HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZIIHERA safely and effectively. See full prescribing information for ZIIHERA.

ZIIHERA® (zanidatamab-hrii) for injection, for intravenous use
Initial U.S. Approval: 2024

WARNING: DIARRHEA and EMBRYO-FETAL TOXICITY
See full prescribing information for complete boxed warning.

- **ZIIHERA, in combination with fluoropyrimidine- and platinum-containing chemotherapy with or without tislelizumab-jsgr can cause severe diarrhea, including life threatening, and fatal cases. Use antidiarrheal prophylaxis during the first cycle when ZIIHERA is given in combination with these drugs. Manage with antidiarrheals and supportive measures as clinically indicated. Interrupt, reduce the dose or discontinue ZIIHERA based on severity. (2.4, 5.1, 8.5)**
- **Exposure to ZIIHERA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception. (5.2)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	08/2026
Indications and Usage (1.1)	08/2026
Dosage and Administration (2.1, 2.2, 2.3, 2.5)	08/2026
Warnings and Precautions (5.1, 5.3, 5.4)	08/2026

----------INDICATIONS AND USAGE----------

ZIIHERA is a bispecific HER2-directed antibody indicated for:

Gastroesophageal Adenocarcinoma (GEA)

- in combination with fluoropyrimidine- and platinum-containing chemotherapy, and tislelizumab-jsgr, as first-line treatment of adult patients with HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable locally advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma, as detected by an FDA-authorized test. (1.1)
- 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. (1.1)

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-authorized test.* (1.2)

*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). (1)

----------DOSAGE AND ADMINISTRATION----------

- Premedicate all patients to reduce the risk of infusion-related reactions (IRRs). (2.2)
- Administer loperamide during the first cycle to patients receiving ZIIHERA in combination with fluoropyrimidine- and platinum-containing chemotherapy for diarrhea prophylaxis. (2.2)

Gastroesophageal Adenocarcinoma (GEA):

- Patients weighing less than 70 kg: ZIIHERA 1,800 mg intravenously every 3 weeks or 1,200 mg every 2 weeks infusion in combination with fluoropyrimidine- and platinum-containing chemotherapy, with or without tislelizumab-jsgr. (2.3)
- Patients weighing 70 kg or greater: ZIIHERA 2,400 mg intravenously every 3 weeks or 1,600 mg every 2 weeks in combination with fluoropyrimidine- and platinum-containing chemotherapy, with or without tislelizumab-jsgr. (2.3)

Biliary Tract Cancer: ZIIHERA 20 mg/kg intravenously every 2 weeks. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 300 mg lyophilized powder in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Left Ventricular Dysfunction: 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. (2.4, 5.3)
- Infusion-Related Reactions (IRRs): Premedicate before each infusion of ZIIHERA. Interrupt the infusion, decrease the infusion rate, and/or permanently discontinue ZIIHERA based on severity. (2.2, 2.4, 5.4)

----------ADVERSE REACTIONS----------

- Most common adverse reactions (≥ 20%) with ZIIHERA in combination with chemotherapy and tislelizumab-jsgr were diarrhea, nausea, decreased appetite, vomiting, hypokalemia, fatigue, rash, peripheral neuropathy, and IRR. (6.1)
- Most common adverse reactions (≥ 20%) with ZIIHERA in combination with chemotherapy were diarrhea, nausea, vomiting, decreased appetite, fatigue, hypokalemia, peripheral neuropathy, IRR, and rash. (6.1)
- Most common adverse reactions (≥ 20%) with ZIIHERA as a single agent were diarrhea, IRR, abdominal pain, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals, Inc. at 1-800-520-5568 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of ZIIHERA. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DIARRHEA and EMBRYO-FETAL TOXICITY

ZIIHERA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, with or without tislelizumab-jsgr, can cause severe diarrhea, including life threatening and fatal cases. Use antidiarrheal prophylaxis during the first cycle when ZIIHERA is given in combination with these drugs. Manage with antidiarrheals and supportive measures as clinically indicated. Interrupt, reduce the dose or discontinue ZIIHERA based on severity *[see Dosage and Administration (2.4), Warnings and Precautions (5.1), Use in Specific Populations (8.5)]*.

Embryo-Fetal Toxicity: Exposure to ZIIHERA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception *[see Warnings and Precautions (5.2), Use in Specific Populations (8.1, 8.3)]*.

1 INDICATIONS AND USAGE

1.1 Gastroesophageal Adenocarcinoma (GEA)

- ZIIHERA, in combination with fluoropyrimidine- and platinum-containing chemotherapy and tislelizumab-jsgr, is indicated for the first-line treatment of adult patients with HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable locally advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma, as detected by an FDA-authorized test *[see Dosage and Administration (2.1)]*.
- ZIIHERA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the 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 *[see Dosage and Administration (2.1)]*.

1.2 Biliary Tract Cancer (BTC)

ZIIHERA, as a single agent, is 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-authorized test *[see Dosage and Administration (2.1)]*.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

HER2-Positive Gastroesophageal Adenocarcinoma (GEA)

Select patients for treatment of unresectable locally advanced or metastatic GEA based on HER2-positive status (IHC 3+ or IHC 2+/ISH+), as detected by FDA-authorized tests *[see Clinical Studies (14.1)]*.

Information on FDA-authorized tests for HER2 protein expression and gene amplification in gastric, gastroesophageal junction, or esophageal adenocarcinoma is available at: http://www.fda.gov/CompanionDiagnostics.

Biliary Tract Cancer (BTC)

Select patients for treatment of unresectable or metastatic biliary tract cancer based on HER2-positive (IHC 3+) tumor specimens, as detected by an FDA-authorized test *[see Clinical Studies (14.2)]*.

Information on FDA-authorized tests for HER2 protein expression in biliary tract cancers is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Premedications and Important Administration Information

Premedicate all patients 30 to 60 minutes prior to each dose of ZIIHERA to reduce the risk of infusion-related reactions *[see Warnings and Precautions (5.4)]*:

- Administer acetaminophen, an antihistamine (such as diphenhydramine) and a corticosteroid (such as hydrocortisone).

ZIIHERA in combination with fluoropyrimidine- and platinum-containing chemotherapy with or without tislelizumab-jsgr

Antidiarrheal prophylaxis:

- Administer loperamide 4 mg twice daily beginning on Day 1 and continue for at least 7 days during the first cycle of treatment.
- If patients experience Grade 1 or higher diarrhea during the first cycle, continue prophylaxis with loperamide 4 mg twice daily for at least the first 7 days of each subsequent cycle *[see Warnings and Precautions (5.1)].*

Fluorouracil-containing regimens:

- When ZIIHERA is administered in combination with fluorouracil-containing regimens, administer fluorouracil as an intravenous infusion. Do NOT administer fluorouracil as an intravenous bolus due to the potential increase in diarrhea *[see Warnings and Precautions (5.1)].*

Missed dose

ZIIHERA in combination with fluoropyrimidine- and platinum-containing chemotherapy with or without tislelizumab-jsgr

If a planned dose of ZIIHERA is delayed or missed, administer the dose as soon as possible if 7 days or fewer have passed since the scheduled time. If more than 7 days have passed since the planned dose, withhold ZIIHERA and resume on day 1 of the next cycle.

ZIIHERA as a single agent

If a planned dose of ZIIHERA is delayed or missed, administer the dose as soon as possible; do not wait until the next planned dose. Adjust the administration schedule to maintain a 2-week interval between doses.

2.3 Recommended Dosage

Gastroesophageal Adenocarcinoma (GEA)

Administer ZIIHERA as an intravenous infusion until disease progression or unacceptable toxicity at the recommended dosages presented in Table 1:

Table 1: Dosage recommendations for patients with GEA

Patient body weight	Dosage
< 70 kg:	• 1,800 mg every 3 weeks or • 1,200 mg every 2 weeks
≥ 70 kg:	• 2,400 mg every 3 weeks or • 1,600 mg every 2 weeks

Refer to the Prescribing Information of each of the individual therapeutic agents used in combination with ZIIHERA for additional dosing information. If chemotherapy is discontinued for reasons other than disease progression, treatment with ZIIHERA, and/or tislelizumab-jsgr can continue until disease progression.

Biliary Tract Cancer

The recommended dosage of ZIIHERA is 20 mg/kg, administered as an intravenous infusion once every 2 weeks until disease progression or unacceptable toxicity.

2.4 Dosage Modifications for Adverse Reactions

The recommended dosage reduction of ZIIHERA for adverse reactions is described in Table 2. Permanently discontinue ZIIHERA in patients who cannot tolerate an initial dose reduction.

Table 2: Recommended Dosage Reductions for Adverse Reactions

Indication	**Recommended dosage**	**Dosage Modification**
Gastroesophageal Adenocarcinoma (GEA)	Patient body weight < 70 kg:	
	1,800 mg every 3 weeks or 1,200 mg every 2 weeks	1,400 mg every 3 weeks or 900 mg every 2 weeks
	Patient body weight ≥ 70 kg:	
	2,400 mg every 3 weeks or 1,600 mg every 2 weeks	1,800 mg every 3 weeks or 1,200 mg every 2 weeks
Biliary Tract Cancer (BTC)	20 mg/kg every 2 weeks	15 mg/kg every 2 weeks

The recommended dosage modifications and management for adverse reactions for ZIIHERA are described in Table 3.

