, and mediastinal disorders		
Cough*	39	0
Dyspnea*	21	0.9†
Nasal congestion	16	0

Adverse reaction	All grades (%)	Grade 3-4 (%)
Infections and infestations		
Upper respiratory tract infection*	35	6†
Pneumonia‡[a]	28	21
COVID-19	17	5
Urinary tract infections*	16	8†
Sepsis	10	6
Gastrointestinal disorders		
Diarrhea	35	1.7†
Nausea	23	0
Vomiting	19	0
Constipation	17	0

*Includes other related terms.
†Only Grade 3 adverse reactions occurred.
‡Includes fatal outcome.
[a]Pneumonia includes atypical pneumonia, COVID-19 pneumonia, PJP, pneumonia, pneumonia cytomegaloviral, pneumonia fungal, pneumonia influenzal, and pneumonia viral.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Embryo-Fetal Toxicity: Based on its mechanism of action, LYNOZYFIC may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LYNOZYFIC and for 3 months after the last dose.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

LYNOZYFIC safety profile (cont'd)

Adverse reactions occurring in ≥10% of patients receiving LYNOZYFIC (N=117)[1]

Adverse reaction (cont'd)	All grades (%)	Grade 3-4 (%)
General disorders and administration site conditions		
Fatigue*	34	0
Edema*	19	0.9†
Pyrexia	17	0
Nervous system disorders		
Headache*	22	0.9†
Encephalopathy‡[a]	18	3.4
Sensory neuropathy*	13	0.9

Adverse reaction (cont'd)	All grades (%)	Grade 3-4 (%)
Metabolism and nutrition disorders		
Decreased appetite	15	0.9†
Skin and subcutaneous tissue disorders		
Rash[b]	15	1.7†
Psychiatric disorders		
Insomnia	13	0
Vascular disorders		
Hypertension	10	4.3†

- Clinically significant adverse reactions that occurred in <10% of patients treated with LYNOZYFIC included **IRR, motor dysfunction, febrile neutropenia, ICANS, CMV infection, and PML**[1]

*Includes other related terms.
†Only Grade 3 adverse reactions occurred.
‡Includes fatal outcome.
[a]Encephalopathy includes agitation, amnesia, cognitive disorder, confusional state, delirium, depressed level of consciousness, encephalopathy (including hyperammonemic and toxic encephalopathy), irritability, lethargy, memory impairment, mental status changes, somnolence, and excludes ICANS.
[b]Rash includes dermatitis acneiform, dermatitis contact, drug eruption, erythema, rash, rash erythematous, rash maculo-papular, rash pruritic, and stasis dermatitis.

CMV, cytomegalovirus.

IMPORTANT SAFETY INFORMATION (cont'd)

Adverse Reactions

The most common adverse reactions (≥20%) are musculoskeletal pain, cytokine release syndrome, cough, upper respiratory tract infection, diarrhea, fatigue, pneumonia, nausea, headache, and dyspnea. The most common Grade 3 or 4 laboratory abnormalities (≥30%) are decreased lymphocyte count, decreased neutrophil count, decreased hemoglobin, and decreased white blood cell count.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

LYNOZYFIC safety profile (cont'd)

Select laboratory abnormalities (≥5% for Grade 3 or 4; worsened from baseline) in patients with R/R multiple myeloma receiving LYNOZYFIC (N=117)[1]*

Laboratory abnormality†	All grades (%)	Grade 3-4 (%)
Hematology		
Lymphocyte count decreased	97	92
Hemoglobin decreased	72	42
Platelet count decreased	64	19
White blood cell count decreased	63	31
Neutrophil count decreased	62	47
Chemistry		
Aspartate aminotransferase increased	61	10
Phosphorus decreased	55	24
Creatinine increased	47	7
Alanine aminotransferase increased	46	6

*The denominator used to calculate the rate varied from 106 to 117, based on the number of patients with a baseline value and at least 1 posttreatment value.
†Laboratory tests were graded according to NCI CTCAE version 5.0.

