Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Ziihera (Zanidatamab-hrii)	MP-RX-FP-167-25	☒ MMM MA ☒ MMM MultiHealth	4/2/2025	2/22/2026
			Last Review Date:	Frequently Revision:
			2/22/2026	2/22/2027

Service Category:

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description:

This document addresses the use of Zanidatamab-hrii (Ziihera), a drug approved by the Food and Drug Administration (FDA) for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC).

Background Information:

The FDA granted accelerated approval to Zanidatamab-hrii (Ziihera), a on November 20, 2024 bispecific HER2-directed antibody, for previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test. Zanidatamab-hrii induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Based on mechanism of action, ZIIHERA can cause fetal harm when administered to a pregnant woman and has the Box Warning for embryo-fetal toxicity.

National Comprehensive Cancer Network® (NCCN) has been updated to include Ziihera. NCCN compendia for Biliary Tract Cancers (V2.2025) provides a 2A recommendation for use in subsequent treatment as a single agent for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease or metastatic disease that is HER2-positive (IHC3+).

Definitions and Measures

Adenocarcinoma: Cancer originating in cells that line specific internal organs and that have gland-like (secretory) properties. Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.

Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).

Cytotoxic: Treatment that is destructive to cells, preventing their reproduction or growth.

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Disease-free survival (DFS): The interval between a complete disappearance of the cancer (complete response) and the time of relapse.

Disease Progression: Cancer that continues to grow or spread.

ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis.

This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
- 5 = Dead.

Hormonal therapy: Treatment that adds, blocks, or removes hormones. Agents that slow or stop the growth of certain cancers, synthetic hormones or other drugs may be given to block the body's natural hormones.

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Locally advanced cancer: Cancer that has spread only to nearby tissues or lymph nodes.

Maintenance therapy: Designed to maintain a condition to prevent a relapse.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Mutation: A permanent, transmissible change in genetic material.

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One line of therapy: Single line of therapy.

Overall-survival (OS): The length of time from either date of diagnosis or the start of treatment for a disease, such as cancer, that individuals diagnosed with the disease remain alive.

Partial response (PR): A decrease in the size of a tumor, or in the amount of cancer in the body, resulting from treatment; also called partial remission.

Primary refractory disease: Cancer that does not respond at the beginning of treatment; may also be called resistant disease.

Primary treatment: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. Also called first-line therapy, induction therapy, and primary therapy.

Progressive Disease (PD): Cancer that is growing, spreading, or getting worse.

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Targeted biologic agent: A newer type of drug developed specifically to target genetic changes in cells that cause cancer. It works differently than standard chemotherapy drugs, often with different side effects

Approved Indications

A. Treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC).

B. N/A

Other Uses

A. N/A

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Codes Information:

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9276	Injection, zanidatamab-hrii, 2 mg

ICD-10	Description
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified

ICD-10 Procedure	Description
XW033CA	Introduction of Zanidatamab Antineoplastic into Peripheral Vein, Percutaneous Approach, New Technology Group 10 [Ziihera]
XW043CA	Introduction of Zanidatamab Antineoplastic into Central Vein, Percutaneous Approach, New Technology Group 10 [Ziihera]

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Medical Necessity Guidelines:

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Zanidatamab-hrii (Ziihera)

A. Criteria For Initial Approval *(Provider must submit documentation [such as office chart notes, lab results or other clinical information] supporting that member has met all approval criteria.)*

i. Individual has a diagnosis of unresectable, locally advanced, or metastatic biliary tract cancer (BTC) (Label, NCCN 2A); **AND**
ii. Individual is not eligible for curative resection, transplantation, or ablative therapies; **AND**
iii. Individual has HER2-positive disease (IHC3+); **AND**
iv. Individual had at least one prior gemcitabine-containing systemic chemotherapy regimen for advanced disease; **AND**
v. Individual is using as a single agent; **AND**
vi. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Zanidatamab-hrii (Ziihera) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression, or the maximum duration of therapy has not been exceeded. The following information should be supplied for reauthorization:
   a. A current oncology note documenting the patient's response to treatment showing no progression of disease.
   b. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.

C. Authorization Duration

i. Initial Approval Duration: 6 Months
ii. Reauthorization Approval Duration: Up to 6 months

D. **Conditions Not Covered**
Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

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i. Individual has untreated or symptomatic progressive central nervous system metastases; **OR**
ii. Individual has leptomeningeal disease (LMD); **OR**
iii. Individual has active, ongoing, or uncontrolled infections (e.g. hepatitis, HIV); **OR**
iv. Acute or chronic uncontrolled pancreatitis or Child Pugh Class C liver disease **OR**
v. When the above criteria are not met and for all other conditions.

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Limits or Restrictions:

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Limit
Ziihera (Zanidatamab-hrii)-Injection	N/A

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Reference Information:

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 9, 2026.
2. Harding JJ, Fan J, Oh DY, Choi HJ, Kim JW, Chang HM, Bao L, Sun HC, Macarulla T, Xie F, Metges JP, Ying J, Bridgewater J, Lee MA, Tejani MA, Chen EY, Kim DU, Wasan H, Ducreux M, Bao Y, Boyken L, Ma J, Garfin P, Pant S; HERIZON-BTC-01 study group. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, phase 2b study. Lancet Oncol. 2023 Jul;24(7):772-782. doi: 10.1016/S1470-2045(23)00242-5. Epub 2023 Jun 2. PMID: 37276871.
3. ICD10Data.com. ICD-10-PCS and ICD-10-CM Code Descriptions and Search Tool. ICD10Data.com. Accessed January 7, 2026.
4. National Comprehensive Cancer Network® (NCCN®). NCCN Drugs & Biologics Compendium®. Ziihera. Version current at time of policy development. NCCN.org. Accessed January 9, 2026.
5. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on January 9, 2026.
    a. Biliary Tract Cancers. V2.2025. Revised July 2, 2025.

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Policy History:

Type of Review	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Updated policy to clarify HER2-positive disease definition, specifying confirmation by immunohistochemistry. Revised wording and formatting for clarity and consistency. Completed coding review, adding ICD-10-PCS codes XW043CA and XW033CA; removing HCPCS codes C9399 and J9999; and adding HCPCS code 9276 effective July 1, 2025. Updated diagnosis criteria by removing the statement “all diagnoses pending for Ziihera” and adding applicable ICD-10-CM diagnosis codes C22.1, C23, C24.0, C24.8, and C24.9.	2/13/2026	2/22/2026
Policy Inception	Elevance Health’s Medical Policy adoption	N/A	4/2/2025