HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LYNOZYFIC safely and effectively. See full prescribing information for LYNOZYFIC.

LYNOZYFIC™ (linvoseltamab-gcpt) injection, for intravenous use
Initial U.S. Approval: 2025

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITY, including IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME
See full prescribing information for complete boxed warning.

- **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. (2.2, 2.4, 2.5, 5.1)**
- **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. (2.2, 2.4, 2.5, 5.2)**
- **LYNOZYFIC is available only through a restricted program called the LYNOZYFIC Risk Evaluation and Mitigation Strategy (REMS). (5.3)**

INDICATIONS 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). (1)

DOSAGE AND ADMINISTRATION

- Premedicate to reduce the risk of CRS and infusion-related reactions (IRR). (2.1, 2.3)
- Administer only as an intravenous infusion. (2.1, 2.6)
- Recommended Dosage (2.2):

Dosing Schedule	Day	Dose of LYNOZYFIC	
Step-Up Dosing Schedule	Day 1	Step-up dose 1	5 mg
	Day 8	Step-up dose 2	25 mg
	Day 15	First treatment dose	200 mg
Weekly Dosing Schedule	One week after Day 15	Second and subsequent treatment doses	200 mg
	treatment dose and once weekly from Week 4 to Week 13 for 10 treatment doses	treatment doses	
Biweekly (Every 2 Weeks) Dosing Schedule	Week 14 and every 2 weeks thereafter	Subsequent treatment doses	200 mg
Patients who have achieved and maintained VGPR or better at or after Week 24 and received at least 17 doses of 200 mg			
Every 4 Weeks Dosing Schedule	At Week 24 or after and every 4 weeks thereafter	Subsequent treatment doses	200 mg

- Patients should be hospitalized for 24 hours after administration of the first step-up dose and for 24 hours after administration of the second step-up dose. (2.1)
- See Full Prescribing Information for instructions on preparation and administration. (2.6)

DOSAGE FORMS AND STRENGTHS

Injection:
- 5 mg/2.5 mL (2 mg/mL) single-dose vial (3)
- 200 mg/10 mL (20 mg/mL) single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Infections: Can cause serious or fatal infections. Monitor patients for signs or symptoms of infection and treat accordingly. (5.4)
- Neutropenia: Monitor complete blood cell counts at baseline and periodically during treatment. (5.5)
- Hepatotoxicity: Can cause hepatotoxicity. Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. (5.6)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.7, 8.1, 8.3)

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. (6.1)

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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-844-467-2998 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING 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 *[see Dosage and Administration (2.2, 2.4, 2.5) and Warnings and Precautions (5.1)]*.**
- **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 *[see Dosage and Administration (2.2, 2.4, 2.5) and Warnings and Precautions (5.2)]*.**
- **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 *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

LYNOZYFIC is 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 *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- Administer LYNOZYFIC intravenously according to the step-up schedule to reduce the incidence and severity of cytokine release syndrome (CRS) *[see Dosage and Administration (2.2)]*.
- Administer only as an intravenous infusion after dilution in 0.9% Sodium Chloride Injection *[see Dosage and Administration (2.6)]*.

- Administer pretreatment medications *[see Dosage and Administration (2.3)]*.
- LYNOZYFIC should be administered by a healthcare provider with immediate access to emergency equipment and appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS), infusion-related reactions (IRR), and neurologic toxicity, including ICANS *[see Warnings and Precautions (5.1 and 5.2)]*.
- Due to the risk of CRS and neurologic toxicity, including ICANS, patients should be hospitalized for 24 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose.

2.2 Recommended Dosage

The recommended dosage for LYNOZYFIC is presented in Table 1. In patients who experience CRS, ICANS, or neurologic adverse reactions, refer to Tables 3, 4, and 5, respectively, for recommendations regarding administration of the next LYNOZYFIC dose. Continue treatment until disease progression or unacceptable toxicity. The recommended dosing schedule for LYNOZYFIC is provided in Table 1. The recommended dosage of LYNOZYFIC is step-up doses of 5 mg, 25 mg, and 200 mg, followed by 200 mg weekly for 10 doses, followed by 200 mg biweekly (every 2 weeks). In patients who have achieved and maintained VGPR or better at or after Week 24 and received at least 17 doses of 200 mg, decrease the dosing frequency to 200 mg every 4 weeks.

