Lazertinib LAZCLUZE
National Drug Mini-Monograph
May 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

FDA PRESCRIBING INFORMATION[1]	
Description / MOA	Lazertinib is a third-generation kinase inhibitor of Epidermal Growth Factor Receptor (EGFR) that inhibits EGFR exon 19 deletions and exon 21 L858R substitution mutations (common EGFR mutations).
Indication Under Review	In combination with amivantamab for first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations.
Dosage Regimen	Lazertinib 240mg orally once a day with or without food in combination with amivantamab IV or SC
Dosage Forms Under Review	Lazertinib tablets 80mg and 240mg
Pretreatment Procedures	□ When given in combination with amivantamab, anticoagulation prophylaxis (not Vitamin K antagonists) for the first 4 months; if no VTE in the first 4 months, consider discontinuation □ Doxycycline or minocycline for first 12 weeks; then clindamycin lotion to the scalp for the next 9 months □ Non-comedogenic moisturizer □ Wash with chlorhexidine 4% daily □ Limit sun exposure and use UVA/UVB sunscreen and protective clothing

EFFICACY CONSIDERATIONS

Trial 1	**Cho, et al. MARIPOSA[2]**
Design	• Phase 3, International, Randomized • Previously untreated locally advanced or metastatic NSCLC with common EGFR mutation (exon 19 del or exon 21 L958R substitution). • Asymptomatic or previously treated and stable brain metastases allowed • Adequate organ and bone-marrow function • ECOG 0-1 • **Arm A:** Amivantamab plus lazertinib • **Arm B:** Osimertinib • **Arm C:** Lazertinib single agent • **Primary Endpoint:** PFS of Amivantamab plus Lazertinib versus Osimertinib
Population	• Med Age: 63-64 Female: 59-64% Asian: 58-59% • ECOG 0: 33-35% • Non-smoking: 69-70% • Adenocarcinoma: 97% • History of brain mets: 40-41% • Exon 19 deletion: 60%
Intervention	**A:** Amivantamab 1050mg (or 1400 mg if ≥80 kg) IV weekly for first 4 weeks, then every 2 weeks plus lazertinib 240mg orally daily
Comparator	**B:** Osimertinib 80mg orally daily **C:** Lazertinib 240mg orally daily
Results	**Primary End Point: PFS amivantamab + lazertinib vs osimertinib** Key Secondary End Points: Overall Survival Other End Points: objective response, duration of response, safety Lazertinib single agent: N=216; Median follow-up 22 months; Median duration of treatment: 18 months

Outcome	Amivantamab plus lazertinib (N=429)	Osimertinib (N=429)	Lazertinib single agent N-216	HR (95% CI)
Med PFS	**23.7 months**	**16.6 months**		**0.70 (0.58-0.85)**
Med Duration of Response	25. months	16.8 months		
Med PFS (lazertinib)			18.5 months	0.72 (0.57-0.90) comparison of combination to lazertinib
OS				Median not reached;
18 months	82%	79%		HR 0.80 (0.61, 1.05)
24 months	74%	69%		
OS (Final analysis)[3] at 3 years	60%	51%		
Median OS (lazertinib)	NE	36.7 mos		HR 0.75 (95%CI 0.61, 0.92) HR 0.82 (0.59, 1.14) comparison of combination to lazertinib Final HR 0.83 (9CI 0.65, 1.06)
ORR	86%	85%		

Authors' Conclusions	• First-line amivantamab plus lazertinib therapy significantly prolonged PFS compared to osimertinib, which was also seen across key subgroups • Serial imaging of head for CNS metastases was performed unlike previous NSCLC trials • The number of deaths was inadequate to provide conclusions about overall survival • More EGFR-MET adverse reactions in the combination arm (especially dermatologic and venous thromboembolism) versus more diarrhea in the osimertinib arm.

Guidelines	
NCCN Guidelines	For first-line treatment of non-squamous non-small cell lung cancer with advanced/metastatic disease and EGFR exon19 del or exon 21 L858R substitution: Preferred: • Osimertinib • Osimertinib plus cisplatin (or carboplatin) plus pemetrexed • Amivantamab plus lazertinib
VA Clinical Pathway	For first-line treatment of non-squamous non-small cell lung cancer with advanced/metastatic disease and EGFR exon19 del or exon 21 L858R substitution: • Osimertinib • Osimertinib plus cisplatin (or carboplatin) plus pemetrexed (shared decision-making)