Table 3: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Treatment Modification
Diarrhea *[see Warnings and Precautions (5.1)]*	Mild/Moderate (Grade 1 or 2)	• No dosage modification of ZIIHERA is required. • Initiate appropriate medical therapy and monitor as clinically indicated.
	Severe (Grade 3)	• Withhold ZIIHERA treatment until severity improves to ≤ Grade 1. • Initiate or intensify appropriate medical therapy and monitor as clinically indicated. • Administer subsequent ZIIHERA treatment at the same dose level or consider a dose reduction. • For recurrent Grade 3 symptoms, withhold ZIIHERA treatment and ensure medical management has been optimized. ○ Resume ZIIHERA treatment at a reduced dose after severity improves to ≤ Grade 1 • Permanently discontinue ZIIHERA for recurrent Grade 3 symptoms that last > 3 days despite optimized medical management.
	Life threatening (Grade 4)	• Permanently discontinue ZIIHERA.
Left Ventricular Dysfunction (LVD) *[see Warnings and Precautions (5.3)]*	Absolute decrease of ≥ 16% points in LVEF from pre-treatment baseline or LVEF < 50% and absolute decrease of ≥ 10% points below pre-treatment baseline	• Withhold ZIIHERA for at least 4 weeks. • Repeat LVEF assessment within 4 weeks. • Resume ZIIHERA treatment within 4 to 8 weeks if LVEF returns to normal limits and the absolute decrease is ≤ 15% points from baseline. • Permanently discontinue ZIIHERA if LVEF has not recovered to within 15% points from pre-treatment baseline.
	Confirmed symptomatic congestive heart failure	• Permanently discontinue ZIIHERA.
Infusion-Related Reactions *[see Warnings and Precautions (5.4)]*	Mild (Grade 1)	• Reduce ZIIHERA infusion rate by 50%. • For subsequent ZIIHERA infusions increase infusion rate gradually to the rate prior to the adverse reaction, as tolerated.

Adverse Reaction	Severity	Treatment Modification
	Moderate (Grade 2)	• Stop ZIIHERA infusion immediately. • Treat with appropriate therapy. • Resume ZIIHERA infusion at 50% of previous infusion rate once symptoms resolve. • For subsequent ZIIHERA infusions, increase infusion rate gradually to the rate prior to the adverse reaction, as tolerated.
	Severe (Grade 3)	• Stop ZIIHERA infusion immediately. • Promptly treat with appropriate therapy; infusion should not be restarted during the same cycle even if signs and symptoms completely resolve. • Subsequent ZIIHERA infusions should be administered at 50% of previous infusion rate. • Permanently discontinue ZIIHERA for recurrent Grade 3 reaction.
	Life threatening (Grade 4)	• Stop ZIIHERA infusion immediately and permanently discontinue. • Promptly treat with appropriate therapy.
Other Adverse Reactions (excluding LVD, IRR and Diarrhea) *[see Adverse Reactions (6.1)]*	Mild/Moderate (Grades 1/2)	• No dosage modification is required for ZIIHERA. • Initiate appropriate medical therapy and monitor as clinically indicated.
	Severe (Grade 3)	• Withhold ZIIHERA treatment until severity improves to ≤ Grade 1. • Initiate appropriate medical therapy and monitor as clinically indicated. • Administer subsequent ZIIHERA treatment at the same dose; consider dose reduction if Grade 3 symptoms recur.
	Life threatening (Grade 4)	• Permanently discontinue ZIIHERA, except as noted below. • Initiate appropriate medical therapy and monitor as clinically indicated. • ZIIHERA treatment may be resumed at the same dose level for Grade 4 electrolyte imbalances or laboratory abnormalities that are corrected within 3 days of onset; do not resume until symptoms improve to ≤ Grade 1. • Permanently discontinue ZIIHERA for recurrent Grade 4 electrolyte imbalances or laboratory abnormalities.

2.5 Preparation and Administration Instructions

Administer as an intravenous infusion after ZIIHERA is reconstituted and diluted.

Reconstitution

- Calculate the recommended dose based on the patient's weight to determine the number of vials needed.
- Remove the vial(s) from the refrigerator and allow the vial(s) to reach room temperature.
- Reconstitute each 300 mg vial of ZIIHERA with 5.7 mL of Sterile Water for Injection by slowly directing the stream toward the inside of the wall of the vial, to obtain a concentration of 50 mg/mL in an extractable volume of 6 mL.
- Swirl the vial gently until completely dissolved. Do not shake or vigorously swirl.
- Allow the reconstituted vial to settle to allow bubbles to dissipate.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted product should be a colorless to light yellow, clear to slightly opalescent solution with no visible particles. Discard the reconstituted vial if any discoloration or particulate matter is observed.
- The product does not contain a preservative. Use the reconstituted ZIIHERA solution immediately or store the reconstituted ZIIHERA solution for up to 4 hours, either at room temperature (18°C to 24°C [64°F to 75°F]) or in a refrigerator (2°C to 8°C [36°F to 46°F]).

Dilution

- Withdraw the necessary volume for the calculated dose from each vial *[see Dosage and Administration (2.3)]*.
- Slowly add the necessary dose volume to an infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection to prepare an infusion solution with a final concentration between 4 mg/mL and 20 mg/mL. Use the least possible volume of diluent necessary, do **not** exceed a maximum volume of 500 mL.
- Gently invert the infusion bag to mix. Do not shake.
- The infusion solution must be a clear, colorless solution with no visible particles. Do not use if visible particles are observed or if the solution is discolored.
- Discard any unused portion left in the vial(s).
- Use the infusion solution immediately upon dilution or store the infusion solution at room temperature (18°C to 24°C [64°F to 75°F]) for up to 12 hours or in the refrigerator (2°C to 8°C [36°F to 46°F]) for up to 24 hours.
    - These time limits include the beginning of reconstitution through the duration of infusion.
    - If these specified times are exceeded, discontinue the current infusion bag and prepare a new bag which contains the remaining dosage of ZIIHERA to be infused.
- Compatibility with intravenous administration materials and the infusion solution has been demonstrated in the following materials:
    - Intravenous (IV) Bag: Polyvinyl chloride (PVC), polyolefin (PO), ethyl vinyl acetate (EVA), polypropylene (PP), and ethylene-propylene copolymer.

- Infusion sets: Polyvinyl chloride/ bis (2-ethylhexyl) phthalate (PVC/DEHP), Polyurethane (PUR), polyethylene-lined (PE-lined), acrylonitrile-butadiene-styrene (ABS).
- Inline filters: Polyethersulfone solution filter (PES), polyvinylidene fluoride air filter (PVDF).
- Closed System Transfer devices: acrylonitrile-butadiene-styrene (ABS), acrylic copolymer, polycarbonate (PC), polyisoprene (PI), polyester, polypropylene (PP) polytetrafluoroethylene (PTFE), silicone, and stainless steel (SS).

Administration

- Administer ZIIHERA as an intravenous infusion with a 0.2 or 0.22 micron filter per the recommended infusion durations listed in Table 4.
- Do not administer as an intravenous push or bolus.
- Do not co-administer ZIIHERA and other intravenous drugs through the same intravenous line.
- Administer ZIIHERA first, followed by tislelizumab-jsgr (if included in the regimen), and then chemotherapy when ZIIHERA is given in combination regimens for the treatment of GEA.

Table 4: Recommended ZIIHERA Infusion Durations

Dose	Infusion Duration
First	120 minutes
Second	90 minutes, if previous infusions were well-tolerated
Subsequent	60 minutes, if previous infusions were well-tolerated

3 DOSAGE FORMS AND STRENGTHS

For injection: 300 mg white lyophilized powder in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

ZIIHERA can cause severe diarrhea.

When ZIIHERA is used in combination with fluoropyrimidine- and platinum-containing chemotherapy with or without tislelizumab-jsgr, severe, life threatening, and fatal cases of diarrhea can occur despite loperamide prophylaxis *[see Adverse Reactions (6.1), Use in Specific Populations (8.5)].* The risk of severe and life threatening diarrhea is higher when ZIIHERA is administered with chemotherapy and tislelizumab-jsgr, with a higher risk in patients aged 65 years or older compared to younger patients *[see Geriatric Use (8.5)]*. Advise patients to increase oral fluids, begin antidiarrheals, and notify their healthcare provider immediately if diarrhea occurs *[see Patient Counseling Information (17)].*

Administer antidiarrheal prophylaxis with loperamide in cycle 1 for all patients receiving ZIIHERA in combination with fluoropyrimidine- and platinum-containing chemotherapy with or without tislelizumab-jsgr. Begin loperamide at the first loose stool when ZIIHERA is administered in combination with chemotherapy or as a single agent. Administer fluids, electrolytes, and additional

antidiarrheal agents as necessary. When ZIIHERA was used in combination with chemotherapy with or without tislelizumab-jsgr, 9% of patients had a dose reduction of ZIIHERA due to diarrhea and concomitant agents were dose reduced in 22% of patients. Before modifying the dose of ZIIHERA, evaluate, modify or discontinue drug(s) contributing to diarrhea in accordance with their respective prescribing information. Withhold, reduce the dose, or permanently discontinue ZIIHERA based on severity *[see Dosage and Administration (2.2, 2.4)].*

In a Phase 2 study evaluating ZIIHERA in combination with FOLFOX in patients with GEA, 57% of patients who received a fluorouracil bolus without loperamide prophylaxis (N=14), experienced Grade 3 diarrhea, while 30% of patients who did not receive a fluorouracil bolus but received loperamide prophylaxis (N=10) experienced Grade 3 diarrhea. If treating patients with ZIIHERA in combination with FOLFOX, do not administer the fluorouracil bolus.

