ZIIHERA®
(zanidatamab-hrii)
50mg/ml Injection for IV

DOSING AND ADMINISTRATION GUIDE

Your guide to the dosing and administration of ZIIHERA

INDICATIONS

ZIIHERA (zanidatamab-hrii) 50 mg/mL is indicated for:

Gastroesophageal Adenocarcinoma (GEA)

- In combination with fluoropyrimidine- and platinum-containing chemotherapy and tislelizumab-jsgr, as first-line treatment for 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.
- In combination with fluoropyrimidine- and platinum-containing chemotherapy, as first-line treatment for 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)

- As a single agent, for adult patients with previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC, as detected by an FDA-authorized 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).

IMPORTANT SAFETY 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.**
- **Embryo-Fetal Toxicity: Exposure to ZIIHERA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.**

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED WARNINGS and Medication Guide.

ZIIHERA IS ADMINISTERED AS AN IV INFUSION[1]

GEA

In HER2+ advanced GEA, ZIIHERA complements your preferred chemotherapy and tislelizumab schedule with flexible dosing[1]

Patient weight: <70 kg	
Every 2 weeks 1200 mg	Every 3 weeks 1800 mg
Patient weight: ≥70 kg	
Every 2 weeks 1600 mg	Every 3 weeks 2400 mg

Until disease progression or unacceptable toxicity[1]

Start antidiarrheal prophylaxis: loperamide 4 mg BID starting on Day 1 of Cycle 1, for at least the first 7 days[1]

- ZIIHERA is administered with chemotherapy, with or without tislelizumab[1]
- For the recommended dosage of fluoropyrimidine- and platinum-containing chemotherapy or tislelizumab, refer to the respective Prescribing Information[1]
- Administer ZIIHERA first, followed by tislelizumab (if included in the regimen) and then chemotherapy[1]
- 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[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

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. 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 compared to younger patients.

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ZIIHERA®
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50 mg/ml Injection for IV

BTC

For patients with HER2+ advanced (IHC 3+) biliary tract cancer

20 mg/kg as an IV infusion once every 2 weeks until disease progression or unacceptable toxicity[1]

- ZIIHERA is given as a single agent in the second-line treatment of biliary tract cancer[1]

GEA + BTC

Infusion duration[1]

1st	**120 minutes**
2nd	**90 minutes** if previous infusion was well-tolerated
3rd+	**60 minutes** if previous infusions were well-tolerated

Premedicate all patients 30 to 60 minutes prior to each dose of ZIIHERA with acetaminophen, an antihistamine, and a corticosteroid.[1]

Prior to initiation of ZIIHERA and at regular intervals during treatment, assess patient left ventricular ejection fraction[1]

BID=twice daily; BTC=biliary tract cancer; GEA=gastroesophageal adenocarcinoma; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; IV=intravenous.

IMPORTANT SAFETY INFORMATION (CONT'D)

Diarrhea (cont'd)

Advise patients to increase oral fluids, begin antidiarrheals, and notify their healthcare provider immediately if diarrhea occurs.

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.

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GEA + BTC

PREPARING AND ADMINISTERING ZIIHERA

Reconstitution[1]

- Determine the number of vials needed based on the patient's weight
- Allow the vial(s) to reach room temperature
- Reconstitute each 300 mg vial of ZIIHERA with 5.7 mL of Sterile Water for Injection to obtain a 50 mg/mL solution (6 mL of extractable volume)
- Swirl the vial gently until completely dissolved; don't shake or vigorously swirl
- Allow the reconstituted vial to settle to allow bubbles to dissipate
- Inspect the vial
  - Solution should be colorless to light yellow, clear to slightly opalescent, with no visible particles. Discard if any discoloration or particulate matter is observed
- Use the reconstituted ZIIHERA solution immediately or store for up to 4 hours 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[1]

- Withdraw required dose
- Slowly add to an infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection for a final concentration of the diluted solution between 4 mg/mL and 20 mg/mL
  - The least possible volume of diluent should be used and should not exceed a maximum volume of 500 mL
- Invert the infusion bag gently to mix; do not shake
- The infusion solution must be clear and colorless 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)

See section 2.5 of the ZIIHERA Prescribing Information for complete preparation and administration instructions.