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

IMPORTANT SAFETY INFORMATION (cont'd)

Use in Specific Populations

Lactation: Advise not to breastfeed.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Management of other adverse reactions[1]

Adverse reactions	Severity*	Recommendations
Infusion-related reactions	Grade 2	▪ Stop infusion and treat symptoms ▪ May resume treatment with the remaining infusion (total infusion time must not exceed 6 hours total) when symptoms are Grade 1 or baseline ▪ Consider decreasing infusion rate by up to 50% when resuming treatment. If tolerated, infusion rate can be increased with subsequent doses

	Grade 3	▪ Stop infusion and treat symptoms
		▪ May resume when symptoms are Grade 1 or baseline
		▪ After resolution of the adverse event, follow the recommendations:
		  ▪ Decrease the infusion rate up to 50% (no more than 6 hours total)
		  ▪ Resume at reduced dose†
		  ▪ If the administered dose is tolerated, continue with the next dose of the recommended dosing regimen at the decreased infusion rate
		  ▪ Infusion rate can be increased if tolerated
		▪ Permanently discontinue LYNOZYFIC if Grade 3 IRR recurs with subsequent infusions

	Grade 4	▪ Permanently discontinue LYNOZYFIC and treat symptoms
Neurologic adverse reactions (excluding ICANS)	Grade 2	▪ Withhold LYNOZYFIC until symptoms resolve to Grade 1 or baseline‡
	Grade 3 (first occurrence)	▪ Withhold LYNOZYFIC until Grade 1 or baseline‡
	Grade 3 (recurrent) or Grade 4	▪ Permanently discontinue LYNOZYFIC

Table continues on page 23

*Based on NCI CTCAE version 5.0.
†If the last dose administered was 5 mg, administer 2.5 mg. If the last dose administered was 25 mg, restart step-up dosing from 5 mg. If the last dose administered was 200 mg, refer to page 6 for recommendations regarding restarting therapy based on time since the last dose.
‡Please see page 6 for recommendations on restarting LYNOZYFIC therapy.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions

Cytokine Release Syndrome (CRS): LYNOZYFIC can cause CRS, which can be serious or life-threatening. In LINKER-MM1, CRS occurred in 46% (54/117) of patients who received LYNOZYFIC at the recommended dose, with Grade 1 CRS occurring in 35% (41/117) of patients, Grade 2 in 10% (12/117), and Grade 3 in 0.9% (1/117). Thirty-eight percent (45/117) of patients had CRS following step-up dose 1, including 1 patient who experienced Grade 3 CRS; 8% (9/117) had an initial CRS event following a subsequent dose. Seventeen percent (19/113) of patients developed CRS after step-up dose 2, 10% (11/111) developed CRS after the first full 200-mg dose of LYNOZYFIC, and 3.6% (4/110) developed CRS after the second full dose. Recurrent CRS occurred in 20% (23/117) of patients. The median time to onset of CRS from the end of infusion was 11 (range: -1 to 184) hours after the most recent dose, with a median duration of 15 (range: 1 to 76) hours.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Management of other adverse reactions (cont'd)[1]

Adverse reactions	Severity*	Recommendations
Infections	Grades 2 or 3	▪ Withhold LYNOZYFIC in patients with active infection until the infection improves to Grade 1 or less‡
	Grade 4	▪ Consider permanent discontinuation of LYNOZYFIC ▪ If LYNOZYFIC is not permanently discontinued, withhold subsequent treatment doses until Grade 1 or baseline‡
Other nonhematologic adverse reactions	Grade 3	▪ Withhold LYNOZYFIC until Grade 1 or baseline†
	Grade 4	▪ Consider permanent discontinuation of LYNOZYFIC ▪ If LYNOZYFIC is not permanently discontinued, withhold subsequent treatment doses until Grade 1 or baseline†
Hematologic adverse reactions	Platelet count less than 50,000/mcL with bleeding OR less than 25,000/mcL	▪ Withhold LYNOZYFIC until 25,000/mcL or higher and no evidence of bleeding†
	Absolute neutrophil count less than 1.0 x 10^9/L with Grade 2 or higher infection OR less than 0.5 x 10^9/L	▪ Withhold LYNOZYFIC until 0.5 x 10^9/L or higher†
	Febrile neutropenia	▪ Withhold LYNOZYFIC until neutrophil count is greater than 1.0 x 10^9/L and fever resolves†
	Hemoglobin less than 8 g/dL	▪ Withhold LYNOZYFIC until hemoglobin is 8 g/dL or higher†

*Based on NCI CTCAE version 5.0.
† Please see page 6 for recommendations on restarting LYNOZYFIC therapy.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Cytokine Release Syndrome (CRS) (cont'd): Clinical signs and symptoms of CRS included, but were not limited to pyrexia, chills, hypoxia, tachycardia, and hypotension. Administer pretreatment medications and initiate therapy according to LYNOZYFIC step-up dosing to reduce the incidence and severity of CRS. Monitor patients for signs and symptoms of CRS after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur.

At the first sign of CRS, immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care; withhold LYNOZYFIC until CRS resolves and modify the next dose or permanently discontinue LYNOZYFIC based on severity.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

LYNOZYFIC REMS[1]

LYNOZYFIC is available only through a restricted program called the LYNOZYFIC REMS

The goal of the LYNOZYFIC REMS is to mitigate the risks of CRS and neurologic toxicity, including ICANS, by ensuring prescribers are aware of the importance of monitoring for signs and symptoms of CRS and neurologic toxicity, including ICANS, in patients exposed to LYNOZYFIC.