Gastroesophageal Adenocarcinoma (GEA)

In Combination with fluoropyrimidine- and platinum-containing chemotherapy and tislelizumab:

When ZIIHERA was used in combination with fluoropyrimidine- and platinum-containing chemotherapy and tislelizumab-jsgr, diarrhea was reported in 85% of 330 patients treated in clinical studies, including Grade 4 (2.1%), Grade 3 (24%), and Grade 2 (31%) events. Fatal outcomes resulting from diarrhea occurred in 1.5% of patients. Diarrhea leading to dose reduction of ZIIHERA occurred in 10% of patients, and permanent discontinuation of ZIIHERA occurred in 3.9% of patients.

In cycle 1, diarrhea at Grade 4 severity occurred in 1.5% and Grade 3 severity occurred in 15% of patients despite use of loperamide prophylaxis. The median time to onset for cycle 1 diarrhea was 6 days and median time to resolution was 18 days.

In Combination with fluoropyrimidine- and platinum-containing chemotherapy:

When ZIIHERA was used in combination with fluoropyrimidine- and platinum-containing chemotherapy, diarrhea was reported in 81% of 395 patients treated in clinical studies, including Grade 4 (1.3%), Grade 3 (20%) and Grade 2 (33%). Diarrhea leading to dose reduction of ZIIHERA occurred in 10% of patients, and permanent discontinuation of ZIIHERA occurred in 1.8% of patients.

In cycle 1, diarrhea at Grade 4 severity occurred in 0.8% and Grade 3 severity occurred in 14% of patients despite use of loperamide prophylaxis. The median time to onset for cycle 1 diarrhea was 6 days and median time to resolution was 18 days.

Biliary Tract Cancer (BTC)

When ZIIHERA was used as a single agent, diarrhea was reported in 49% of 233 patients treated in clinical studies, including Grade 3 (6%) and Grade 2 (17%). Grade 3 diarrhea occurred in 2.6% of patients during cycle 1 of treatment. Of all diarrhea events occurring during the first cycle of treatment, median time to onset was 4 days and median time to resolution was 21 days.

5.2 Embryo-Fetal Toxicity

Based on the mechanism of action, ZIIHERA can cause fetal harm when administered to a pregnant woman. There are no human or animal data on the use of ZIIHERA in pregnancy. In literature reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Verify the pregnancy status of females of reproductive potential prior to the initiation of ZIIHERA. Advise pregnant women and females of reproductive potential that exposure to ZIIHERA during pregnancy or within 4 months prior to conception can result in fetal harm. Advise females of

reproductive potential to use effective contraception while receiving ZIIHERA and for 4 months following the last dose of ZIIHERA.

5.3 Left Ventricular Dysfunction (LVD)

ZIIHERA can cause decreases in left ventricular ejection fraction (LVEF).

Assess LVEF prior to initiation of ZIIHERA and at regular intervals during treatment. Withhold dose or permanently discontinue ZIIHERA based on severity of adverse reactions *[see Dosage and Administration (2.4)]*.

The safety of ZIIHERA has not been established in patients with a baseline ejection fraction that is below 50% *[see Dosage and Administration (2.4)]*.

Gastroesophageal Adenocarcinoma (GEA)

In patients who received ZIIHERA in combination with chemotherapy and tislelizumab-jsgr, LVEF decrease (an absolute decline in LVEF of more than 10%, resulting in a final value below 50%) was observed in 9% of 330 patients. LVD leading to permanent discontinuation of ZIIHERA was reported in 3% of patients. Fatal outcomes due to LVD occurred in one patient (0.3%). The median time to first occurrence of LVD was 6.9 months (range: 1.2 to 29.1 months). Left ventricular dysfunction resolved in 78% of patients.

In patients who received ZIIHERA in combination with chemotherapy, LVEF decrease was observed in 5% of 395 patients. LVD leading to permanent discontinuation of ZIIHERA was reported in 1.0% of patients. The median time to first occurrence of left ventricular dysfunction was 6.0 months (range: 1.4 to 15.0 months). Left ventricular dysfunction resolved in 70% of patients.

Biliary Tract Cancer (BTC)

In patients who received ZIIHERA as a single agent, LVEF decrease was observed in 4.3% of 233 patients. LVD leading to permanent discontinuation of ZIIHERA was reported in 0.9% of patients. The median time to first occurrence of left ventricular dysfunction was 5.6 months (range: 1.6 to 18.7 months). LVD resolved in 70% of patients.

5.4 Infusion-Related Reactions

ZIIHERA can cause infusion-related reactions (IRRs).

Prior to each dose of ZIIHERA, administer premedication to prevent potential IRRs *[see Dosage and Administration (2.2)]*. Monitor patients for signs and symptoms of IRR during ZIIHERA administration and as clinically indicated after completion of infusion. Have medications and emergency equipment to treat IRRs available for immediate use.

If an IRR occurs, slow or stop the infusion, and administer appropriate medical management. Monitor patients until complete resolution of signs and symptoms before resuming. Permanently discontinue ZIIHERA in patients with recurrent severe or life-threatening IRRs *[see Dosage and Administration (2.4)]*.

Gastroesophageal Adenocarcinoma (GEA)

An IRR was reported in 22% of 330 patients treated with ZIIHERA and chemotherapy with tislelizumab-jsgr in clinical studies, including Grade 4 (0.3%), Grade 3 (1.2%), and Grade 2 (16%) despite use of prophylaxis. IRRs leading to permanent discontinuation of ZIIHERA were reported in 0.3% of patients. IRRs occurred on the first day of dosing in 17% of patients. Of all patients who experienced IRRs, 60% of reactions resolved within the first day.

An IRR was reported in 24% of 395 patients treated with ZIIHERA and chemotherapy in clinical studies, including Grade 4 (0.3%), Grade 3 (1.5%), and Grade 2 (18%) despite use of prophylaxis. IRRs leading to permanent discontinuation of ZIIHERA were reported in 1.3% of patients. IRRs occurred on the first day of dosing in 22% of patients. Of all patients who experienced IRRs, 83% of reactions resolved within the first day.

Biliary Tract Cancer (BTC)

An IRR was reported in 31% of 233 patients treated with ZIIHERA as a single agent in clinical studies, including Grade 3 (0.4%), and Grade 2 (25%). IRRs leading to permanent discontinuation of ZIIHERA were reported in 0.4% of patients despite use of prophylaxis. IRRs occurred on the first day of dosing in 28% of patients. Of all patients who experienced IRRs, 97% of reactions were resolved within the first day.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail in other sections of the labeling:

- Diarrhea *[see Warnings and Precautions (5.1)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.2)]*
- Left Ventricular Dysfunction *[see Warnings and Precautions (5.3)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Gastroesophageal Adenocarcinoma (GEA)

The pooled safety population of ZIIHERA described in WARNINGS AND PRECAUTIONS, reflects exposure to ZIIHERA in combination with chemotherapy, with or without tislelizumab-jsgr, in 725 patients with GEA from four open-label studies, including HERIZON-GEA-01 (N=605), ZWI-ZW25-201 (N=46), ZWI-ZW25-101 (N=41), and BGB-A317-ZW25-101 (N=33) at doses of 1,800 mg every 3 weeks (< 70 kg), 2,400 mg every 3 weeks (≥ 70 kg), 1,200 mg every 2 weeks (< 70 kg), 1,600 mg every 2 weeks (≥ 70 kg), or other doses.

Among the 330 patients who received ZIIHERA in combination with chemotherapy and tislelizumab-jsgr for GEA, 64% were exposed for 6 months or longer, and 41% were exposed for 1 year or more.

Among the 395 patients who received ZIIHERA in combination with chemotherapy for GEA, 57% were exposed for 6 months or longer, and 34% were exposed for 1 year or more.

Biliary Tract Cancer (BTC)

The pooled safety population of ZIIHERA administered 20 mg/kg intravenously as a single agent, described in WARNINGS AND PRECAUTIONS reflects exposure in 233 patients in two single-arm, open-label studies (ZWI-ZW25-101 and HERIZON-BTC-01): 109 patients with biliary tract cancer, and 124 patients with other cancers. Among 233 patients who received ZIIHERA as a single agent, 39% were exposed for 6 months or longer, and 17% were exposed for greater than one year.

