

5.21.233

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Subsection:	Antineoplastic Agents	Original Policy Date:	December 13, 2024
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Last Review Date: March 6, 2026

Ziihera

Description

Ziihera (zanidatamab-hrii)

Background

Ziihera (zanidatamab-hrii) is a bispecific human epidermal growth factor receptor 2 (HER2)-directed antibody that binds to two extracellular sites on HER2. Binding of Ziihera with HER2 results in internalization leading to a reduction of the receptor on the tumor cell surface. Ziihera induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms result in tumor growth inhibition and cell death in vitro and in vivo (1).

Regulatory Status

FDA-approved indications: 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), as detected by an FDA-approved test (1).

Ziihera has a boxed warning for embryo-fetal toxicity. Ziihera can cause harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to Ziihera treatment. Advise females of reproductive potential to use effective contraception while receiving Ziihera and for 4 months following the last dose (1).

Ziihera has been associated with left ventricular dysfunction, infusion-related reactions (IRRs), and severe diarrhea. Assess left ventricular ejection fraction (LVEF) prior to initiation of Ziihera and at regular intervals during treatment. Withhold or permanently discontinue Ziihera based on severity. Prior to each dose of Ziihera, administer premedications to prevent potential IRRs.

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Monitor patients for signs and symptoms of IRRs during Ziihera administration and as clinically indicated after completion of infusion. If an IRR occurs, slow, or stop the infusion, and administer appropriate medical management. Monitor until complete resolution of signs and symptoms before resuming. Permanently discontinue Ziihera in patients with severe or life-threatening infusion-related reactions. If diarrhea occurs with Ziihera use, administer antidiarrheal treatment as clinically indicated. Withhold or permanently discontinue Ziihera based on severity (1).

The safety and effectiveness of Ziihera in pediatric patients less than 18 years of age have not been established (1).

Related policies

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Ziihera may be considered **medically necessary** if the conditions indicated below are met.

Ziihera may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

Unresectable or metastatic biliary tract cancer (BTC)

AND ALL of the following:

- HER2-positive (IHC 3+) as detected by an FDA-approved test
- Patient has been treated with prior therapy
- Prescriber agrees to monitor left ventricular ejection fraction (LVEF) prior to initiation and at regular intervals during treatment

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- d. Females of reproductive potential **only**: patient has had a negative pregnancy test **AND** patient will be advised to use effective contraception during treatment with Ziihera and for 4 months after the last dose

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:
Unresectable or metastatic biliary tract cancer (BTC)

AND ALL of the following:

- NO** disease progression or unacceptable toxicity
- Prescriber agrees to monitor left ventricular ejection fraction (LVEF) at regular intervals during treatment
- Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Ziihera and for 4 months after the last dose

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

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Ziihera is a bispecific HER-2 directed antibody indicated for the treatment of HER2-positive biliary tract cancer. Ziihera has a boxed warning for embryo-fetal toxicity and has been associated with left ventricular dysfunction, infusion-related reactions (IRRs), and severe diarrhea. The safety and effectiveness of Ziihera in pediatric patients less than 18 years of age have not been established (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Ziihera while maintaining optimal therapeutic outcomes.

References

1. Ziihera [package insert]. Dublin, Ireland: Jazz Pharmaceuticals Ireland Limited; July 2025.
2. NCCN Drugs & Biologics Compendium[®] Zanidatamab-hrii 2026. National Comprehensive Cancer Network, Inc. Accessed on January 21, 2026.

Policy History

Date	Action
December 2024	Addition to PA
March 2025	Annual review and reference update
March 2026	Annual review and reference update

Keywords

This policy was approved by the FEP[®] Pharmacy and Medical Policy Committee on March 6, 2026 and is effective on April 1, 2026.