Linvoseltamab-gcpt (LYOZYFIC) in Multiple Myeloma
National Drug Mini-Monograph
July 2026
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Abbreviations: AC, active-controlled; CO, crossover; DB, double-blind; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; MC, multicenter; MN, multinational; PC, placebo-controlled; Q, GRADE quality of evidence; RCT, randomized clinical trial

SUMMARY OF PRESCRIBING INFORMATION[1,2]	
Description / MOA	Linvoseltamab-gcpt is a bispecific T-cell engaging antibody that binds to the CD3 receptor on T-cells and the B-cell maturation antigen (BCMA) expressed on multiple myeloma cells. This dual binding redirects cytotoxic T-cells to malignant B-cells, leading to T-cell activation and tumor cell lysis
Indication Under Review	Treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody; approved under accelerated approval based on response rate and durability of response.
Dosage Regimen	Administration follows a step-up dosing schedule to reduce the risk of Cytokine Release Syndrome (CRS) . Dosing consists of 5 mg on Day 1, 25 mg on Day 8, and 200 mg on Day 15 (also first treatment dose) . Followed by 200 mg weekly for 10 doses, then 200 mg biweekly (every 2 weeks) . Responders achieving ≥VGPR at or after Week 24 (after ≥17 doses of 200 mg) may transition to every 4-week dosing
Dosage Forms Under Review	Injection: 5 mg/2.5 mL (2 mg/mL) and 200 mg/10 mL (20 mg/mL) sterile, preservative-free solution in single-dose vials
Boxed Warnings	Cytokine Release Syndrome (CRS) and Neurologic Toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
Contraindications	none
Other Warnings	□ Infections □ Neutropenia □ Hepatotoxicity □ Embryo-fetal toxicity
Most Common AEs	Musculoskeletal pain (53%), CRS (46%), cough (39%), upper respiratory tract infection (35%), diarrhea (35%), fatigue (34%), and pneumonia (28%)
Drug Interactions	Cytokine release may suppress CYP450 enzyme activity, potentially increasing exposure to CYP substrates
Pregnancy	May cause fetal harm; verify pregnancy status before initiation; Use effective contraception during treatment and for 3 months after the last dose
Lactation	Advise patients not to breastfeed during treatment and for 3 months after the last dose
Renal Impairment	No clinically significant PK differences in mild to moderate renal impairment; effects of severe renal impairment or end-stage renal disease are unknown
Hepatic Impairment	No clinically significant PK differences in mild hepatic impairment; effects of moderate to severe hepatic impairment are unknown

CLINICAL EVIDENCE SUMMARY	
Trial	**LINKER-MM1**
Design	Phase 1/2, open-label, multi-center, multi-cohort study
Primary Endpoint	Overall Response Rate (ORR), Duration of Response (DOR)
Population	Patients with RRMM who had progressed on or after ≥3 prior lines of therapy including a PI, IMiD, and anti-CD38 antibody, or were triple-class refractory. • Prior BCMA-directed bispecific antibody therapy or BCMA CAR-T cell therapy was excluded
Interventions	• Two phase 2 dose cohorts (50 mg and 200 mg) were studied • 200 mg selected as the recommended dose based on superior efficacy, particularly in high disease burden subgroups
Demographics	Median age 70 years; 39% high-risk cytogenetics; 28% penta-refractory disease
Efficacy Results [2, 3]	For the FDA approval, the efficacy population comprised 80 patients who had received ≥4 prior lines of therapy. Key results assessed by blinded independent review committee using IMWG criteria: ORR: 70% (95% CI: 59–80); ≥ CR rate 45% [sCR 39; CR 6; VGPR 19; PR 6%] and median DOR N/R (12, Not estimable) Estimated DOR at 9 months: 89% (95% CI: 77–95); Estimated DOR at 12 months: 72% (95% CI: 54–84) In the 200 mg cohort (N = 117) at a median follow-up of 14.3 months, the ORR was 71% with 50% achieving ≥ CR and a median DOR of 29.4 months (95% CI: 19.2 to not evaluable). An updated analysis at a median follow-up of 21.3 months confirmed durable results: ORR 71%, ≥CR rate 52%, and MRD negativity (10^{-5} threshold) achieved in 94% of evaluable patients with ≥CR. Median overall survival was 31.4 months; median PFS had not been reached
Safety Results	• The prescribing information carries a Boxed Warning for CRS and neurologic toxicity including ICANS • CRS: 46% overall; grade 3 in <1% (most events occurred during step-up dosing) o Grade 1 in 35%; Grade 2 in 10% o Most events following first step up 5mg dose; 8% experienced after subsequent doses • Neurologic toxicity including ICANS: 54% overall; grade 3–4 in 8% o ICANS noted in 8%: Grade 1 in 2.6%; Grade 2 in 2.6%; Grade 3 in 2.6% • **Neutropenia: 44% (grade ≥3 in 43%); most common reason for dose interruption in 29%** • **Infections: 75% (grade ≥3 in 48%), with frequency declining after 6 months of treatment** • Anemia: grade 3 in ~31% • SAEs: 74% • Discontinuation due to adverse events: 16% • Warnings/Precautions include hepatotoxicity and embryo-fetal toxicity Linvoseltamab is available only through a REMS program (Lynozyfic REMS) due to CRS and neurotoxicity risks. Hospitalization is required after the first two step-up doses.
Authors' Conclusions	Linvoseltamab induced deep and durable responses, with a median duration of response (DOR) of 29.4 months, in patients with RRMM with an acceptable safety profile. Key findings supporting this conclusion included an ORR of 71%, with 50% achieving ≥CR, in a heavily pretreated population (median 5 prior lines, 28% penta-refractory, 39% high-risk cytogenetics). The safety profile was characterized by predominantly low-grade CRS (Grade 3 in only 0.9%), manageable neutropenia, and infections that declined in frequency and severity over time. With longer follow-up at 21.3 months, the authors concluded that long-term treatment with linvoseltamab provided deep and durable responses, with no new safety signals, and thus represents an effective therapeutic option in RRMM. Key updated findings included an ORR of 71% (≥CR 52%), median DOR of 29.4 months, median PFS not reached, median OS of 31.4 months, and MRD negativity (10^{-5}) in 94% of evaluable patients with ≥CR.
Trial Limitations	Single-arm, open-label design with no randomized comparator; Only accelerated approval granted by FDA based upon surrogate endpoints of ORR and duration of response; confirmatory trials will verify clinical benefit Any comparisons to other BCMA-directed therapies are indirect; Small sample size. FDA approval based surrogate endpoints of 80 patients.