Gastroesophageal Adenocarcinoma (GEA) (HERIZON-GEA-01)

The safety of ZIIHERA administered in combination with chemotherapy, with or without tislelizumab-jsgr for the treatment of GEA was evaluated in 901 patients *[see Clinical Studies (14.1)]*.

Patients received ZIIHERA by IV infusion every 3 weeks at 1,800 mg (< 70 kg body weight) or 2,400 mg (≥ 70 kg), with or without tislelizumab-jsgr and an investigator choice of a fluoropyrimidine- and platinum-based chemotherapy (CAPOX or FP) or trastuzumab with CAPOX or FP *[see Clinical Studies (14.1)]*. Treatment in each arm continued until disease progression or unacceptable toxicity.

ZIIHERA in combination with tislelizumab-jsgr and chemotherapy

Sixty-three percent (63%) of patients were exposed to ZIIHERA for 6 months or longer and 39% 1 year or longer).

Serious adverse reactions occurred in 59% of patients who received ZIIHERA. Serious adverse reactions in > 2% of patients included diarrhea (17%), infusion-related reactions (5%), vomiting (4.8%), hypokalemia (4.4%), acute kidney injury (3.7%), pneumonia (3.7%), nausea (2.4%), decreased appetite (2.4%), and anemia (2.4%). Fatal adverse reactions occurred in 2.4% of patients who received ZIIHERA in combination with tislelizumab-jsgr and chemotherapy include acute kidney injury (N=2), cardiac failure, diarrhea, dehydration, hypovolemic shock and intestinal obstruction (all N=1).

Permanent discontinuation of ZIIHERA occurred in 13% of patients. Adverse reactions that resulted in permanent discontinuation of ZIIHERA in ≥ 1% of patients included diarrhea (4.4%) and ejection fraction decreased (2.7%).

Dosage interruptions of ZIIHERA, excluding temporary interruptions of ZIIHERA infusions due to infusion-related reactions, occurred in 65% of patients. Adverse reactions requiring a dose interruption of ZIIHERA in > 3% of patients, excluding infusion-related reactions, were diarrhea (14%), neutropenia (11%), platelet count decreased (9%), fatigue (7%), ejection fraction decreased (7%), anemia (6%), hypokalemia (4.8%), decreased appetite (4.4%), vomiting (3.4%), and rash (3.1%).

Dosage reductions of ZIIHERA occurred in 14% of patients. The adverse reactions requiring dosage reduction of ZIIHERA in ≥ 1% of patients were diarrhea (10%) and hypokalemia (1.0%).

The most common adverse reactions (≥ 20%) were diarrhea (83%), nausea (56%), decreased appetite (46%), vomiting (44%), hypokalemia (39%), fatigue (37%), rash (36%), peripheral neuropathy (27%), and infusion-related reaction (25%).

ZIIHERA in combination with chemotherapy

Fifty-seven percent (57%) of patients were exposed to ZIIHERA for 6 months or longer and 32% for 1 year or longer.

Serious adverse reactions occurred in 49% of patients who received ZIIHERA. Serious adverse reactions in > 2% of patients included diarrhea (11%), vomiting (3.3%), decreased appetite (2.6%), pneumonia (2.6%), sepsis (2.6%), hypokalemia (2.3%), and nausea (2.3%).

Permanent discontinuation of ZIIHERA occurred in 10% of patients. Adverse reactions that resulted in permanent discontinuation of ZIIHERA in ≥ 1% of patients included ejection fraction decreased (2.0%), infusion-related reaction (1.6%), and diarrhea (1.6%).

Dosage interruptions of ZIIHERA, excluding temporary interruptions of ZIIHERA infusions due to infusion-related reactions, occurred in 56% of patients. Adverse reactions requiring a dose interruption of ZIIHERA, excluding infusion-related reactions, occurring in > 3% of patients were

diarrhea (14%), neutropenia (10%), platelet count decreased (10%), anemia (6%), ejection fraction decreased (6%), fatigue (6%), and hypokalemia (3.9%).

Dosage reductions of ZIIHERA occurred in 15% of patients who received ZIIHERA in combination with chemotherapy. Adverse reactions requiring dosage reductions of ZIIHERA in ≥ 1% of patients were diarrhea (11%), decreased appetite (1.0%), and ejection fraction decreased (1.0%).

The most common adverse reactions in patients receiving ZIIHERA in combination with chemotherapy (≥ 20%) were diarrhea (79%), nausea (54%), vomiting (44%), decreased appetite (40%), fatigue (36%), hypokalemia (33%), peripheral neuropathy (32%), infusion-related reaction (25%), and rash (22%).

Table 5 summarizes the adverse reactions in HERIZON-GEA-01.

Table 5: Adverse Reactions (≥ 10%) With an Increased Incidence (≥ 5% Increase in All Grades) in a ZIIHERA-containing arm in HERIZON-GEA-01

Adverse Reaction*	ZIIHERA with chemotherapy and tislelizumab-jsgr N = 294		ZIIHERA with chemotherapy N = 305		Trastuzumab with chemotherapy N = 302	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders						
Diarrhea[a]	83	26	79	21	53	14
Nausea	56	8	54	4.3	48	3.0
Vomiting[b]	44	6	44	3.6	34	4.3
Metabolism and nutrition disorders						
Decreased appetite	46	8	40	7	36	6
General disorders and administration site conditions						
Fatigue[c]	37	7	36	7	30	6
Skin and subcutaneous tissue disorders						
Rash[d]	36	5	22	2.6	25	5
Pruritus	17	0.7	8	0.3	3.6	0
Injury, poisoning, and procedural complications						
Infusion-related reaction	25	1.7	25	2.3	13	0.7
Investigations						
Ejection fraction decreased[e]	12	3.1	9	2.3	7	1.3

* Graded per CTCAE version 5.

[a] Diarrhea includes colitis, diarrhea, enteritis, enterocolitis and enterocolitis hemorrhagic.

[b] Vomiting includes hematemesis and vomiting.

[c] Fatigue includes asthenia and fatigue.

[d] Rash includes dermatitis, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash maculo-papular, rash pustular and urticaria.

[e] Ejection fraction decreased includes cardiac failure, ejection fraction decreased, left ventricular dysfunction and right ventricular failure.

Table 6 summarizes the laboratory abnormalities in HERIZON-GEA-01.

Table 6: Laboratory Abnormalities (≥ 30%) with an Increased Incidence (at least 5% of all Grades or 2% Grade 3-4) in a ZIIHERA-containing arm in HERIZON-GEA-01

Laboratory Abnormalities	ZIIHERA with chemotherapy and tislelizumab-jsgr N = 294		ZIIHERA with chemotherapy N = 305		Trastuzumab with chemotherapy N = 302	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology						
Hemoglobin decreased	97	19	92	16	92	16
Chemistry						
Potassium decreased	61	27	56	23	38	12
Blood calcium decreased	62	1.7	52	1.6	56	1.7
Aspartate aminotransferase increased	51	4.8	46	2.3	53	0.7
Blood magnesium decreased	42	0.3	43	3	24	0
Alanine aminotransferase increased	41	3.4	38	1.6	37	0
Sodium decreased	43	2	35	2.3	35	1
Creatinine increased	34	4.1	23	2.6	21	2.3

Biliary Tract Cancer (HERIZON-BTC-01)

The safety of ZIIHERA was evaluated in 80 patients with previously treated, unresectable or metastatic HER2-positive biliary tract cancer who received at least one prior gemcitabine-containing chemotherapy regimen in HERIZON-BTC-01 *[see Clinical Studies (14.2)].* Patients received ZIIHERA 20 mg/kg by IV infusion once every 2 weeks until disease progression or unacceptable toxicity. The median duration of exposure to ZIIHERA was 5.6 months (range: 0.5 to 27.2 months).

Serious adverse reactions occurred in 54% of patients who received ZIIHERA. Serious adverse reactions in > 2% of patients included biliary obstruction (15%), biliary tract infection (8%), sepsis (8%), pneumonia (5%), diarrhea (3.8%), gastric obstruction (3.8%), and fatigue (2.5%). A fatal adverse reaction of hepatic failure occurred in one patient who received ZIIHERA.

Permanent discontinuation due to an adverse reaction occurred in 2.5% of patients who received ZIIHERA. Adverse reactions which resulted in permanent discontinuation in ≥ 1% of patients who received ZIIHERA included decreased ejection fraction and pneumonitis.

Dosage interruptions due to adverse reactions, excluding temporary interruptions of ZIIHERA infusions due to infusion-related reactions, occurred in 41% of patients who received ZIIHERA. The most frequent adverse reactions (> 2% of patients) that required dosage interruption were diarrhea, increased alanine aminotransferase, increased aspartate aminotransferase, decreased ejection

fraction, pneumonia, cholangitis, fatigue, biliary obstruction, abdominal pain, increased blood creatinine, and decreased potassium.

Dosage reductions due to an adverse reaction occurred in 4% of patients who received ZIIHERA. Adverse reactions requiring dosage reductions in > 1% of patients were diarrhea, nausea, and decreased weight.