Table 1: LYNOZYFIC Dosing Schedule

Dosing Schedule	Day[a]	LYNOZYFIC Dose		Duration of Infusion
Step-up Dosing Schedule	Day 1	Step-up dose 1	5 mg	4 hours
	Day 8	Step-up dose 2	25 mg	
	Day 15	First treatment dose	200 mg	
Weekly Dosing Schedule	One week after Day 15 treatment dose and once weekly from Week 4 to Week 13 for 10 treatment doses	Second and subsequent treatment doses	200 mg	1 hour for the second treatment dose, and 30 minutes for subsequent doses[b]
Biweekly (Every 2 Weeks) Dosing Schedule	Week 14 and every 2 weeks thereafter	Subsequent treatment doses	200 mg	30 minutes

Dosing Schedule	Day[a]	LYNOZYFIC Dose	Duration of Infusion
Patients who have achieved and maintained VGPR or better at or after Week 24 and received at least 17 doses of 200 mg			
Every 4 Weeks Dosing Schedule	At Week 24 or after and every 4 weeks thereafter	200 mg	30 minutes

[a] 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.
[b] 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 (e.g., 4 hours, 1 hour, then 30 minutes).

2.3 Recommended Pretreatment Medications

Administer the following pre-treatment medications before each dose of the LYNOZYFIC 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 (see Tables 1, 2, and 3), to reduce the risk of CRS and/or IRR *[see Warnings and Precautions (5.1)]*:

- acetaminophen (or equivalent) 650 mg to 1,000 mg orally 30 to 60 minutes prior to infusion
- diphenhydramine (or equivalent) 25 mg orally or intravenously 30 to 60 minutes prior to infusion
- dexamethasone (or equivalent) intravenously 1 to 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 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

Pre-treatment medications may be discontinued once a treatment dose of LYNOZYFIC is tolerated without CRS and/or IRR following pre-treatment with 10 mg dexamethasone (or equivalent), acetaminophen (or equivalent), and diphenhydramine (or equivalent) as described.

2.4 Restarting LYNOZYFIC After Dosage Delay

Table 2 provides recommendations for restarting therapy after a dose delay. Refer to Table 3, Table 4, and Table 5 for recommendations about management of CRS, ICANS, or other adverse reactions.

Table 2: Recommendations for Restarting Therapy with LYNOZYFIC After a Dose Delay

Last Dose Administered	Time since the last dose administered[a]	Action for next dose. (For CRS/IRR or ICANS, refer to the dose modifications in Table 3, Table 4, and Table 5.)
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 pre-treatment medications prior to step-up dose 1, step-up dose 2, the first treatment dose, the second treatment dose, and if indicated, subsequent treatment doses *[see Dosage and Administration (2.3)]*. [a] Consider benefit-risk of restarting LYNOZYFIC in patients who require a dose delay of more than 30 days.		

2.5 Management of Adverse Reactions

Table 3 describes the management of CRS. Table 4 describes the management of ICANS. Table 5 describes the management of other adverse reactions.

Cytokine Release Syndrome

Identify CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, withhold LYNOZYFIC until CRS resolves. CRS should be managed according to the recommendations in Table 3 and per current practice guidelines. Supportive therapy for CRS should be administered, which may include intensive care for severe or life-threatening CRS.

Table 3: Recommendations for Management of Cytokine Release Syndrome

Grade[a]	Presenting Symptoms	Recommendations
Grade 1	Fever ≥100.4ºF (38ºC)[b]	• Withhold LYNOZYFIC until CRS resolves. • Provide supportive care, which may include intensive care. • When CRS resolves, resume LYNOZYFIC.[c,d]
Grade 2	Fever ≥100.4ºF (38ºC)[b] with:	• Withhold LYNOZYFIC until CRS resolves.

Grade[a]	Presenting Symptoms	Recommendations
	Hypotension responsive to fluids and not requiring vasopressors and/or hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by	• Provide supportive care, which may include intensive care. • When CRS resolves, resume treatment with LYNOZYFIC.[c,d] o 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. o Monitor patients within proximity of a healthcare facility for 24 hours following this dose, and consider hospitalization.
Grade 3	Fever ≥100.4ºF (38ºC)[b] with: Hypotension requiring a vasopressor (with or without vasopressin) and/or hypoxia requiring high-flow oxygen[e] by nasal cannula, face mask, non-rebreather mask, or Venturi mask.	• Withhold LYNOZYFIC until CRS resolves. • Provide supportive care, which may include intensive care. • When CRS resolves, resume treatment with LYNOZYFIC at reduced dose:[c, f] o Decrease infusion rate up to 50% (no more than 6 hours total). o Hospitalize for 24 hours after the administration for this dose. • After resuming treatment, if the administered dose is tolerated: o Continue with the next dose of the recommended dosing regimen per Table 1. o If the full dose is tolerated, infusion rate can be increased to the rate prior to the adverse reaction. • Permanently discontinue LYNOZYFIC if Grade 3 CRS recurs with subsequent infusions.
Grade 4	Fever ≥100.4°F (38°C)[b] with: Hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring oxygen by positive pressure (e.g., continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, and mechanical ventilation).	• Discontinue LYNOZYFIC permanently. • CRS should be managed per Grade 3 recommendations.

