

# Medical Drug Clinical Criteria

**Subject:** Ziihera (zanidatamab-hrii)  
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## Overview

This document addresses the use of Ziihera (zanidatamab-hrii). Ziihera is a bispecific HER2-directed antibody indicated for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), Ziihera will be provided by intravenous infusion every 2 weeks. Ziihera carries a black box warning for embryo-fetal harm if exposure during pregnancy.

National Comprehensive Cancer Network® (NCCN) has been updated to include Ziihera. NCCN compendia for Biliary Tract Cancers (V5.2024) 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.

**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 house work, 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.

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.

## Clinical Criteria

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.

### Ziihera (zanidatamab-hrii)

Requests for Ziihera (zanidatamab-hrii) may be approved if the following criteria are met:

- I. Individual is under 19 years of age;

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**OR**

- 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 (**IHC3+**) disease; **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.

**Ziihera (zanidatamab-hrii)**

Requests for Ziihera (zanidatamab-hrii) may not be approved for the following criteria (Harding 2023):

- 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.

**Coding**

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**HCPCS**

J9276 Injection, zanidatamab-hrii, 2 mg [Ziihera]

**ICD-10 Procedure**

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 \[Ziihera\]](#)

**ICD-10 Diagnosis**

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

**Document History**

Reviewed: 11/14/2025

Document History:

- 11/15/2025 – Annual Review: Clarify HER2-positive disease with immunohistochemistry. Wording and formatting. Administrative update for age. Coding Reviewed: Added ICD-10 Procedure XW043CA, XW033CA.
- 05/28/2025 – Coding Update: Removed HCPCS C9302 effective 6/30/25 and added J9276 effective 7/1/25.
- 03/04/2025 – Coding Update: Removed HCPCS NOC C9399, J9999, and all diagnosis pend for Ziihera. Added HCPCS C9302 effective 4/1/25. Added ICD-10-CM C22.1, C23, C24.0, C24.8, C24.9.

- 12/09/2024 – Select Review: Add new PA clinical criteria document for Ziihera. Coding reviewed: Added HCPCS NOC C9399, J9999 and all diagnosis pend for Ziihera.

## References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Accessed: October 7, 2025.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Harding JJ, Fan J, Oh DY, et al. 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;24:772-782. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37276871>
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2024; Updated periodically.
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 October 7, 2025.
  - a. Biliary Tract Cancers. V2.2025. Revised July 2, 2025.

Federal and state laws or requirements, contract language, and Plan utilization management programs or policies may take precedence over the application of this clinical criteria.

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