The most common adverse reactions in patients receiving ZIIHERA (≥ 20%) were diarrhea, infusion-related reaction, abdominal pain, and fatigue.

Table 7 summarizes the adverse reactions that occurred in HERIZON-BTC-01.

Table 7: Adverse Reactions (≥ 15%) in HERIZON-BTC-01

Adverse Reaction*	ZIIHERA N=80	
	All Grades (%)	Grades 3 or 4 (%)
Gastrointestinal disorders		
Diarrhea[a]	50	10
Abdominal pain[b]	29	1
Nausea	18	1
Vomiting	15	1
Injury, poisoning, and procedural complications		
Infusion-related reaction	35	1
General disorders and administration site conditions		
Fatigue[c]	24	4
Skin and subcutaneous tissue disorders		
Rash[d]	19	0
Metabolism and nutrition disorders		
Decreased appetite	16	0

* Graded per CTCAE version 5.
[a] Diarrhea includes diarrhea and enteritis
[b] Abdominal pain includes abdominal pain and abdominal pain upper
[c] Fatigue includes asthenia and fatigue
[d] Rash includes dermatitis, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, rash, rash maculo-papular, and rash pustular

Table 8 summarizes the laboratory abnormalities in HERIZON-BTC-01.

Table 8: Laboratory Abnormalities (≥ 30%) that Worsened from Baseline in Patients with Unresectable or Metastatic HER2-Positive BTC Receiving ZIIHERA in HERIZON-BTC-01

Laboratory Abnormalities	ZIIHERA*	
	All Grades (%)	Grades 3 or 4 (%)
Hematology		
Hemoglobin decreased	88	14
Lymphocytes decreased	44	8
Chemistry		
Lactate dehydrogenase increased	55	0
Albumin decreased	53	0
Aspartate aminotransferase increased	47	10
Alanine aminotransferase increased	46	8
Alkaline phosphatase increased	41	5
Sodium decreased	35	10
Potassium decreased	34	5

* The denominator used to calculate the rate varied from 78 to 80 based on the number of patients with a baseline value and at least one post-treatment value.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on mechanism of action, ZIIHERA can cause fetal harm when administered to a pregnant woman. There are no human or animal data on the use of ZIIHERA in pregnancy. In literature reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Use of ZIIHERA is not recommended during pregnancy (see CLINICAL CONSIDERATIONS). Advise patients of potential risks to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received ZIIHERA during pregnancy or within 4 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with local standard of care.

8.2 Lactation

Risk Summary

There are no data on the presence of zanidatamab-hrii in human milk, the effects on the breastfed child, or the effects on milk production. Published data suggest human IgG is present in human milk but does not enter neonatal or infant circulation in substantial amounts. Consider developmental and health benefits of breastfeeding along with the mother's clinical need for ZIIHERA treatment and any

potential adverse effects on the breastfed child from ZIIHERA or from the underlying maternal condition. This consideration should also take into account the ZIIHERA half-life of approximately 24 days and a washout period of 4 months *[see Clinical Pharmacology (12.3)]*.

8.3 Females and Males of Reproductive Potential

ZIIHERA can cause fetal harm when administered to a pregnant woman *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of ZIIHERA *[see Use in Specific Populations (8.1)]*.

Contraception

Females

ZIIHERA can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment with ZIIHERA and for 4 months following the last dose of ZIIHERA.

8.4 Pediatric Use

Safety and efficacy of ZIIHERA have not been established in pediatric patients.

8.5 Geriatric Use

Gastroesophageal Adenocarcinoma (GEA)

ZIIHERA in combination with tislelizumab-jsgr and chemotherapy

Of 302 patients randomized to ZIIHERA in combination with chemotherapy and tislelizumab-jsgr in HERIZON-GEA-01, there were 139 (46%) patients 65 years of age and older. One hundred and six (35%) were aged 65-74 years old and 33 (11%) were aged 75 years or older *[see Clinical Studies (14.1)]*.

There was a higher incidence of Grade ≥ 3 adverse reactions observed in patients 65 years of age and older (87%) as compared to younger patients (80%). The incidence of Grade 3 or 4 diarrhea was higher in patients 65 years and older (32%) compared to patients younger than 65 years (20%).

There was an increased incidence of fatal adverse reactions in patients 65 years and older (4.4%); including acute kidney injury (N=2), cardiac failure, dehydration, hypovolemic shock and intestinal obstruction (all N=1), compared to younger patients (0.6%), including diarrhea (N=1).

ZIIHERA in combination with chemotherapy

Of 304 patients randomized to ZIIHERA in combination with chemotherapy in HERIZON-GEA-01, there were 130 (43%) patients 65 years of age and older. One hundred (33%) were aged 65-74 years old and 30 (10%) were aged 75 years or older *[see Clinical Studies (14.1)]*.

No overall differences in safety were observed between patients 65 years of age and older and younger adult patients.

Biliary Tract Cancer

Of the 80 patients who received ZIIHERA for unresectable or metastatic biliary tract cancer in HERIZON-BTC-01 as a single agent, there were 39 (49%) patients 65 years of age and older. Thirty-

seven (46%) were aged 65-74 years old and 2 (3%) were aged 75 years or older *[see Clinical Studies (14.2)]*.

No overall differences in safety or effectiveness were observed between patients 65 years of age and older compared to younger adult patients.

11 DESCRIPTION

Zanidatamab-hrii is a humanized, IgG1-like, bispecific HER2-directed antibody. Zanidatamab-hrii is produced in mammalian (Chinese hamster ovary) cell culture via recombinant DNA technology and has a molecular weight of 124.8 kDa.

ZIIHERA (zanidatamab-hrii) for injection is supplied as a sterile, preservative free, white lyophilized powder that requires reconstitution and dilution for intravenous use. Each single-dose vial of reconstituted product contains 300 mg of zanidatamab-hrii and the inactive ingredients: polysorbate 20 (0.63 mg), sodium succinate (4.3 mg), succinic acid (4.3 mg), and sucrose (567 mg). Following reconstitution with 5.7 mL Sterile Water for Injection, a solution containing 50 mg/mL zanidatamab-hrii is produced with a deliverable volume of 6 mL, with pH of 4.6. The resulting solution is diluted and administered by intravenous infusion.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zanidatamab-hrii is a bispecific HER2-directed antibody that binds to extracellular domains 2 (ECD2) and 4 (ECD4) on HER2. Similar to other HER2-directed antibodies, in vitro binding of zanidatamab-hrii with HER2 causes clustering and results in internalization leading to a reduction of the receptor on the tumor cell surface. Zanidatamab-hrii 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.

12.2 Pharmacodynamics

Zanidatamab-hrii exposure-response relationships for safety and efficacy and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

A mean increase in the QTc interval > 20 ms is unlikely at the approved recommended dosage.

12.3 Pharmacokinetics

Zanidatamab-hrii pharmacokinetics were characterized at steady-state in patients with BTC and GEA at the approved recommended dosages and are presented as mean (coefficient of variation [CV]%) in Table 9.

Table 9: Zanidatamab-hrii steady-state pharmacokinetics in patients with BTC and GEA at the approved recommended dosages

Parameters	ZIIHERA Dosage		
	1,800 mg /2,400 mg every 3 weeks in patients with GEA (%CV)	1,200 mg /1,600 mg every 2 weeks in patients with GEA (%CV)	20 mg/kg every 2 weeks in patients with BTC (%CV)
C_{min} (µg/mL)	176 (39%)	203 (36%)	200 (52%)
C_{avg} (µg/mL)	319 (27%)	319 (27%)	319 (36%)
C_{max} (µg/mL)	783 (20%)	609 (21%)	624 (26%)

The C_{max} of zanidatamab-hrii is dose proportional and the total systemic exposure (AUC) of zanidatamab-hrii is greater than dose proportional. Steady state was approached after approximately 16 weeks following multiple doses. Zanidatamab-hrii median C_{trough} accumulation is 1.8-fold.

Distribution

Zanidatamab-hrii volume of distribution is 8.1 L (28.4%).

Elimination

Zanidatamab-hrii elimination half-life is 24 days with an apparent clearance (CL) of 0.3 L/day (30%).

Metabolism

Zanidatamab-hrii is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of zanidatamab-hrii were observed based on age (22 to 87 years), sex, body weight (35 to 142 kg), race (White 39%, Asian 56%, or Black 0.7%), cancer type, creatinine clearance 30 to 89 mL/min (estimated by the Cockcroft-Gault equation), mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN or total bilirubin 1 to 1.5 times ULN and any AST), or moderate hepatic (total bilirubin 1.5 to ≤ 3 ULN and any AST).

The effect of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR < 15 mL/min) with or without hemodialysis, and severe (total bilirubin > 3 ULN and any AST) hepatic impairment on zanidatamab-hrii pharmacokinetics is unknown.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those for zanidatamab-hrii or of other zanidatamab products.

In patients who received ZIIHERA at the approved recommended dosages, 3.4% (18/534) of patients developed treatment-emergent anti-zanidatamab antibodies. Of the patients who developed treatment-emergent anti-zanidatamab antibodies, 17% (3/18) also developed neutralizing antibodies.

Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, safety, and efficacy of zanidatamab products is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been conducted to evaluate the carcinogenic or mutagenic potential of zanidatamab-hrii.

Fertility studies with zanidatamab-hrii have not been conducted.

14 CLINICAL STUDIES

14.1 Gastroesophageal Adenocarcinoma (GEA)

The efficacy of ZIIHERA in combination with fluoropyrimidine- and platinum-based chemotherapy, with or without tislelizumab-jsgr was evaluated for the treatment of GEA in HERIZON-GEA-01 (NCT05152147), a randomized, 3-arm, open-label, active-comparator, global trial in patients with advanced or metastatic HER2-positive GEA, including those with gastric, gastroesophageal junction, and esophageal adenocarcinoma. Eligible patients were those with untreated, unresectable locally advanced/metastatic GEA that was HER2-positive (IHC 3+ or IHC 2+/ISH+) per central testing, an Eastern Cooperative Oncology Group (ECOG) Performance status (PS) 0 or 1, and adequate organ function, including LVEF ≥ 50%. Patients were enrolled regardless of their PD-L1 expression.

Randomization was stratified by geographic region (Asia, EU/North America, or Rest of world), HER2 status per central assessment (3+ IHC staining, 2+ IHC staining with ISH-positivity), and ECOG PS (0, 1). Patients were randomized 1:1:1 to one of three treatment arms:

- Arm A: Trastuzumab 8 mg/kg IV loading dose (Cycle 1 Day 1), and 6 mg/kg IV in subsequent cycles, followed by investigator's choice of combination therapy of CAPOX or FP for at least 6 cycles.
- Arm B: ZIIHERA 1,800 mg (weight < 70 kg) or 2,400 mg (body weight ≥ 70 kg) IV in combination with CAPOX or FP.
- Arm C: ZIIHERA 1,800 mg (weight < 70 kg) or 2,400 mg (weight ≥ 70 kg) IV + tislelizumab-jsgr 200 mg IV in combination with CAPOX or FP.

CAPOX consisted of oxaliplatin 130 mg/m^2 intravenously and capecitabine 1,000 mg/m^2 orally for 14 days; FP consisted of cisplatin 80 mg/m^2 intravenously and fluorouracil 800 mg/m^2/day intravenously for 5 days. All study medications, except oral capecitabine, were administered as an intravenous infusion every 3-week cycle. Treatment with ZIIHERA, with or without tislelizumab-jsgr continued in each arm until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

The dual major efficacy outcome measures were progression-free survival (PFS) assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and overall survival (OS). Additional efficacy outcome measures included Objective response rate (ORR) and Duration of Response (DOR) per BICR.

A total of 914 GEA patients were randomized into HERIZON-GEA-01, including 638 patients with gastric adenocarcinoma, 195 patients with a gastroesophageal junction adenocarcinoma, and 81 patients with an esophageal adenocarcinoma. The trial population characteristics were median age 63 years old (range: 21 to 87), 45% of patients were ≥ 65 years old; 79% were male; 55% were Asian, 39% were White, 1.9% were American Indian or Alaskan Native, and for 1.4% race was other or multiple; 84% were Non-Hispanic or Latino, 13% Hispanic/Latino, and for 3.2% ethnicity was unknown or not reported; 41% ECOG PS 0; and 59% ECOG PS 1. Eighty-three percent (83%) of

patients had central HER2 IHC 3+ and 17% had central HER2 IHC 2+/ISH+. Eighty-nine percent (89%) of patients received CAPOX and 8.3% received FP.

ZIIHERA in combination with tislelizumab-jsgr and chemotherapy

Efficacy results comparing Arm C and Arm A in the overall population are summarized in Table 10, Figure 1 and Figure 2. Statistically significant improvements in PFS and OS were demonstrated for the comparison of Arm C to Arm A.

Table 10: Efficacy Results in HERIZON-GEA-01 Comparing Arm C and Arm A in the overall population

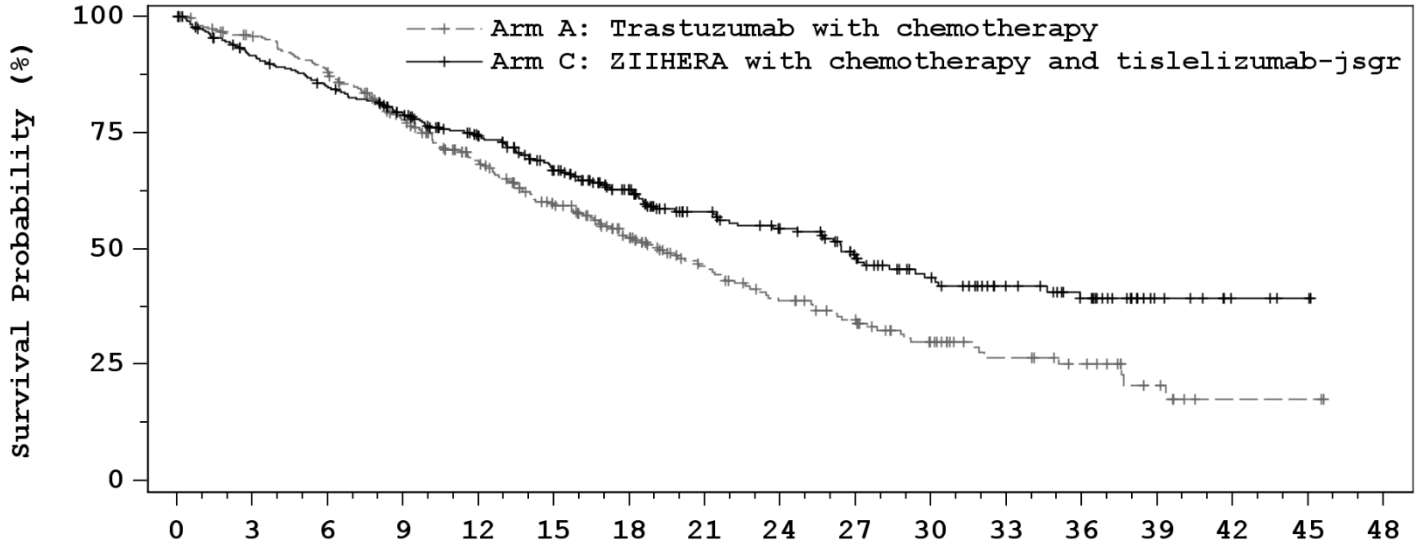
	Arm C ZIIHERA with chemotherapy and tislelizumab-jsgr N=302	**Arm A Trastuzumab with chemotherapy N=308**
Overall Survival		
Deaths (%)	134 (44%)	170 (55%)
Median, months[a]	26.4	19.2
(95% CI)[a]	(21.5, 30.3)	(16.8, 21.8)
Hazard ratio (95% CI)[b]	0.72 (0.57, 0.90)	
p-value[c]	0.0043	
Progression-Free Survival		
Number of events (%)	154 (51%)	196 (64%)
Median, months[a]	12.4	8.1
(95% CI)[a]	(9.8, 18.5)	(7.0, 8.9)
Hazard ratio (95% CI)[b]	0.63 (0.51, 0.78)	
p-value[c]	< 0.0001	
Objective Response Rate (ORR)		
ORR (95% CI[d])	67% (61, 72)	63% (57, 68)
Complete response rate	20%	12%
Partial response rate	47%	50%
Duration of Response (DOR)	N=202	N=193
Median in months (95% CI)[a]	18.9 (12.1, 37.7)	8.3 (6.8, 10.1)

[a] Estimates per Kaplan-Meier method; CIs based on Brookmeyer and Crowley method with log-log transformation.
[b] Hazard ratio and 95% CIs were calculated in comparison with treatment arm Trastuzumab + Chemotherapy stratified by geographic region, HER2 status, and ECOG performance status.
[c] The p-values were calculated by stratified log-rank test.
[d] Two-sided 95% exact confidence interval using the Clopper-Pearson method.
CI=confidence interval

In pre-specified exploratory analyses comparing Arm C and Arm A in the HER2 IHC3+ population, the PFS HR was 0.54 (95% CI: 0.43, 0.69), with a median 16.1 months (95% CI: 10.9, 22.0) in Arm C and 7.6 months (95% CI: 6.9, 8.5) in Arm A; the OS HR was 0.70 (95% CI: 0.55, 0.91), with a median 27.3 months (95% CI: 22.3, NE) in Arm C and 19.8 months (95% CI: 16.2, 22.8) in Arm A. In the HER2 IHC2+/ISH+ population, the PFS HR was 1.08 (95% CI: 0.65, 1.78), with a median 8.6 months (95% CI: 6.7, 11.1) in Arm C and 10.0 months (95% CI: 6.9, 18.4) in Arm A; the OS HR was 0.83

(95% CI: 0.50, 1.39), with a median 21.5 months (95% CI: 16.0, 26.4) in Arm C and 18.7 months (95% CI: 13.6, 23.1) in Arm A.