Grade[a]	Presenting Symptoms	Recommendations
Other	AST/ALT greater than 5 times ULN associated with CRS Grade 3 or less	• Withhold LYNOZYFIC until CRS resolves and AST/ALT are less than 3 times ULN if baseline was normal or 1.5 to 3 times baseline if baseline was abnormal. • Provide supportive care, which may include intensive care, and monitor. • No change in dose is needed in patients without CRS symptoms with transaminase levels that are trending towards baseline within 7 days. • If values do not trend towards baseline in 7 days, decrease the dose.[f] • See infusion rate information by CRS grade.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) criteria for grading CRS (2019).
[b] 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.
[c] Administer pretreatment medications prior to next dose *[see Dosage and Administration (2.3)]*.
[d] Follow the recommendations in Table 2 for restarting dosing.
[e] Low-flow oxygen defined as oxygen delivered at less than 6 L/minute: high-flow oxygen defined as oxygen delivered at greater than or equal to 6 L/minute.
[f] 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 Table 2 for recommendations regarding restarting therapy based on time since the last dose.

Neurologic Toxicity, including ICANS

Management recommendations for ICANS and neurologic toxicity are summarized in Table 4 and Table 5. At the first sign of suspected neurologic toxicity, including ICANS, withhold LYNOZYFIC and consider consultation with neurologist and other specialists for further evaluation and management. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care for severe or life-threatening ICANS. Manage per current practice guidelines.

Table 4: Recommendations for Management of ICANS

Grade[a]	Presenting Symptoms[b]	Recommendations
Grade 1	ICE[c] score 7-9, or depressed level of consciousness[d]: awakens spontaneously.	• Withhold until neurologic symptoms resolve or return to baseline.[e] • Provide supportive therapy. Manage per current practice guidelines. • Consider non-sedating, anti-seizure medications for seizure prophylaxis.
Grade 2	ICE[c] score 3-6, or depressed level of consciousness[d]: awakens to voice.	• Withhold until neurologic symptoms resolve or return to baseline.[e] • Provide supportive therapy. Manage per current practice guidelines.

Grade[a]	Presenting Symptoms[b]	Recommendations
		• Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Consider non-sedating, anti-seizure medications for seizure prophylaxis. • Monitor patients within proximity of a healthcare facility for 24 hours following the next dose of LYNOZYFIC and consider hospitalization.
Grade 3	ICE[c] score 0-2, or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures, either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local edema on neuroimaging.	• Withhold until neurologic symptoms resolve or return to baseline. • Provide supportive therapy, which may include intensive care. Manage per current practice guidelines. • Consider neurology evaluation. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Consider non-sedating, anti-seizure medications for seizure prophylaxis. • Permanently discontinue LYNOZYFIC for recurrent Grade 3 ICANS. • Resume treatment with LYNOZYFIC at a reduced dose[g] and hospitalize for 24 hours after the administration of the dose. After resuming treatment, if the administered dose is tolerated, continue with the next dose of the recommended dosing regimen per Table 1.
Grade 4	ICE[c] score 0, or depressed level of consciousness[d]: 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	• Permanently discontinue LYNOZYFIC. • Provide supportive therapy, which may include intensive care. Manage per current practice guidelines. • Consider neurology evaluation. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Consider non-sedating, anti-seizure medications for seizure prophylaxis.

Grade[a]	Presenting Symptoms[b]	Recommendations
	• 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.	

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.
[b] Management is determined by the most severe event, not attributable to any other cause.
[c] 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, e.g., point to clock, pen, button=3 points); Following Commands (e.g., "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.
[d] Not attributable to any other cause.
[e] Follow the recommendations in Table 2 for restarting dosing.
[f] All references to dexamethasone administration are dexamethasone or equivalent.
[g] 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 Table 2 for recommendations regarding restarting therapy based on time since the last dose.

Other Adverse Reactions

Management recommendations for other adverse reactions are summarized in Table 5.

Table 5: Recommendations for Management of Other Adverse Reactions

Adverse Reaction	Severity[a]	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.