IMPORTANT SAFETY INFORMATION (CONT'D)

Diarrhea (cont'd)

Administer fluids, electrolytes, and additional antidiarrheal agents as necessary. 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.

If treating patients with ZIIHERA in combination with FOLFOX, do not administer the fluorouracil bolus.

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Dilution (cont'd)[1]

- Use infusion immediately upon dilution or store:
  - For up to 12 hours at room temperature (18°C to 24°C [64°F to 75°F]) or
  - For up to 24 hours in the refrigerator (2°C to 8°C [36°F to 46°F])
    - These time limits include the beginning of reconstitution through the duration of infusion
    - If times are exceeded, prepare new infusion bag containing the remaining dosage of ZIIHERA to be infused

Administration[1]

- Administer only as an intravenous infusion after ZIIHERA is reconstituted and diluted
- **Premedicate all patients 30 to 60 minutes prior to each dose of ZIIHERA to prevent infusion-related reactions**
  - Administer acetaminophen, an antihistamine, and corticosteroid
- Administer ZIIHERA as an intravenous infusion with a 0.2 or 0.22 micron filter
- Do not administer as an intravenous push or bolus
- Do not co-administer ZIIHERA and other intravenous drugs through the same intravenous line

ZIIHERA with 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.[1]

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.[1]

See section 2.5 of the ZIIHERA Prescribing Information for complete preparation and administration instructions.

BTC=biliary tract cancer; GEA=gastroesophageal adenocarcinoma.

IMPORTANT SAFETY INFORMATION (CONT'D)

Diarrhea (cont'd)

Gastroesophageal Adenocarcinoma (GEA)

ZIIHERA in combination with chemotherapy and tislelizumab-jsgr

Diarrhea was reported in 85% of 330 patients 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.

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DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS

GEA

Patient weight: <70 kg[1]		
Every 2 weeks		Every 3 weeks
1200 mg	Starting dose	1800 mg
900 mg	Dose reduction	1400 mg

Patient weight: ≥70 kg[1]		
Every 2 weeks		Every 3 weeks
1600 mg	Starting dose	2400 mg
1200 mg	Dose reduction	1800 mg

BTC

Reduce dose to 15 mg/kg[1]

GEA + BTC

Permanently discontinue ZIIHERA in patients who cannot tolerate an initial dose reduction.[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

Diarrhea (cont'd)

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.

ZIIHERA in combination with chemotherapy

Diarrhea was reported in 81% of 395 patients 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.

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GEA + BTC

Dosage modifications for diarrhea[1]

Diarrhea is a common side effect for people who receive ZIIHERA and when used in combination with fluoropyrimidine- and platinum-containing chemotherapy, with or without tislelizumab, severe, life-threatening, and fatal cases of diarrhea can occur despite loperamide prophylaxis.[1]

GEA

Proactive use of loperamide is crucial to help mitigate adverse reactions of diarrhea.[1]

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.[1]

Diarrhea by severity[2]	Treatment modification[1]
Mild (Grade 1) Increase of <4 stools per day; mild increase in ostomy output compared to baseline **Moderate (Grade 2)** Increase of 4-6 stools per day; moderate increase in ostomy output compared to baseline	• No dosage modification of ZIIHERA is required • Initiate appropriate medical therapy and monitor as clinically indicated
Severe (Grade 3) Increase of ≥7 stools per day; hospitalization indicated; severe increase in ostomy output compared to baseline	• 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

IMPORTANT SAFETY INFORMATION (CONT'D)

Diarrhea (cont'd)

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.

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GEA + BTC

Dosage modifications for left ventricular dysfunction[1]

LVD by severity	Treatment modification
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

IMPORTANT SAFETY INFORMATION (CONT'D)

Diarrhea (cont'd)

Biliary Tract Cancer (BTC)

When ZIIHERA was used as a single agent, diarrhea was reported in 49% of 233 patients 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.