Notable requirements of the LYNOZYFIC REMS include the following:

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

Further information about the LYNOZYFIC REMS program is available at **LynozyficREMS.com** or by **telephone at 1-855-212-6391**. See the **REMS Fact Sheet** to learn more.

LYNOZYFIC Patient Wallet Cards are available in multiple languages at LynozyficREMS.com.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Cytokine Release Syndrome (CRS) (cont'd):

Infusion Related Reactions

Infusion-related reactions (IRR) may be clinically indistinguishable from manifestations of CRS. In the patients who were treated with the recommended step-up dosing regimen and pretreatment medications, the rate of IRR was 9% [11/117 including Grade 2 IRR (4.3%) and Grade 3 IRR (1.7%)]. For IRR, interrupt or slow the rate of infusion or permanently discontinue LYNOZYFIC based on severity of reaction.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Patient counseling

Counseling patients receiving LYNOZYFIC on CRS and neurologic toxicity, including ICANS[1]

Counsel patients:

- To seek immediate medical attention should signs and symptoms of CRS or neurologic toxicity, including ICANS, occur at any time
- To carry their Patient Wallet Card with them at all times and show it to all of their healthcare providers
  - The Patient Wallet Card describes symptoms of CRS and neurologic toxicity, including ICANS, which, if experienced, should prompt the patient to seek immediate medical attention
- To refrain from driving, or operating heavy or potentially dangerous machinery, for 48 hours after completion of each of the step-up doses and in the event of new onset of any neurological symptoms, until the symptoms resolve
  - This is because, due to the potential for neurologic toxicity, including ICANS, patients receiving LYNOZYFIC are at risk of confusion, lethargy, and depressed consciousness

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Neurologic Toxicity, including Immune Effector Cell Associated Neurotoxicity Syndrome: LYNOZYFIC can cause serious or life-threatening neurologic toxicity, including ICANS. In LINKER-MM1, neurologic toxicity occurred in 54% of patients, with Grade 3 or 4 neurologic toxicity occurring in 8%, at the recommended dose.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Nurse Educators are available to help

The Regeneron Nurse Educator team is available to provide educational support to healthcare providers as they integrate LYNOZYFIC into their practice. A locally designated Nurse Educator can:

Deliver in-service education on product dosing, administration, and adverse reaction management.

Support the incorporation of LYNOZYFIC into your practice.

Provide print and digital educational resources for healthcare providers and their patients.

Prior to your first administration of LYNOZYFIC, you may reach out to your local Nurse Educator to discuss the educational support available for your practice.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Neurologic Toxicity, including Immune Effector Cell Associated Neurotoxicity Syndrome (cont'd): Neurologic toxicities included ICANS, depressed level of consciousness, encephalopathy, and toxic encephalopathy. ICANS occurred in 8% of patients who received LYNOZYFIC with the recommended dosing regimen, including Grade 3 events in 2.6%. Most patients experienced ICANS following step-up dose 1 (5%). Two patients (1.8%) experienced initial ICANS following step-up dose 2 and one patient developed the first occurrence of ICANS following a subsequent full dose of LYNOZYFIC. Recurrent ICANS occurred in one patient. The median time to onset of ICANS was 1 (range: 1 to 4) day after the most recent dose with a median duration of 2 (range: 1 to 11) days. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

Neurologic Toxicity, including Immune Effector Cell Associated Neurotoxicity Syndrome (cont'd): The most common clinical signs and symptoms of ICANS are confusion, depressed level of consciousness, and lethargy. Monitor patients for signs and symptoms of neurologic toxicity, including ICANS during treatment. At the first sign of neurologic toxicity, including ICANS, immediately evaluate the patient; provide supportive therapy and consider further management per current practice guidelines. Withhold LYNOZYFIC until ICANS resolves and modify the next dose or permanently discontinue LYNOZYFIC based on severity. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity, including ICANS occur at any time.

Due to the potential for neurologic toxicity, including ICANS, patients receiving LYNOZYFIC are at risk of confusion and depressed consciousness. Advise patients to refrain from driving, or operating heavy or potentially dangerous machinery, for 48 hours after completion of each of the step-up doses and in the event of new onset of any neurological symptoms, until symptoms resolve.

LYNOZYFIC REMS: LYNOZYFIC is available only through a restricted program under a REMS called the LYNOZYFIC REMS because of the risks of CRS and neurologic toxicity, including ICANS.