Adverse Reaction	Severity[a]	Recommendations
		• 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: o Decrease the infusion rate up to 50% (no more than 6 hours total). o Resume at reduced dose.[b] o If the administered dose is tolerated, continue with the next dose of the recommended dosing regimen at the decreased infusion rate. o 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.[c]
	Grade 3 (First occurrence)	• Withhold LYNOZYFIC until Grade 1 or baseline.[c]
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue LYNOZYFIC.
Infections	Grades 2 or 3	• Withhold LYNOZYFIC in patients with active infection until the infection improves to Grade 1 or less.[c]
	Grade 4	• Consider permanent discontinuation of LYNOZYFIC. If treatment is not permanently discontinued, withhold subsequent treatment doses until Grade 1 or baseline.[c]
Other Non-hematologic Adverse Reactions	Grade 3	• Withhold LYNOZYFIC until Grade 1 or baseline.[c]
	Grade 4	• Consider permanent discontinuation of LYNOZYFIC.

Adverse Reaction	Severity[a]	Recommendations
		• If LYNOZYFIC is not permanently discontinued, withhold subsequent treatment doses until Grade 1 or baseline.[c]
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.[c]
	Absolute neutrophil count less than 1 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.[c]
	Febrile neutropenia	• Withhold LYNOZYFIC until neutrophil count is greater than 1 x 10^9/L and fever resolves.[c]
	Hemoglobin less than 8 g/dL	• Withhold LYNOZYFIC until hemoglobin is 8 g/dL or higher.[c]

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0
[b] 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 Table 2 for recommendations regarding restarting therapy based on time since the last dose.
[c] Follow the recommendations in Table 2 for restarting dosing.

2.6 Preparation and Administration

Preparation

- Use aseptic technique to prepare LYNOZYFIC. Each vial is intended for one time use only. Do not shake.
- 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.
- Determine the dose, total volume of LYNOZYFIC solution, and the number of LYNOZYFIC vials needed (see Table 6).

Dilution

- Withdraw the desired dose from the vial of LYNOZYFIC and transfer into an intravenous infusion bag [polyvinyl chloride (PVC) or polyolefin (PO)] of 0.9% Sodium Chloride Injection, according to Table 6. Discard any unused portion left in the vial.
- Mix diluted solution by gentle inversion. Do not shake the solution.

Table 6: Dilution of LYNOZYFIC

LYNOZYFIC dose	LYNOZYFIC vial strength	Volume of LYNOZYFIC to be added to the infusion bag	Size of 0.9% Sodium Chloride Injection Infusion Bag (PVC or PO)
2.5 mg[a]	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

[a] Modified dose due to adverse reaction. For instructions on when to use the modified dose refer to Table 3, Table 4, and Table 5.

Diluted LYNOZYFIC Storage

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

- Administer as an intravenous infusion only.
- Refer to *Dosage and Administration (2.2)* for infusion rates.
- Connect the prepared intravenous infusion bag containing the final LYNOZYFIC solution to intravenous 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.
- Prime with LYNOZYFIC to the end of the intravenous tubing.
- Do not mix LYNOZYFIC with other drugs or concurrently administer other drugs through the same intravenous line.

- 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.
- Total infusion time should include flushing of the infusion line.

3 DOSAGE FORMS AND STRENGTHS

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

- Injection: 5 mg/2.5 mL (2 mg/mL) single-dose vial
- Injection: 200 mg/10 mL (20 mg/mL) single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS)

LYNOZYFIC can cause cytokine release syndrome (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) *[see Adverse Reactions (6.1)]*. 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.

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 *[see Dosage and Administration (2.2)* and *Dosage and Administration (2.3)]*.

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 *[see Dosage and Administration (2.5)]*.

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 *[see Dosage and Administration (2.2)* and *Dosage and Administration (2.3)]*, 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 *[see Dosage and Administration (2.5)]*.

LYNOZYFIC is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.2 Neurologic Toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome

LYNOZYFIC can cause serious or life-threatening neurologic toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS) *[see Adverse Reactions (6.1)]*.

In LINKER-MM1, neurologic toxicity occurred in 54% of patients, with Grade 3 or 4 neurologic toxicity occurring in 8%, at the recommended dose *[see Adverse Reactions (6.1)]*. 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.

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 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 *[see Dosage and Administration (2.5)]*. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity 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 *[see Dosage and Administration (2.2)]* and in the event of new onset of any neurological symptoms, until symptoms resolve.

LYNOZYFIC is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.3 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 *[see Warnings and Precautions (5.1, 5.2)]*.