Embryo-Fetal Toxicity

Based on the mechanism of action, ZIIHERA can cause fetal harm when administered to a pregnant woman.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED WARNINGS and Medication Guide.

GEA + BTC

Dosage modifications for infusion-related reactions[1]

IRR by severity	Treatment modification[1]
Mild (Grade 1) Transient flushing or rash, mild itching, anxiety, or mild disorientation[3]	• Reduce ZIIHERA infusion rate by 50% • For subsequent ZIIHERA infusions, increase infusion rate gradually to the rate prior to the adverse reaction, as tolerated
Moderate (Grade 2) Fever, rash, arthralgia, noisy breathing without respiratory distress, dyspnea with minimal exertion, intense itching, or moderate disorientation[3]	• 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) Severe arthralgia, extensive rash, symptomatic bronchospasm with or without urticaria, hypotension, angioedema, dyspnea with stridor, decrease in oxygen saturation and respiratory distress at rest, rash covering 30% of the body with widespread itching, severe disorientation, or hallucinations[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) Severe cardiac or respiratory compromise requiring urgent intervention such as ventilator support, tracheostomy, or intubation[3]	• Stop ZIIHERA infusion immediately and permanently discontinue • Promptly treat with appropriate therapy

BTC=biliary tract cancer; GEA=gastroesophageal adenocarcinoma; IRR=infusion-related reaction.

IMPORTANT SAFETY INFORMATION (CONT'D)

Embryo-Fetal Toxicity (cont'd)

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.

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Dosage modifications for adverse reactions beyond LVD, IRR, and diarrhea[1]

AR	Severity	Treatment modification
Other adverse reactions (excluding LVD, IRR and diarrhea)	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

AR=adverse reaction; BTC=biliary tract cancer; GEA=gastroesophageal adenocarcinoma; IRR=infusion-related reaction; LVD=left ventricular dysfunction; LVEF=left ventricular ejection fraction.

IMPORTANT SAFETY INFORMATION (CONT'D)

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.

The safety of ZIIHERA has not been established in patients with a baseline ejection fraction that is < 50%.

Gastroesophageal Adenocarcinoma (GEA)

ZIIHERA in combination with chemotherapy and tislelizumab-jsgr

LVEF decrease (an absolute decline in LVEF of > 10%, resulting in a final value of < 50%) was observed in 9% of 330 patients in clinical studies. LVD leading to permanent discontinuation of ZIIHERA was reported in 3% of patients.

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GEA

ZIIHERA TREATMENT CHECKLIST FOR GEA

This tool is intended as a practical reminder when administering ZIIHERA. It is not comprehensive. Your clinical training, institutional protocols, and professional judgment should always guide care.

CYCLE 1

Before Day 1: Pre-treatment[1]

- ☐ Review ZIIHERA dosing schedule (every 2 or 3 weeks) and dosage modifications for ARs
- ☐ Assess baseline LVEF
- ☐ Confirm premeds were ordered
  - ZIIHERA premeds (loperamide, acetaminophen, an antihistamine, and a corticosteroid); other premeds for other components of the treatment regimen as applicable
  - Ensure patient has loperamide and has taken it prior to infusion; administer loperamide (4 mg) if they haven't

CYCLE 1

Day 1: Infusion[1]

- ☐ Administer ordered premeds
- ☐ Infuse in order: ZIIHERA, then tislelizumab (if applicable), then chemotherapy
- ☐ When administered in combination with fluorouracil-containing regimens, **do NOT administer fluorouracil as an intravenous bolus** due to the potential increase in diarrhea
- ☐ Monitor for infusion-related reactions during the infusion and as clinically indicated once it is completed
- ☐ Remind patient to take loperamide BID for at least 7 days

IMPORTANT SAFETY INFORMATION (CONT'D)

Left Ventricular Dysfunction (LVD) (cont'd)

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). LVD resolved in 78% of patients.