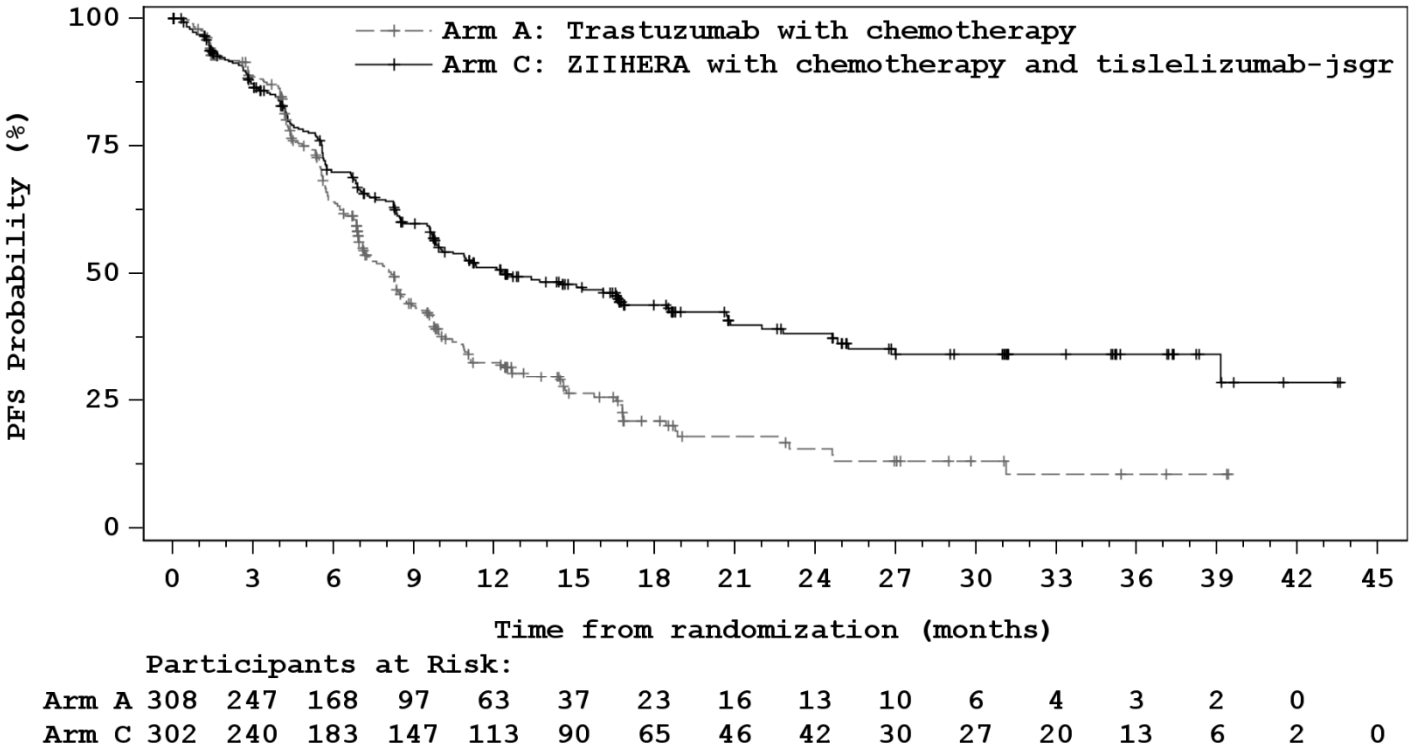
Figure 1: Kaplan-Meier Plot of Overall Survival for Arm A and Arm C in HERIZON-GEA-01



Participants at Risk:

Arm A	308	284	261	219	178	140	106	77	61	50	33	22	17	8	2	2	0
Arm C	302	267	246	222	190	157	125	96	82	64	49	36	27	10	4	2	0

Figure 2: Kaplan-Meier Plot of Progression-Free-Survival for Arm A and Arm C in HERIZON-GEA-01



ZIIHERA in combination with chemotherapy

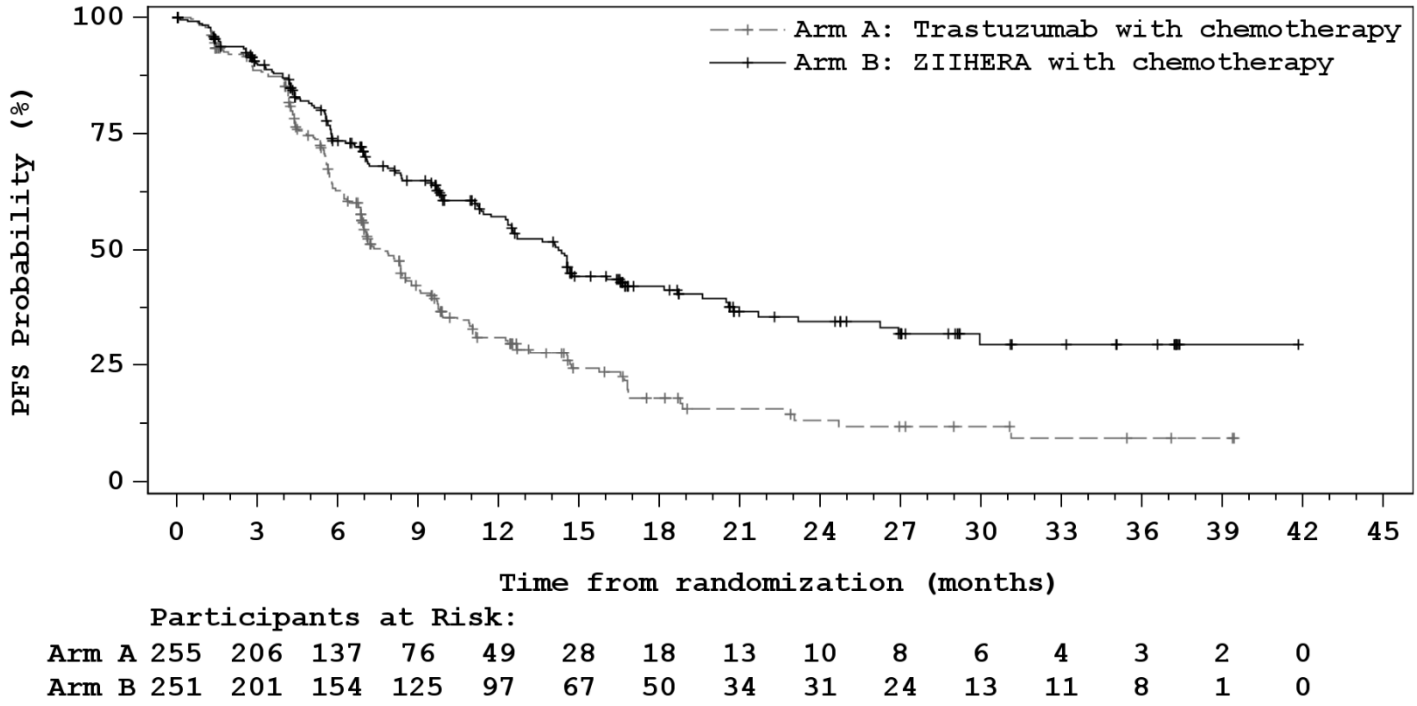
Efficacy results comparing Arm B and Arm A in the HER2 IHC3+ population are summarized in Table 11 and Figure 3. A statistically significant improvement in PFS was demonstrated in the overall population comparing Arm B and Arm A; however, an exploratory analysis of PFS in the HER2 IHC2+/ISH+ population showed a HR of 1.73 (95% CI: 1.06, 2.83), with a median of 6.2 months (95% CI: 3.0, 8.5) for Arm B and 10.0 months (95% CI: 6.9, 18.4) for Arm A, indicating that the improvement in the overall population was primarily attributed to the results observed in the subgroup of patients with HER2 IHC3+. OS in the overall population did not achieve statistical significance at the current interim analysis.

Table 11: Efficacy Results in HERIZON-GEA-01 Comparing Arm B and Arm A in Patients with HER2 IHC3+

	Arm B ZIIHERA with chemotherapy N=251	Arm A Trastuzumab with chemotherapy N=255
Overall Survival*		
Deaths (%)	116 (46%)	138 (54%)
Median, months[a]	25.5	19.8
(95% CI)[a]	(21.9, 30.3)	(16.2, 22.8)
Hazard ratio (95% CI)[b]	0.74 (0.58, 0.95)	
Progression-Free Survival		
Number of events (%)	125 (50%)	167 (65%)
Median, months[a]	14.2	7.6
(95% CI)[a]	(11.7, 16.7)	(6.9, 8.5)
Hazard ratio (95% CI)[b]	0.55 (0.43, 0.69)	
Objective Response Rate (ORR)		
ORR (95% CI)[c]	71% (64, 76)	64% (57, 69)
Complete response rate	19%	12%
Partial response rate	51%	52%
Duration of Response (DOR)	N=177	N=162
Median in months (95% CI)[a]	16.9 (12.8, 25.3)	8.1 (6.5, 9.8)

[a] Estimates per Kaplan-Meier method; CIs based on Brookmeyer and Crowley method with log-log transformation.
[b] Hazard ratio and 95% CIs were calculated in comparison with treatment arm Trastuzumab + Chemotherapy stratified by geographic region, HER2 status, and ECOG performance status.
[c] Two-sided 95% exact confidence interval using the Clopper-Pearson method.
* Overall survival data was immature at the time of this analysis.