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 LYNOZYFIC about the risk of CRS and neurologic toxicity, including ICANS, and provide patients with LYNOZYFIC Patient Wallet Card.
- 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.
- 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.

5.4 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% *[see Adverse Reactions (6.1)]*. 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 *[see Dosage and Administration (2.3)]*.

Withhold LYNOZYFIC or consider permanent discontinuation of LYNOZYFIC based on severity of the infection *[see Dosage and Administration (2.5)]*.

5.5 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 *[see Adverse Reactions (6.1)]*.

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 *[see Dosage and Administration (2.5)]*.

5.6 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 *[see Adverse Reactions (6.1)]*. 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 *[see Dosage and Administration (2.5)]*.

5.7 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 *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*
- Neurologic Toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome *[see Warnings and Precautions (5.2)]*
- Infections *[see Warnings and Precautions (5.4)]*
- Neutropenia *[see Warnings and Precautions (5.5)]*
- Hepatotoxicity *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Relapsed or Refractory Multiple Myeloma

The safety of LYNOZYFIC was evaluated in LINKER-MM1 *[see Clinical Studies (14)]*. Patients (n=117) received LYNOZYFIC as step-up doses of 5 mg on Day 1 and 25 mg on Day 8, and the first treatment dose of 200 mg on Day 15. Patients then received 200 mg intravenously once weekly from Week 4 to Week 13, followed by 200 mg every 2 weeks from Week 14. In the Phase 2 portion of the study, patients who achieved and maintained VGPR or better at or after Week 24 and received at least 17 doses of 200 mg were able to receive every 4-week dosing. The median duration of treatment was 47 weeks (range 1, 151); 55% of patients were exposed for 9 months or longer and 36% were exposed for 1 year or longer.

The median age of patients who received LYNOZYFIC was 70 years (range: 37 to 91 years); 55% were male; 71% were White, 17% were Black or African American, and 9% were Asian.

Serious adverse reactions occurred in 74% of patients who received LYNOZYFIC. Serious adverse reactions that occurred in >5% of patients included cytokine release syndrome (27%), pneumonia (13%), COVID-19 (7%), and acute kidney injury (5%). 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%).

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, and encephalopathy.

Dosage interruptions or delays of LYNOZYFIC due to adverse reactions occurred in 74% of patients. Adverse reactions which required a dosage interruption or delay in >10% of patients included neutropenia (29%), upper respiratory tract infection (18%), pneumonia (15%), and COVID-19 infection (11%).

The most common adverse reactions (≥20%) were musculoskeletal pain, cytokine release syndrome, cough, upper respiratory tract infection, diarrhea, fatigue, pneumonia, nausea, headache, and dyspnea. 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.

Table 7 summarizes the adverse reactions in LINKER-MM1.

Table 7: Adverse Reactions (≥10%) in Patients with Relapsed or Refractory Multiple Myeloma Who Received LYNOZYFIC in LINKER-MM1

Adverse Reaction	LYNOZYFIC (N=117)	
	All Grades (%)	Grade 3 or 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
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
General disorders and administration site conditions		
Fatigue[*]	34	0
Edema[*]	19	0.9[#]
Pyrexia	17	0
Nervous system disorders		
Headache[*]	22	0.9[#]
Encephalopathy[±,b]	18	3.4
Sensory Neuropathy[*]	13	0.9

Adverse Reaction	LYNOZYFIC (N=117)	
	All Grades (%)	Grade 3 or 4 (%)
Metabolism and nutrition disorders		
Decreased appetite	15	0.9[#]
Skin and subcutaneous tissue disorders		
Rash[c]	15	1.7[#]
Psychiatric disorders		
Insomnia	13	0
Vascular disorders		
Hypertension	10	4.3[#]

* 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.
[b] 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.
[c] Rash includes dermatitis acneiform, dermatitis contact, drug eruption, erythema, rash, rash erythematous, rash maculo-papular, rash pruritic, and stasis dermatitis.

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

Table 8 summarizes the laboratory abnormalities in LINKER-MM1.

Table 8: Select Laboratory Abnormalities (≥5% for Grade 3 or 4) That Worsened from Baseline in Patients with Multiple Myeloma Treated with LYNOZYFIC in LINKER-MM1

Laboratory Abnormality[a]	LYNOZYFIC (N=117)[b]	
	All Grades (%)	Grades 3 or 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

Laboratory Abnormality[a]	LYNOZYFIC (N=117)[b]	
	All Grades (%)	Grades 3 or 4 (%)
Chemistry		
Aspartate aminotransferase increased	61	10
Phosphorus decreased	55	24
Creatinine increased	47	7
Alanine aminotransferase increased	46	6

[a] Laboratory tests were graded according to NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 5.0.