SAFETY CONSIDERATIONS	
Boxed Warnings	None
Contraindications	None
Other Warnings	• **Venous Thromboembolic Events**: 36%; Gr 3: 10%; Gr 4 0.5%; Fatal: 0.5%; most occur during first 4 months of treatment. Recommend anticoagulation prophylaxis for first 4 months (but no Vitamin K antagonists). • **ILD/pneumonia**: 3.1%; Gr 3: 1.0%; Gr 4: 0.1; n=1 fatality • **Dermatologic Adverse Events**: severe rash including dermatitis acneiform, pruritus, dry skin in 86%; G3: 26%; avoid sun exposure, use sunscreen and protective clothing; if rash develops use topical steroids and/or oral antibiotics; for severe reactions use oral steroids and refer to dermatology. • **Ocular toxicity** (including keratitis): 16%; Gr 3 or 4: 0.7% • **EF Toxicity**
Top 5 AEs	In combination with amivantamab: Rash, nail toxicity, infusion-related reactions, musculoskeletal pain, edema
Drug Interactions	•Avoid concomitant use with strong or moderate CYP3A4 inducers •CYP3A4 substrates with narrow therapeutic window •BCRP substrates with narrow therapeutic window
Pregnancy	May cause fetal harm based on its mechanism of action.
Lactation	No data, but potential for serious adverse reactions; advise women not to breastfeed

OTHER CONSIDERATIONS	
FDA Review	Results of the MARIPOSA trial demonstrate effectiveness and clinically meaningful advantage in progression-free survival compared to osimertinib, supported by improvement in duration of response and a trend in improved overall survival with a favorable risk-benefit.
NICE Review	Amivantamab plus lazertinib is an option for untreated advanced non-small cell lung cancer in adults with an EGFR exon 19del or exon L858R substitution mutation.

THERAPEUTIC ALTERNATIVES AND THEIR PLACE IN THERAPY

DRUG	VANF	CFU	FDA	GUIDELINES
Osimertinib	PA-F	Yes	• First line treatment of metastatic non-small cell lung cancer in tumors with exon 19 deletion or exon 21 L858R mutation	NCCN and VA Oncology Clinical Pathway
Osimertinib plus platinum and pemetrexed	PA-F (all drugs)	Yes for osimertinib	• In combination with pemetrexed and platinum-based chemotherapy, first line treatment of metastatic non-small cell lung cancer in tumors with exon 19 deletion or exon 21 L858R mutation	NCCN and VA Oncology Clinical Pathway

POTENTIAL PLACE IN THERAPY OF ——

1. Lazertinib is a third-generation kinase inhibitor of EGFR exon 19 deletion or exon 21 L858R substitution mutations.
2. FDA-approved in combination with amivantamab for the first-line treatment of adults with locally advanced or metastatic NSCLC harboring EGFR exon 19 deletions or exon 21 L858R mutations.
3. In the MARIPOSA trial, the combination improved progression-free survival compared to osimertinib and improved overall survival at 3 years of follow-up.
4. Key toxicities include rash (requiring prophylactic antibiotics and topical emollient), paronychia, and VTE events requiring anticoagulation prophylaxis. Administration with amivantamab includes VTE prophylaxis, oral antibiotics for skin rash, moisturizing cream, and sunscreen.
5. An exploratory analysis of MARIPOSA comparing lazertinib monotherapy and osimertinib monotherapy found comparative efficacy and safety.[4]
6. Lazertinib plus amivantamab is a first-line option for patients with advanced non-squamous non-small cell lung cancer whose tumor has an EGFR exon 19 deletion or exon 21 L858R substitution mutation. Adverse events with the combination may limit use in the VA population.

Original: May 2026.

Contact person: Mark C. Geraci, Pharm.D., BCOP, National Program Manager, VA Pharmacy Benefits Management Services – Formulary Management (12PBM)

References

1 Lazcluze (lazertinib) tab [prescribing information online]. Horshan, PA: Janssen. November 2025.

[2] Cho BC, Lu S, Felip E, et al. Amivantamab plus lazertinib in previously untreated EGFR-mutated advanced NSCLC. New Eng J Med 2024; 391: 1486-1498. doi: 10.1056/NEJMoa2403614

[3] Yang JC-H, Lu S, Hayashi H, et al. Overall survival analysis with amivantamab-lazertinib in EGFR-mutated advanced NSCLC. New Eng J Med 2025; 393: 1681-93.

[4] Lee S-H, Lu S, Hayashi H, et al. Lazertinib versus osimertinib in previously untreated EGFR-mutant advanced NSCLC: a randomized, double-blind, exploratory analysis from MARIPOSA. J Thoracic Oncology 2025; 20: 1655-1668.