ZIIHERA in combination with chemotherapy

LVEF decrease was observed in 5% of 395 patients in clinical studies. LVD leading to permanent discontinuation of ZIIHERA was reported in 1.0% of patients. The median time to first occurrence of LVD was 6.0 months (range: 1.4 to 15.0 months). LVD resolved in 70% of patients.

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CYCLE 1
Day 1: Discharge[1]

- ☐ Counsel patient on mandatory loperamide BID for at least 7 days, and to take loperamide with first loose stool
- ☐ Advise patient to increase oral fluids and notify their care team if diarrhea occurs
- ☐ Schedule Day 7 check-in

CYCLE 1
Day 7: Proactive check-in[1]

- ☐ Check in with patient to assess whether loperamide should be continued (eg, beyond 7 days or in subsequent cycles); review potential ARs

CYCLE 2
Day 1: Second infusion[1]

- ☐ Prior to second infusion check in on ARs; if Grade ≥1 diarrhea occurred in Cycle 1, continue prophylaxis with loperamide 4 mg BID for at least the first 7 days of Cycle 2 and each subsequent cycle
- ☐ Follow same infusion sequence (if applicable)
  - When administered in combination with fluorouracil-containing regimens, **do NOT administer fluorouracil as an intravenous bolus** due to the potential increase in diarrhea
  - Reconfirm expectations on median duration of diarrhea as needed

AR=adverse reaction; BID=twice daily; GEA=gastroesophageal adenocarcinoma; LVEF=left ventricular ejection fraction.

IMPORTANT SAFETY INFORMATION (CONT'D)

Left Ventricular Dysfunction (LVD) (cont'd)

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 LVD was 5.6 months (range: 1.6 to 18.7 months). LVD resolved in 70% of patients.

Infusion-Related Reactions

ZIIHERA can cause infusion-related reactions (IRRs).

Prior to each dose of ZIIHERA, administer premedication to prevent potential IRRs. 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.

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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. 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 compared to younger patients. Advise patients to increase oral fluids, begin antidiarrheals, and notify their healthcare provider immediately if diarrhea occurs.

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.

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IMPORTANT SAFETY INFORMATION (CONT'D)

Diarrhea (cont'd)

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.

If treating patients with ZIIHERA in combination with FOLFOX, do not administer the fluorouracil bolus.

Gastroesophageal Adenocarcinoma (GEA)
ZIIHERA in combination with chemotherapy and tislelizumab-jsgr
Diarrhea was reported in 85% of 330 patients 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.

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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.

Left Ventricular Dysfunction (LVD)

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

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED WARNINGS and Medication Guide.

IMPORTANT SAFETY INFORMATION (CONT'D)

Left Ventricular Dysfunction (LVD) (cont'd)

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.

The safety of ZIIHERA has not been established in patients with a baseline ejection fraction that is < 50%.

Gastroesophageal Adenocarcinoma (GEA)
ZIIHERA in combination with chemotherapy and tislelizumab-jsgr
LVEF decrease (an absolute decline in LVEF of > 10%, resulting in a final value of < 50%) was observed in 9% of 330 patients in clinical studies. 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). LVD resolved in 78% of patients.

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Infusion-Related Reactions

ZIIHERA can cause infusion-related reactions (IRRs).

Prior to each dose of ZIIHERA, administer premedication to prevent potential IRRs. 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.

Gastroesophageal Adenocarcinoma (GEA)
ZIIHERA in combination with chemotherapy and tislelizumab-jsgr
An IRR was reported in 22% of 330 patients 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.

ZIIHERA in combination with chemotherapy
An IRR was reported in 24% of 395 patients 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.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED WARNINGS and Medication Guide.

IMPORTANT SAFETY INFORMATION (CONT'D)

Infusion-Related Reactions (cont'd)

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.

Adverse Reactions

Gastroesophageal Adenocarcinoma (GEA)
ZIIHERA in combination with chemotherapy and tislelizumab-jsgr
Serious adverse reactions occurred in 59% of 294 patients in HERIZON-GEA-01. Serious adverse reactions in > 2% of patients included diarrhea (17%), IRR (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 and included 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%).

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 IRR (25%).