[b] 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 one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effects of LYNOZYFIC on Other Drugs

Certain CYP substrates

Monitor for toxicity unless otherwise recommended in the Prescribing Information of certain CYP substrates where minimal changes in the concentration may lead to serious adverse reactions when used concomitantly with LYNOZYFIC.

Linvoseltamab-gcpt causes the release of cytokines *[see Clinical Pharmacology (12.2)]* that may suppress cytochrome P450 (CYP) enzyme activity. Concomitant use with LYNOZYFIC increases CYP substrate exposure which may increase the risk of adverse reactions related to these substrates. Increased CYP substrate exposure is more likely to occur from initiation of the LYNOZYFIC step-up dosing schedule up to 14 days after the first 200 mg dose, and during and after CRS *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanism of action, LYNOZYFIC may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of LYNOZYFIC in pregnant women to evaluate for a drug associated risk. No animal reproductive or developmental toxicity studies have been conducted with LYNOZYFIC.

Linvoseltamab-gcpt causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. In addition, based on the finding of B-cell

depletion in non-pregnant animals, linvoseltamab-gcpt can cause B-cell lymphocytopenia in infants exposed to linvoseltamab-gcpt in-utero. Human immunoglobulin (IgG) is known to cross the placenta after the first trimester of pregnancy; therefore, linvoseltamab-gcpt has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

LYNOZYFIC is associated with hypogammaglobulinemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with LYNOZYFIC should be considered.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of linvoseltamab-gcpt in human milk, the effects on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk.

Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with LYNOZYFIC and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

LYNOZYFIC may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with LYNOZYFIC.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of LYNOZYFIC.

8.4 Pediatric Use

The safety and effectiveness of LYNOZYFIC have not been established in pediatric patients.

8.5 Geriatric Use

Of the 117 patients with relapsed or refractory multiple myeloma who received LYNOZYFIC, 42 (36%) of patients were 65 to 74 years of age and 31 (26%) were 75 years of age and older *[see Clinical Studies (14)]*. 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, when compared with younger patients.

11 DESCRIPTION

Linvoseltamab-gcpt, a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager, is a recombinant human immunoglobulin (Ig)G4 antibody. Linvoseltamab-gcpt is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. The molecular weight of linvoseltamab-gcpt is approximately 146 kDa.

LYNOZYFIC (linvoseltamab-gcpt) injection for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution with a pH 6.0.

Each LYNOZYFIC 5 mg/2.5 mL vial contains 5 mg of linvoseltamab-gcpt. Each mL contains 2 mg of linvoseltamab-gcpt, histidine (0.7 mg), L-histidine hydrochloride monohydrate (1.1 mg), polysorbate 80 (1 mg), sucrose (100 mg), and Water for Injection, USP.

Each LYNOZYFIC 200 mg/10 mL vial contains 200 mg of linvoseltamab-gcpt. Each mL contains 20 mg of linvoseltamab-gcpt, histidine (0.7 mg), L-histidine hydrochloride monohydrate (1.1 mg), polysorbate 80 (1 mg), sucrose (100 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Linvoseltamab-gcpt is a bispecific T-cell engaging antibody that binds to the CD3 receptor expressed on the surface of T-cells and B-cell maturation antigen (BCMA) expressed on the surface of multiple myeloma cells and some healthy B-lineage cells.

In vitro, linvoseltamab-gcpt activated T-cells, caused the release of various proinflammatory cytokines, and resulted in the lysis of multiple myeloma cells. Linvoseltamab-gcpt had anti-tumor activity in mouse models of multiple myeloma.

12.2 Pharmacodynamics

The 200 mg once weekly dosing regimen was associated with better objective response rate and complete response rate when compared to the 50 mg once weekly (0.25 times the recommended dosage) dosing regimen in patients with relapsed or refractory multiple myeloma.

Linvoseltamab-gcpt exposure-response relationships have not been fully characterized.

Effect on Circulating Cytokines

Transient elevation of circulating cytokines (IL-2, IL-6, and IFN-γ) was primarily observed during the step-up dose regimen and the first full 200 mg dose. The highest elevation of cytokines was generally observed 4 hours after each infusion and generally

returned to baseline prior to the next dose. Limited cytokine release was observed following subsequent doses.

12.3 Pharmacokinetics

Pharmacokinetic (PK) parameters were evaluated at the recommended dosage in patients with relapsed or refractory multiple myeloma and are presented as geometric mean (CV%) unless otherwise specified.