Infections: LYNOZYFIC can cause serious, life-threatening, or fatal infections. In patients who received LYNOZYFIC at the recommended dose in LINKER-MM1, 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 infection reported (≥10%) were pneumonia and sepsis. Two cases of progressive multifocal leukoencephalopathy (PML) occurred in patients receiving LYNOZYFIC.

Monitor patients for signs and symptoms of infection and immunoglobulin levels prior to and during treatment with LYNOZYFIC and treat appropriately. Administer prophylactic antimicrobials, antibiotics, antifungals, antivirals, vaccines, and subcutaneous or intravenous immunoglobulin (IVIG) according to guidelines, including prophylaxis for PJP and herpesviruses. Withhold LYNOZYFIC or consider permanent discontinuation of LYNOZYFIC based on severity of the infection.

Neutropenia: LYNOZYFIC can cause neutropenia and febrile neutropenia. In patients who received LYNOZYFIC at the recommended dose in LINKER-MM1, decreased neutrophil count occurred in 62% of patients with Grade 3 or 4 decreased neutrophil count in 47%. Febrile neutropenia occurred in 8% of patients.

Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local guidelines. Monitor patients with neutropenia for signs of infection. Withhold LYNOZYFIC based on severity.

Hepatotoxicity: LYNOZYFIC can cause hepatotoxicity. In LINKER-MM1, 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% of patients who received the recommended dose. Grade 3 or 4 total bilirubin elevations occurred in 1.7% of patients. Liver enzyme elevation can occur with or without concurrent CRS.

Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold LYNOZYFIC or consider permanent discontinuation of LYNOZYFIC based on severity.

Embryo-Fetal Toxicity: Based on its mechanism of action, LYNOZYFIC may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LYNOZYFIC and for 3 months after the last dose.

Please see additional IMPORTANT SAFETY INFORMATION throughout and full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

Summary

LYNOZYFIC is administered with a step-up dosing schedule. After step-up dosing, LYNOZYFIC is administered with QW dosing. All patients may switch to Q2W dosing at Week 14. At or after Week 24 and after at least 17 full doses, patients with ≥VGPR may switch to Q4W dosing, or continue with Q2W dosing for responses <VGPR, until disease progression or unacceptable toxicity.[1]

Premedicate and initiate treatment with step-up dosing to reduce the risk of CRS and IRR.[1]
Patients should be hospitalized for 24 hours after administration of the first and second step-up dose.[1]

CRS occurred in 46% of patients. The median time to onset was 11 hours (range: -1 to 184), and the median duration of CRS was 15 hours (range: 1 to 76).[1]

Neurologic toxicity occurred in 54% of patients. ICANS occurred in 8% of patients. The median time to onset of ICANS was 1 day (range: 1 to 4), and the median duration of ICANS was 2 days (range: 1 to 11).[1]

Serious infections occurred in 42% of patients (Grade 3-4: 38%). Prophylaxis is recommended to reduce the risk of infection.[1]

References: 1. LYNOZYFIC (linvoseltamab-gcpt) full U.S. prescribing information. Regeneron Pharmaceuticals, Inc; 2025. **2.** van de Donk NWCJ, Zweegman S. *Lancet*. 2023;402(10396):142-158. doi:10.1016/S0140-6736(23)00521-4 **3.** Leclercq G, Steinhoff N, Haegel H, De Marco D, Bacac M, Klein C. *Oncoimmunology*. 2022;11(1):e2083479. doi:10.1080/2162402X.2022.2083479 **4.** Ludwig H, Terpos E, van de Donk N, et al. *Lancet Oncol*. 2023;24(6):e255-e269. doi:10.1016/s1470-2045(23)00159-6 **5.** Data on file. Regeneron Pharmaceuticals, Inc. **6.** Jagannath S, Richter J, Dhodapkar M, et al. Linvoseltamab, a B-cell maturation antigen-targeted T-cell-engaging bispecific antibody in patients with relapsed or refractory multiple myeloma, including difficult-to-treat subgroups. Paper presented at: American Association for Cancer Research Annual Meeting; April 5-10, 2024; San Diego, California**. 7.** Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758

IMPORTANT SAFETY INFORMATION (cont'd)

Adverse Reactions

The most common adverse reactions (≥20%) are musculoskeletal pain, cytokine release syndrome, cough, upper respiratory tract infection, diarrhea, fatigue, pneumonia, nausea, headache, and dyspnea. The most common Grade 3 or 4 laboratory abnormalities (≥30%) are decreased lymphocyte count, decreased neutrophil count, decreased hemoglobin, and decreased white blood cell count.

Use in Specific Populations

Lactation: Advise not to breastfeed.

Please see full Prescribing Information, including Boxed WARNING, for LYNOZYFIC.

REGENERON®