Figure 3: Kaplan-Meier Plot of Progression-Free-Survival for IHC3+ patients in Arm A and Arm B in HERIZON-GEA-01



14.2 HER2-positive (IHC 3+) Biliary Tract Cancer (BTC)

The efficacy of ZIIHERA was evaluated in 62 patients with HER2-positive (IHC 3+ by central assessment) BTC in Cohort 1 of HERIZON-BTC-01 (NCT04466891), an open-label, multicenter, single arm trial in patients with unresectable or metastatic disease. Patients were required to have received at least one prior gemcitabine-containing systemic chemotherapy regimen in the advanced disease setting and adequate cardiac function (defined as LVEF ≥ 50%).

Patients received ZIIHERA 20 mg/kg intravenously every 2 weeks. ZIIHERA was administered until disease progression or unacceptable toxicity. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as determined by an independent central review (ICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age was 64 years (range: 38 to 79 years), 47% of patients were age 65 or older; 55% were female; 61% were Asian, 31% were White, 2% were American Indian or Alaskan Native, and for 6% race was unknown or not reported; 89% were Non-Hispanic or Latino, 8% Hispanic/Latino, and for 3% ethnicity was unknown or not reported. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (32%) or 1 (68%). Fifty-three percent of patients had gallbladder cancer, 27% had intrahepatic cholangiocarcinoma, and 19% had extrahepatic cholangiocarcinoma. All patients received at least 1 prior line of gemcitabine-based therapy, 31% had 2 prior lines of therapy, and 10% had 3 or more prior lines of therapy for unresectable or metastatic disease.

Efficacy results are summarized in Table 12.

Table 12: Efficacy Results in HERIZON-BTC-01

Efficacy Parameter*	**ZIIHERA (N=62)**
Objective Response Rate (95% CI)	**52% (39, 65)**
Complete response, n (%)	3 (4.8)
Partial response, n (%)	29 (47)
Duration of Response (DOR)	**N=32**
Median†, months (95% CI)	14.9 (7.4, 24.0)
DOR ≥ 6 months, n (%)‡	20 (63)
DOR ≥ 12 months, n (%)‡	14 (44)

* Assessed by independent central review
† Based on Kaplan-Meier estimate
‡ Based on observed duration of response

16 HOW SUPPLIED/STORAGE AND HANDLING

ZIIHERA is supplied as a sterile, preservative free, white lyophilized powder in a single-dose vial. Each single-dose vial (NDC 68727-950-01) contains 300 mg zanidatamab-hrii. Each carton of ZIIHERA (NDC 68727-950-02) contains 2 single-dose vials.

Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF) in the original carton until time of reconstitution. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Diarrhea

Advise patients that ZIIHERA can cause severe diarrhea, and that prophylaxis with loperamide is required at treatment initiation when ZIIHERA is given with fluoropyrimidine- and platinum-containing chemotherapy for the treatment of GEA. Advise patients to notify their healthcare provider immediately if they experience new or worsening diarrhea, and to start loperamide with the first loose stool *[see Warnings and Precautions (5.1)].*

Embryo-Fetal Toxicity

Advise female patients of the potential risk to a fetus. Advise female patients to contact their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with ZIIHERA and for 4 months following the last dose *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.3)].*

Left Ventricular Dysfunction

Advise patients that ZIIHERA can cause cardiac dysfunction and to contact a healthcare provider immediately for signs and symptoms of cardiac dysfunction *[see Warnings and Precautions (5.3)].*

Infusion-Related Reactions

Advise patients of the risk of infusion-related reactions and to inform a healthcare provider immediately for symptoms of an infusion-related reaction *[see Warnings and Precautions (5.4)]*.

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MEDICATION GUIDE
ZIIHERA® (zye HAYR rah)
(zanidatamab-hrii)
for injection, for intravenous use

What is the most important information I should know about ZIIHERA?

ZIIHERA can cause serious side effects, including:

- **Diarrhea.** Diarrhea during treatment with ZIIHERA can be severe, life threatening, and can lead to death. Diarrhea may cause loss of fluids and body salts (electrolytes). To help prevent or reduce diarrhea during treatment with ZIIHERA, your healthcare provider:
  - will tell you to drink more fluids.
  - start you on an antidiarrheal medicine such as loperamide or other treatment, as needed.
  - may temporarily stop, reduce your dose or permanently stop treatment with ZIIHERA, or other medicines you take.

  If you get new or worsening diarrhea, tell your healthcare provider right away and take antidiarrheal medicine as prescribed. Follow all of your healthcare providers instructions to help with your diarrhea.
- **Harm to your unborn baby.** Taking ZIIHERA during pregnancy or within 4 months before pregnancy can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with ZIIHERA.

  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with ZIIHERA.
  - Use effective birth control (contraception) during treatment with ZIIHERA and for 4 months after the last dose.

See "What are the possible side effects of ZIIHERA?" for more information about side effects.

What is ZIIHERA?

ZIIHERA is a prescription medicine used to treat adults with:

- gastroesophageal cancer (GEA) including gastric cancer, esophageal cancer, and gastroesophageal junction (GEJ) cancer. ZIIHERA is used in combination with fluoropyrimidine-and platinum- containing chemotherapy with or without tislelizumab-jsgr as the first treatment when your GEA:
  - cannot be removed by surgery or has spread to other parts of your body (metastatic) **and**
  - your tumor tests positive for human epidermal growth factor receptor 2 (HER2 IHC3+ or IHC 2+/ISH+).
- biliary tract cancer (BTC) that includes cancer of the bile duct (cholangiocarcinoma) and cancer of the gallbladder. ZIIHERA is used alone when your BTC:
  - cannot be removed by surgery or has spread to other parts of your body (metastatic), **and**
  - was previously treated, **and**
  - your tumor tests positive for human epidermal growth factor receptor 2 (HER2 IHC3+).

Your healthcare provider will perform a test to make sure ZIIHERA is right for you.

It is not known if ZIIHERA is safe and effective in children.

Before receiving ZIIHERA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had any heart problems.
- are breastfeeding or plan to breastfeed. It is not known if ZIIHERA passes into your breastmilk. Talk to your healthcare provider about the best way to feed your baby if you receive treatment with ZIIHERA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I receive ZIIHERA?

- ZIIHERA is given through a vein by an intravenous (IV) infusion over 120 minutes for your first infusions. If you tolerate the first infusion well, your second infusion will be given to you over 90 minutes. Each additional infusion may be given to you over 60 minutes.
- ZIIHERA is given every 2 or 3 weeks.
- Your healthcare provider:
  - will give you medicines 30 to 60 minutes before each treatment to help prevent infusion-related reactions or make them less severe
  - will give you diarrhea medicines during your first cycle of treatment, if you are being treated for GEA
  - may slow down your infusion, temporarily stop, or permanently stop your treatment with ZIIHERA if you have certain side effects
  - may do certain tests to check you for side effects
  - will decide how many treatments you need
- If you miss a dose, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of ZIIHERA?

ZIIHERA can cause serious side effects, including:

- See **"What is the most important information I should know about ZIIHERA?"**
- **Heart problems** that may affect how well your heart pumps blood. Your healthcare provider will check your heart function before and during treatment with ZIIHERA. Tell your healthcare provider right away if you get any of the following signs and symptoms of a heart problem:
  - new or worsening shortness of breath
  - feeling more tired than usual
  - swelling of your ankles or feet
  - loss of consciousness
  - irregular heartbeat
  - sudden weight gain
  - dizziness or feeling light-headed
- **Infusion-related reactions**. Your healthcare provider will check for side effects during your infusions. Tell your healthcare provider right away if you get any of the following symptoms during or after your infusions of ZIIHERA:
  - shortness of breath or trouble breathing
  - fever
  - chills
  - rash
  - flushing
  - nausea or vomiting
  - dizziness or feeling lightheaded
  - chest discomfort

Other common side effects when ZIIHERA is given in combination with chemotherapy and tislelizumab-jsgr include:

- diarrhea
- nausea
- decreased appetite
- vomiting
- low levels of blood potassium
- feeling tired
- numbness, pain, tingling, or burning in your hands or feet
- rash
- infusion-related reactions

Other common side effects when ZIIHERA is given in combination with chemotherapy include:

- diarrhea
- nausea
- vomiting
- numbness, pain, tingling, or burning in your hands or feet
- decreased appetite
- feeling tired
- low levels of blood potassium
- infusion-related reactions
- rash

Other common side effects of ZIIHERA when used alone include:

- diarrhea
- infusion-related reactions
- stomach pain
- feeling tired

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of ZIIHERA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ZIIHERA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about ZIIHERA that is written for health professionals.

What are the ingredients in ZIIHERA?

Active ingredient: zanidatamab-hrii

Inactive ingredients: polysorbate 20, sodium succinate, succinic acid, and sucrose

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For more information, go to www.ZIIHERA.com or call 1-800-520-5568.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 08/2026