Linvoseltamab-gcpt PK exposures following use of the recommended dosing schedule are presented in Table 9. Linvoseltamab-gcpt C_{trough} increased more than proportionally over a dose range of 96 mg to 800 mg (0.48 to 4 times the recommended full dose). Linvoseltamab-gcpt maximum concentration (127 mg/L [51%]) is achieved after the first dose of the every-2-weeks dosing regimen (i.e., the 12th dose of 200 mg).

Table 9: Geometric Mean (CV%) Exposure Following the Recommended Dosage for Linvoseltamab-gcpt

Dosing Period	C_{max} (mg/L)	C_{trough} (mg/L)	C_{avg} (mg /L)
First 200 mg weekly dose	52.7 (37.2)	15.5 (64.8)	27.4 (34.2)
End of 200 mg weekly dosing (11th dose of 200 mg)	124 (50.4)	61.8 (123)	84.6 (74.6)
End of 200 mg every 2 weeks dosing (16th dose of 200 mg)	97.9 (52.7)	30.2 (213)	51.9 (95.3)
Steady state[a] with 200 mg every 4 weeks dosing	64.8 (45.1)	6.3 (362)	20.5 (84.6)
[a] Steady state values are approximated at Week 28.			

Distribution

Linvoseltamab-gcpt volume of distribution (Vd) is 7.05 L (33.6%).

Elimination

Linvoseltamab-gcpt clearance is 0.68 L/day (52.2%) at baseline and 0.43 L/day (83.8%) at steady state.

Linvoseltamab-gcpt clearance decreases over time because its elimination is mediated by two parallel processes: a linear, non-saturable catabolic process and a nonlinear, saturable target-mediated pathway. Patients who discontinue linvoseltamab-gcpt are expected to have a 97% reduction from C_{max} at a median (5th to 95th percentile) time of 77.7 (18 to 154) days after last dose.

Metabolism

Linvoseltamab-gcpt is expected to be metabolized into small peptides by catabolic pathways.

Reference ID: 5618212

Specific Populations

No clinically significant differences in the pharmacokinetics of linvoseltamab-gcpt were observed based on age (37 to 91 years), weight (44 to 172 kg), sex, race (White, Asian, or Black), ethnicity (Hispanic/Latino or not Hispanic/Latino), mild to moderate renal impairment (creatinine clearance [CrCL] 30 to 89 mL/min, by Cockcroft-Gault [C-G] equation), or mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST).

The effect of severe renal impairment (CrCL 15 to 29 mL/min), end-stage renal disease (CrCL less than 15 mL/min), and moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN with any AST) on the pharmacokinetics of linvoseltamab-gcpt is unknown.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the study described below with the incidence of anti-drug antibodies in other studies, including those of linvoseltamab-gcpt.

During treatment in LINKER-MM1 (evaluated through 30 months) *[see Clinical Studies (14)]*, 1% (2/192) of LYNOZYFIC-treated patients developed anti-linvoseltamab-gcpt antibodies. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of linvoseltamab products is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with linvoseltamab-gcpt.

No animal studies have been performed to evaluate the effects of linvoseltamab-gcpt on fertility.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory Multiple Myeloma

The efficacy of LYNOZYFIC was evaluated in patients with relapsed or refractory multiple myeloma in an open-label, multi-center, multi-cohort study: LINKER-MM1 (NCT03761108). The study included patients who had previously received at least 3 prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 antibody. The study included patients with Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 and adequate baseline hematologic (absolute neutrophil count > 1 x 10^9/L, platelet count > 50 x 10^9/L,

hemoglobin level >8 g/dL), renal (CrCL > 30 mL/min), and hepatic (AST and ALT ≤ 2.5 x ULN, total bilirubin ≤ 1.5 x ULN, alkaline phosphatase ≤ 2.5 x ULN) function.

The study excluded patients with known multiple myeloma brain lesions or meningeal involvement, history of a neurodegenerative condition, history of seizure within 12 months prior to study enrollment, active infection, a history of an allogeneic or autologous stem cell transplantation within 12 weeks, prior BCMA-directed bispecific antibody therapy, prior bispecific T-cell engaging therapy, or prior BCMA CAR-T cell therapy.

Patients received a step-up dose of 5 mg on Day 1, 25 mg on Day 8, and the first treatment dose of 200 mg on Day 15 of LYNOZYFIC by intravenous infusion. Then, patients received 200 mg of LYNOZYFIC weekly from Week 4 to Week 13, followed by 200 mg every other week thereafter. After at least 24 weeks, the Phase 2 patients who achieved a very good partial response (VGPR) or greater received 200 mg of LYNOZYFIC every 4 weeks. Patients were treated until disease progression or unacceptable toxicity.

