Clinical Policy: Zanidatamab-hrii (Ziihera)

Reference Number: CP.PHAR.709
Effective Date: 03.01.25
Last Review Date: 02.26
Line of Business: Commercial, HIM/ICHRA, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Zanidatamab-hrii (Ziihera®) is a bispecific human epidermal growth receptor 2 (HER2)-directed antibody.

FDA Approved Indication(s)

Ziihera is indicated:

Gastroesophageal Adenocarcinoma (GEA)

- In combination with fluoropyrimidine- and platinum-containing chemotherapy, and tislelizumab-jsgr, as first-line treatment of adult patients with HER2-positive (immunohistochemistry [IHC] 3+ or IHC 2+/ in situ hybridization [ISH] +) unresectable locally advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma, as detected by an FDA-authorized test
- In combination with fluoropyrimidine- and platinum-containing chemotherapy, as first-line treatment of adult patients with HER2-positive (IHC 3+) unresectable locally advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma, as detected by an FDA-authorized test

Biliary Tract Cancer (BTC)

- For the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC, as detected by an FDA-approved test*

**This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).*

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Ziihera is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Biliary Tract Cancer (must meet all)**:**

1. Diagnosis of BTC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is HER2-positive (IHC 3+);
5. Disease is unresectable, resected gross residual (R2), or metastatic;

6. Failure of at least one prior systemic treatment (*see Appendix B for examples*);
7. Prescribed as a single agent;
8. Request meets one of the following (a or b):*
   a. Dose does not exceed 20 mg/kg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM/ICHRA – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Gastric, Esophageal, or Gastroesophageal Junction Cancer (must meet all)**:**

1. Diagnosis of gastric, esophageal, or gastroesophageal junction adenocarcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥18 years;
4. Disease is unresectable, locally advanced, or metastatic;
5. Request is for first-line treatment;
6. Ziihera is prescribed in one of the following ways (a or b):
   a. In combination with fluoropyrimidine (e.g., capecitabine, fluorouracil)- and platinum (e.g., cisplatin, oxaliplatin)- containing chemotherapy, and (i):
      i. Disease is HER2-positive (IHC 3+);
   b. In combination with Tevimbra® plus fluoropyrimidine- and platinum-containing chemotherapy, and (i):
      i. Disease is HER2-positive (IHC 3+ or IHC 2+/ISH+);
7. Request meets one of the following (a or b):*
   a. Dose does not exceed one of the following (i or ii):
      i. For weight < 70 kg, one of the following (1 or 2):
         1) 1,800 mg every 3 weeks;
         2) 1,200 mg every 2 weeks;
      ii. For weight ≥ 70 kg, one of the following (1 or 2):
         1) 2,400 mg every 3 weeks;
         2) 1,600 mg every 2 weeks;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM/ICHRA – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Biliary Tract Cancer (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Ziihera for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Prescribed as a single agent;
4. Dose requested is ≥ 15 mg/kg;
5. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 20 mg/kg every 2 weeks;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM/ICHRA – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Gastric, Esophageal, or Gastroesophageal Junction Cancer (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Ziihera for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed one of the following (i or ii):
      i. For weight < 70 kg, one of the following (1 or 2):
         1) 1,800 mg every 3 weeks;
         2) 1,200 mg every 2 weeks;
      ii. For weight ≥ 70 kg, one of the following (1 or 2):
         1) 2,400 mg every 3 weeks;
         2) 1,600 mg every 2 weeks;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM/ICHRA – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace/ICHRA, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace/ICHRA, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace/ICHRA, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BTC: biliary tract cancer
FDA: Food and Drug Administration
GEA: gastroesophageal adenocarcinoma
HER2: human epidermal growth factor receptor 2
IHC: immunohistochemistry (assay)
ISH: in situ hybridization

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of systemic therapies for BTC include: • Imfinzi® + gemcitabine + cisplatin • Keytruda® + gemcitabine + cisplatin • gemcitabine + cisplatin/oxaliplatin • capecitabine (Xeloda®) + oxaliplatin • FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) • gemcitabine + Abraxane® (paclitaxel, protein-bound) • gemcitabine + capecitabine (Xeloda)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
• Single agents: 5-fluorouracil, capecitabine (Xeloda), gemcitabine		

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): diarrhea and embryo-fetal toxicity

Appendix D: General Information

- A HER2 IHC test determines HER2 protein levels using scores that range from 0 to 3+. The higher the score, the more HER2 is overexpressed. In patients with borderline HER2 protein levels (IHC 2+), the ISH test confirms extra copies of the HER2 gene.
- The distinction between indications requiring IHC 3+ alone versus allowing both IHC 3+ and IHC 2+/ISH+ is driven by the clinical evidence supporting each indication, recognizing that although both subgroups are HER2-positive, certain studies have reported higher response rates in patients with IHC 3+ tumors.
  - For BTC, the efficacy of Ziihera was established in 62 patients with HER2-positive (IHC 3+) in the HERIZON-BTC-302 trial.
  - For GEA, the efficacy of Ziihera was established in 914 patients with HER2-positive (IHC 3+ or IHC 2+/ISH+) in the HERIZON-GEA-01 trial.
    - The evidence supporting Ziihera plus chemotherapy alone was generated in the ICH 3+ population, leading to approval limited to that subgroup.
    - The evidence supporting Ziihera plus tislelizumab and chemotherapy demonstrated statistically significant survival benefit in the overall HER2-positive study population, supporting approval for both ICH3+ and ICH2+/ISH+ disease.
- Ziihera should be permanently discontinued in patients who cannot tolerate an initial dose reduction per the product labeling.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
BTC	20 mg/kg IV once every 2 weeks until disease progression or unacceptable toxicity	20 mg/kg/2 weeks
GEA	Weight < 70 kg: 1,800 mg IV every 3 weeks or 1,200 mg IV every 2 weeks until disease progression or unacceptable toxicity Weight ≥ 70 kg: 2,400 mg IV every 3 weeks or 1,600 mg IV every 2 weeks until disease progression or unacceptable toxicity	See regimen

VI. Product Availability

Lyophilized powder in single-dose vial for injection: 300 mg

VII. References

1. Ziihera Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; August 2026. Available at: https://www.ziihera.com/. Accessed September 15, 2026.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 5, 2025.
3. National Comprehensive Cancer Network. Biliary Tract Cancers 2.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf. Accessed November 5, 2025.
4. National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers, Version 3.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed September 8, 2026
5. National Comprehensive Cancer Network. Gastric Cancer Version 3.2026. Available at: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed September 8, 2026.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9276	Injection, zanidatamab-hrii, 2 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	12.05.24	02.25
HCPCS code added [C9302], removed codes [J9999, C9399].	04.02.25	
HCPCS code added [J9276] replacing [C9302].	05.16.25	
1Q 2026 annual review: no significant changes; for Medicaid/HIM, extended initial approval duration from 6 to 12 months; for Commercial, revised initial approval duration to include "or to the member's renewal date, whichever is longer"; references reviewed and updated.	11.05.25	02.26
RT4: updated criteria to include new indications in combination with fluoropyrimidine- and platinum-containing chemotherapy ± tislelizumab-jsgr for first-line HER2+ gastric, gastroesophageal junction, or esophageal adenocarcinoma per updated PI; added ICHRA line of business.	09.15.26	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional

organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in 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.

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