CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Amivantamab-vmjw (Rybrevant®)

Version: 3.0

EFFECTIVE DATE: 5/27/2025

NantHealth® | Eviti®

Please note the following:

For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Amivantamab-ymjw (Rybrevant®)

Discussion

Amivantamab-vmjw is a fully human epidermal growth factor receptor (EGFR) and mesenchymal epithelial transition (MET) bispecific antibody with an immune cell-directing activity designed to engage two distinct driver pathways in non-small cell lung cancer (NSCLC). The mechanism of action is binding to each receptor's extracellular domain, amivantamab-vmjw can inhibit ligand binding and, in exon 20 insertion mutation models, degradation of EGFR and MET. EGFR is a signaling pathway that regulates cell differentiation, proliferation, migration, angiogenesis, and apoptosis. MET is a reversible biological process that involves the transition from motile, multipolar, or spindle-shaped mesenchymal cells to planar arrays of polarized cells called epithelia. The presence of EGFR and MET on the surface of tumor cells also allows for the targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.[1,2,3]

Clinically significant adverse reactions included infusion-related reactions, interstitial lung disease/pneumonitis, venous thromboembolic (VTE) events with concomitant use with lazertinib, dermatologic reactions, and ocular toxicity.[2]

The NCCN NSCLC Panel recommends testing for EGFR exon 20 insertion mutations in all patients with metastatic nonsquamous NSCLC or NSCLC NOS based on data showing the efficacy of several agents as subsequent therapy options for patients with EGFR exon 20 insertion-positive metastatic NSCLC. EGFR exon 20 insertion mutation testing can be considered in patients with metastatic squamous cell carcinoma.[3]

Amivantamab-vmjw is approved by the Food and Drug Administration (FDA) and endorsed by the National Comprehensive Cancer Network (NCCN) for non-small cell lung cancer (NSCLC).[2,3]

Definitions

- **Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)** - A cytolytic process where immune cells, such as natural killer (NK) cells, monocytes/macrophages, NKT cells, or T cells, target and destroy cells coated with IgG antibodies.[4]
- **Trogocytosis Mechanisms** - A process where one cell extracts lymphocytes (such as B cells, T cells, and natural killer cells), small portions of the membrane, and other components from another cell during direct contact. This interaction can lead to various biological outcomes, including immune responses and cell signaling changes.[5]
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.[6]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of over 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical

standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.[7]

Policy

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when all criteria are met:

Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. First-line treatment in combination with lazertinib for locally advanced or metastatic disease with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations; OR
4. In combination with carboplatin and pemetrexed for the treatment of locally advanced or metastatic disease with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor; OR
5. First-line treatment in combination with carboplatin and pemetrexed for locally advanced or metastatic disease with EGFR exon 20 insertion mutations; OR
6. Single agent for locally advanced or metastatic disease with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy;[2] OR

For **NCCN** required criteria coverage:

7. First-line therapy for EGFR exon 20 insertion mutation positive recurrent, advanced, or metastatic disease (nonsquamous) in combination with carboplatin and pemetrexed; OR
8. In combination with lazertinib for EGFR exon 19 deletion or exon 21 L858R recurrent, advanced, or metastatic disease for one of the following:
   a) First-line therapy
   b) Continuation of therapy following disease progression on amivantamab-vmjw + lazertinib for asymptomatic disease, symptomatic brain lesions, or symptomatic systemic limited progression; OR
9. Subsequent therapy (if not previously given) for EGFR exon 19 deletion or exon 21 L858R mutation positive recurrent, advanced, or metastatic disease (nonsquamous) in combination with carboplatin and pemetrexed following disease progression on osimertinib for symptomatic systemic disease with multiple lesions; OR
10. Subsequent therapy as a single agent for EGFR exon 20 insertion mutation positive recurrent, advanced, or metastatic disease.[3]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Coding (CPT®, ICD-10 and HCPCS)

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment.

Code	Description
C34	Malignant neoplasm of bronchus or lung
J9061	Injection, amivantamab-vmjw

Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Annual Review Dates:	5/12/2023, 6/10/2024, 5/15/2025
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	6/27/2023, 6/18/2024, 5/27/25
5	Revision Changes:	6/10/2024 Added indication in combination with carboplatin and pemetrexed, adverse reactions, and definitions 5/15/2025 Added 4 FDA indications and 1 NCCN for NSCLC; v.3.0

References

[1] Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol. 2021;39(30):3391-3402. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8791812. Accessed April 15, 2025.

[2] Rybrevant (Amivantamab-vmjw) [Package Insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761210s007lbl.pdf. Accessed May 2, 2025.

[3] National Comprehensive Cancer Network. NCCN Guidelines: Non-Small Cell Lung Cancer https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed May 2, 2025.

[4] Ochoa MC, Minute L, Rodriguez I, et al. Antibody-dependent cell cytotoxicity: immunotherapy strategies enhancing effector NK cells. Immunol Cell Biol. 2017;95(4):347-355. https://pubmed.ncbi.nlm.nih.gov/28138156/. Accessed April 28, 2025.

[5] Uribe-Querol E, Rosales C. The Multiple Roles of Trogocytosis in Immunity, the Nervous System, and Development. Biomed Res Int. 2021;2021:1601565. Published 2021 Sep 22. https://pmc.ncbi.nlm.nih.gov/articles/PMC8483919/. Accessed April 28, 2025.

[6] U.S. Food & Drug Administration. https://www.fda.gov/about-fda/what-we-do. Accessed April 23, 2025.

[7] National Comprehensive National Cancer Network. https://www.nccn.org/home. Accessed April 23, 2025.