Medical Policy:

Bizengri (zenocutuzumab-zbco), intravenous infusion

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.427	February 6, 2025	February 6, 2025

The treating physician or primary care provider must submit to EmblemHealth, or ConnectiCare, as applicable (hereinafter jointly referred to as "EmblemHealth"), the clinical evidence that the member meets the criteria for the treatment or surgical procedure. Without this documentation and information, EmblemHealth will not be able to properly review the request preauthorization or post-payment review. The clinical review criteria expressed below reflects how EmblemHealth determines whether certain services or supplies are medically necessary. This clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Health care providers are expected to exercise their medical judgment in rendering appropriate care.

EmblemHealth established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). EmblemHealth expressly reserves the right to revise these conclusions as clinical information changes and welcomes further relevant information. Each benefit program defines which services are covered. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered and/or paid for by EmblemHealth, as some programs exclude coverage for services or supplies that EmblemHealth considers medically necessary.

If there is a discrepancy between this guideline and a member's benefits program, the benefits program will govern. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test or procedure over another. In addition, coverage may be mandated by applicable legal requirements of a state, the Federal Government or the Centers for Medicare & Medicaid Services (CMS) for Medicare and Medicaid members. All coding and web site links are accurate at time of publication.

EmblemHealth may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. EmblemHealth Services Company, LLC, has adopted this policy in providing management, administrative and other services to EmblemHealth Plan, Inc., EmblemHealth Insurance Company, EmblemHealth Services Company, LLC, and Health Insurance Plan of Greater New York (HIP) related to health benefit plans offered by these entities. ConnectiCare, an EmblemHealth company, has also adopted this policy. All of the aforementioned entities are affiliated companies under common control of EmblemHealth Inc.

Definitions

Bizengri is a bispecific human epidermal growth factor receptor (HER) 2- and HER3-directed antibody indicated for the treatment of:

- Adults with advanced, unresectable, or metastatic non–small cell lung cancer (NSCLC) harboring a neuregulin 1 (NRG1) gene fusion with disease progression on or after prior systemic therapy.
- Adults with advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring a NRG1 gene fusion with disease progression on or after prior systemic therapy.

Length of Authorization

Coverage will be provided for 6 months and may be renewed.

Dosing Limits [Medical Benefit]

Max Units (per dose and over time) [HCPCS Unit]:

• 750 mg every 14 days

Guideline

I. Initial Approval Criteria

1. Patient is at least 18 years of age; **AND**
2. Females of reproductive potential have a negative pregnancy test prior to initiating treatment and will use effective contraception during treatment and for 2 months after the last dose; **AND**
3. Left ventricular ejection fraction (LVEF) is within normal limits prior to initiating therapy and will be assessed at regular intervals (e.g., every 3 months) during treatment; **AND**
4. Patient tumor has the presence of a neuregulin-1 *(NRG1)* gene fusion partners***** *(Lung: CD74, SLC3A2, SDC4, CDH1 or VAMP2)* or *(Pancreatic: ATP1B1, NOTCH2, SLC4A4, AGRN, APP, CDH1, SDC4, or VTCN1)* as determined by an FDA-approved or CLIA-compliant test; **AND**

   **Note: Requests for NRG1 gene fusion partners not listed above will be reviewed on a case-by-case basis.*

A. <u>Non-Small Cell Lung Cancer (NSCLC)</u>

i. Patient has a diagnosis of advanced unresectable or metastatic disease; **AND**
ii. Used as subsequent therapy after disease progression

B. <u>Pancreatic Adenocarcinoma</u>

i. Patient has a diagnosis of advanced unresectable or metastatic disease; **AND**
ii. Used as subsequent therapy after disease progression

II. Renewal

Coverage may be renewed based upon the following criteria:

1. Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements **AND**
2. Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
3. Absence of unacceptable toxicity from the drug. (*Examples of unacceptable toxicity include: severe infusion-related reactions, congestive heart failure/left ventricular cardiac dysfunction, interstitial pneumonitis or lung disease, etc.)* **AND**
4. Left ventricular ejection fraction (LVEF) obtained within the previous 3 months as follows:
   i. LVEF is ≥ 50%; **OR**
   ii. LVEF is between 45-49%, and has NOT had an absolute decrease of ≥ 10% from pre-treatment baseline

Dosing and Administration

Indication	Dose
All indications	Administer 750 mg as an intravenous (IV) infusion every 2 weeks until disease progression or unacceptable toxicity

	Note: Administer pre-medications (corticosteroid [optional], antipyretic, H1-antihistamine) before each infusion as recommended to reduce the risk of infusion-related reactions.

Applicable Procedure Codes

Code	Description
J9999	Not otherwise classified, antineoplastic drugs

Applicable NDCs

Code	Description
83077-0100-xx	Bizengri 375 mg/18.75 mL (20 mg/mL) p/f solution in a single-dose vial

ICD-10 Diagnoses

Code	Description
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of the pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus or lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung

C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
Z85.07	Personal history of malignant neoplasm of pancreas
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	02/06/2025	New Policy

References

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2. Kim DW, Schram AM, Hollebecque A, et al. The phase I/II eNRGy trial: zenocutuzumab in patients with cancers harboring *NRG1* gene fusions. *Future Oncol*. 2024;20(16):1057-1067.
3. Schram AM, Goto K, Kim DW, et al. Durable efficacy of zenocutuzumab, a HER2xHER3 bispecific antibody, in advanced NRG1 fusion-positive (NRG1+) non small cell lung cancer (NSCLC) [Poster 595P]. Presented at: European Society of Medical Oncology (ESMO) Asia Congress; Singapore; December 1-3, 2023.
4. Schram AM, Macarulla T, Cleary J. et al. Durable efficacy of zenocutuzumab, a HER2 x HER3 bispecific antibody, in advanced NRG1 fusion-positive (NRG1+) pancreatic ductal adenocarcinoma (PDAC) [abstract 1618p]. *ESMO Annals of Oncology*. 2023;34(supplement 2):S895-S896.
5. Schram AM, Goto K, Kim DW et al. Efficacy and safety of zenocutuzumab, a HER2 x HER3 bispecific antibody, across advanced NRG1 fusion (NRG1+) cancers [abstract 105]. Presented at: American Society of Clinical Oncology 2022 Annual Meeting; Chicago, IL; June 3-7, 2022.
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7. Schram AM, Odintsov I, Espinosa-Cotton M, et al. Zenocutuzumab, a HER2xHER3 bispecific antibody, is effective therapy for tumors driven by NRG1 gene rearrangements. *Cancer Discov*. 2022;12:1233-47.
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9. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2025 – December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 26, 2024.
10. The NCCN Pancreatic Adenocarcinoma Cancer Clinical Practice Guidelines in Oncology (version 1.2025 – December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 26, 2024.