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY					
DRUG	**VANF**	**VA Restrictions**	**FDA Labeling for Adults**	**Outcomes**	**NCCN GUIDELINES / VA Oncology Clinical Pathway**
linvoseltamab	TBD	TBD	treatment of relapsed/refractory multiple myeloma in patients who have received at least 4 prior lines of therapy that included a proteasome inhibitor, immunomodulatory agent and anti-CD38 monoclonal antibody	LINKER-MM1 ORR 71% DOR 29.4 mos	NCCN MM guideline: options for relapsed/refractory disease after ≥4 prior lines of therapy as **preferred Cat 2A:** elranatamab linvoseltamab talquetamab teclistamab VA Onc Clin Pathway: includes teclistamab
Teclistamab	PA-F	CFU	1. treatment of relapsed/refractory multiple myeloma in patients who have received at least 4 prior lines of therapy that included a proteasome inhibitor, immunomodulatory agent and anti-CD38 monoclonal antibody	MajesTEC-1 ORR 62% ≥ CR 28%	
			2. in combo with daratumumab/hyaluronidase for R/R myeloma after ≥ 1 prior line (PI + IMiD)	MajesTEC-3 Tec-dara vs. DPd or DVd: mPFS NR vs. 18 mos; 36-mos OS 83 vs. 65% ORR 90 vs. 75% ≥ CR 82 vs. 32%	
Elranatamab	NF	CFU	treatment of relapsed/refractory multiple myeloma in patients who have received at least 4 prior lines of therapy that included a proteasome inhibitor, immunomodulatory agent and anti-CD38 monoclonal antibody	MagnetisMM-3 ORR 61% ≥ CR 35%	
Talquetamab	NF	CFU	treatment of relapsed/refractory multiple myeloma in patients who have received at least 4 prior lines of therapy that included a proteasome inhibitor, immunomodulatory agent and anti-CD38 monoclonal antibody	MonumenTAL-1 ORR 73%	

POTENTIAL PLACE IN THERAPY	
Summary of Evidence	• Linvoseltamab is the newest bispecific B-cell maturation (BCMA)-directed CD3 T-cell engager approved for the treatment of relapsed/refractory multiple myeloma in patients who have received at least 4 prior lines of therapy that included a proteasome inhibitor, immunomodulatory agent and anti-CD38 monoclonal antibody • FDA-approval was expedited based upon surrogate endpoints of ORR and DOR • Responses appear to be deep and durable with 50% achieving a complete response or better and included high risk subgroups; Of those achieving a CR, MRD negativity was noted in 94% • An updated analysis at a median follow-up of 21 months indicates that responses are durable with no new safety signals • Indirect comparisons vs. teclistamab and elranatamab suggested potentially higher response rates and longer PFS with linvoseltamab, although these are non-randomized comparisons with inherent limitations. • Linvoseltamab is given via IV infusion, which may be more time-consuming than other bispecifics administered via SubQ, but the dosing regimen extends from weekly to biweekly to monthly dosing, which may provide convenience to the patient and less clinic time. • A boxed warning for risk of CRS, neurologic toxicity/ICANS exists; Drug is available only through the LYNOZYFIC REMS program • CRS and neurotoxicity events are primary grade 1 or 2; major adverse events to anticipate include neutropenia, which is a major reason for dose-interruption and infections

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References

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