The efficacy population included 80 patients who had received at least four prior lines of therapy. The median age was 71 (range: 37 to 83) years with 30% of patients 75 years or older; 64% were male and 36% were female; 69% were White, 14% were Black or African American, 13% were Asian, and 2.5% were Hispanic/Latino.

The International Staging System (ISS) at study entry was Stage I in 39%, Stage II in 36%, and Stage III in 19%. High-risk cytogenetics (presence of del(17p), t(4;14) and t(14;16)) were present in 40% of patients. Eighteen percent of patients had extramedullary disease at baseline.

The median number of prior lines of therapy was 5 (range: 4 to 13); 83% of patients were refractory to the last line of therapy. Sixty-five percent of patients received prior stem cell transplantation. Seventy-nine percent of patients were triple-class refractory (refractory to a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody). Thirteen percent of patients were previously treated with a BCMA antibody-drug conjugate.

Efficacy was established based on objective response rate (ORR) as determined by blinded independent review committee (IRC), as measured using the International Myeloma Working Group (IMWG) criteria (see Table 10). The median time to first response was 0.95 months (range: 0.5 to 6 months). With a median follow-up of 11.3 months among responders, the estimated duration of response (DOR) rate was 89% (95% CI: 77, 95) at 9 months and 72% (95% CI: 54, 84) at 12 months.

Table 10: Efficacy Results for LINKER-MM1

Efficacy Endpoints	**LYNOZYFIC N=80**
Objective Response Rate (ORR) % (n) (95% CI)	70% (56) (59,80)
Complete response (CR) or better, % (n) (95% CI)	45% (36) (34,57)

Efficacy Endpoints	LYNOZYFIC N=80
Stringent complete response (sCR), % (n)	39% (31)
Complete response (CR), % (n)	6% (5)
Very good partial response (VGPR) % (n)	19% (15)
Partial response (PR), % (n)	6% (5)
Duration of Response (DOR)[a]	
Median, months (95% CI)	NR (12, NE)
CI=confidence interval; NE=not estimable [a] Based on Kaplan-Meier estimation.	

16 HOW SUPPLIED/STORAGE AND HANDLING

LYNOZYFIC (linvoseltamab-gcpt) injection is a clear to slightly opalescent, colorless to pale yellow solution in a single-dose vial. It is supplied as provided in Table 11.

Table 11: Packaging Configurations

Carton contents	NDC
One 5 mg/2.5 mL (2 mg/mL) single-dose vial	61755-054-01
One 200 mg/10 mL (20 mg/mL) single-dose vial	61755-056-01

Store unopened vial in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Cytokine Release Syndrome (CRS)

Advise patients that they should be hospitalized for 24 hours after administration of the first and second step-up doses of LYNOZYFIC *[see Dosage and Administration (2.2)]*. Inform patients of the risk of CRS, and discuss the signs and symptoms associated with CRS, including fever, chills, hypoxia, tachycardia, and hypotension. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Warnings and Precautions (5.1)]*.

Neurologic Toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome

Discuss the signs and symptoms associated with neurologic toxicity, including ICANS, including confusion, depressed level of consciousness, and lethargy. Advise patients to immediately contact their healthcare provider if they experience any signs or symptoms of neurologic toxicity. 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 or if they experience new onset of neurologic toxicity symptoms until the symptoms resolve *[see Warnings and Precautions (5.2)]*.

LYNOZYFIC REMS

LYNOZYFIC is available only through a restricted program called the LYNOZYFIC REMS. Inform patients that they will be given a Patient Wallet Card that they should carry with them at all times and show to all of their healthcare providers. This card describes symptoms of CRS and neurologic toxicity, including ICANS which, if experienced, should prompt the patient to seek immediate medical attention *[see Warnings and Precautions (5.3)]*.

Infections

Advise patients of the risk of serious infections. Instruct patients to immediately report infection-related signs or symptoms of infection (e.g., fever, chills, weakness) *[see Warnings and Precautions (5.4)]*.

Neutropenia

Discuss the signs and symptoms associated with neutropenia and febrile neutropenia *[see Warnings and Precautions (5.5)]*.

Hepatotoxicity

Advise patients that liver enzymes elevations may occur and that they should report symptoms that may indicate liver toxicity, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential to use effective contraception during treatment with LYNOZYFIC and for 3 months after the last dose *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with LYNOZYFIC and for 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
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