ZIIHERA in combination with chemotherapy
Serious adverse reactions occurred in 49% of 305 patients in HERIZON-GEA-01. 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%), IRR (1.6%), and diarrhea (1.6%).

The most common adverse reactions (≥ 20%) were diarrhea (79%), nausea (54%), vomiting (44%), decreased appetite (40%), fatigue (36%), hypokalemia (33%), peripheral neuropathy (32%), IRR (25%), and rash (22%).

Biliary Tract Cancer (BTC)
Serious adverse reactions occurred in 54% of 80 patients with unresectable or metastatic HER2-positive BTC who received ZIIHERA as a single agent in HERIZON-BTC-01. 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.

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IMPORTANT SAFETY INFORMATION (CONT'D)

Adverse Reactions (cont'd)

The most common adverse reactions in 80 patients with unresectable or metastatic HER2-positive BTC who received ZIIHERA (≥20%) were diarrhea (50%), IRR (35%), abdominal pain (29%), and fatigue (24%).

Pediatric Use

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

Geriatric Use

Gastroesophageal Adenocarcinoma (GEA)
ZIIHERA in combination with chemotherapy and tislelizumab-jsgr
Of 302 patients randomized to ZIIHERA in combination with chemotherapy and tislelizumab-jsgr in HERIZON-GEA-01, there were 139 (46%) patients aged ≥ 65 years. One hundred and six (35%) were aged 65-74 years and 33 (11%) were aged ≥ 75 years.

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

There was an increased incidence of fatal adverse reactions in patients aged ≥ 65 years (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 aged ≥ 65 years. One hundred (33%) were aged 65-74 years and 30 (10%) were aged ≥ 75 years.

No overall differences in safety were observed between patients aged ≥ 65 years and younger adult patients.

Biliary Tract Cancer (BTC)
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 aged ≥ 65 years. Thirty-seven (46%) were aged 65-74 years and 2 (3%) were aged ≥ 75 years.

No overall differences in safety or effectiveness were observed between patients aged ≥ 65 years and younger adult patients.

ZIIHERA®
(zanidatamab-hrii)
50mg/ml Injection for IV

GEA + BTC

AIM TO HELP PATIENTS MITIGATE ADVERSE REACTIONS

Anticipate

Recognize that adverse reactions may occur.

- Premedicate all patients with acetaminophen, an antihistamine, and a corticosteroid 30-60 minutes prior to each dose of ZIIHERA[1]

GEA

Start loperamide 4 mg BID on Day 1 of Cycle 1 (minimum of 7 days).[1]

Encourage patients to increase oral fluids.[1]

Intervene

Identify when to take action in response to emerging adverse reactions.

- **Evaluate the severity and progression** of ARs to guide treatment modifications[1]

GEA

Initiate loperamide at the first sign of loose stool. Administer fluids, electrolytes, and additional antidiarrheal agents as necessary.[1]

Manage

Monitor, adjust, or discontinue treatment to mitigate adverse reactions.

Modify and resume therapy as appropriate, adjusting dosages, withholding, or discontinuing treatment as recommended.[1]

AIM=Anticipate, Intervene, Manage; AR=adverse reaction; BID=twice daily; BTC=biliary tract cancer; GEA=gastroesophageal adenocarcinoma.

IMPORTANT SAFETY INFORMATION (CONT'D)

Adverse Reactions

Gastroesophageal Adenocarcinoma (GEA)

ZIIHERA in combination with chemotherapy and tislelizumab-jsgr

Serious adverse reactions occurred in 59% of 294 patients in HERIZON-GEA-01. Serious adverse reactions in > 2% of patients included diarrhea (17%), IRR (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%).

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED WARNINGS and Medication Guide.

References: 1. ZIIHERA (zanidatamab-hrii) Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2026. **2.** U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017. Accessed August 19, 2026. dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v5-5x7.pdf **3.** Chichelo L, Colopoulos K. Hypersensitivity infusion reaction management. *American Nurse Journal*. 2025;20(1). Accessed April 1, 2026. myamericannurse.com/hypersensitivity-infusion-reaction management/