

A GUIDE TO DIARRHEA MANAGEMENT IN **HER2+ ADVANCED GEA**

Proactive management strategies are essential to help mitigate diarrhea.

GEA=gastroesophageal adenocarcinoma; HER2=human epidermal growth factor receptor 2.

INDICATIONS

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

- 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.

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 on pages 8-10 and full [Prescribing Information](#), including **BOXED WARNINGS** and [Medication Guide](#).

AIM to help patients mitigate diarrhea

Anticipate

Recognize that diarrhea may occur.

Start loperamide **4 mg BID on Day 1 of Cycle 1** (minimum of 7 days).¹
Encourage patients to increase oral intake of fluids and to notify their care team if diarrhea or uncontrolled symptoms occur.¹

Intervene

Identify when to take action in response to the onset of diarrhea.

Initiate loperamide **at the first sign of loose stool** and administer fluids, electrolytes, and additional antidiarrheal agents as necessary.¹
Evaluate the severity and progression of diarrhea to guide treatment modifications.¹

Manage

Monitor, adjust, or discontinue treatment to mitigate severe diarrhea.

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

Prophylaxis and early intervention can help support the management of diarrhea. Knowing the right mitigation strategies can help you support patients receiving ZIIHERA.^{1,2}

BID=twice daily.

Please see Important Safety Information on pages 8-10 and full [Prescribing Information](#), including **BOXED WARNINGS and **Medication Guide**.**

Managing diarrhea starts before treatment

Start loperamide on Day 1 of Cycle 1¹

4 mg twice daily **LOPERAMIDE** for at least **7 days**

Don't wait until diarrhea occurs to start loperamide¹

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

In a Phase 2 study evaluating ZIIHERA in combination with FOLFOX, Grade 3 diarrhea occurred in 57% of patients who received a fluorouracil bolus without loperamide prophylaxis and in 30% of patients who did not receive a fluorouracil bolus but received loperamide prophylaxis.¹



In HERIZON-GEA-01, use of antidiarrheal prophylaxis beyond the mandatory prophylaxis period was at the discretion of the treating physician.³

If patients experience Grade 1 or higher diarrhea during Cycle 1 of treatment, **continue prophylaxis with loperamide 4 mg twice daily for at least the first 7 days of each subsequent cycle.**¹

Tips for patients to further reduce the risk of diarrhea⁴:



Avoid greasy
or spicy foods



Minimize
caffeine



Avoid
alcohol



Avoid foods
high in fiber

FOLFOX=leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin.

Please see Important Safety Information on pages 8-10 and full [Prescribing Information](#), including **BOXED WARNINGS** and **Medication Guide**.

	ZIIHERA + tislelizumab + CT* (n=294)⁵	ZIIHERA + CT* (n=305)⁵	Trastuzumab + CT (n=302)⁵
Diarrhea			
All Grades	83%	79%	53%
Grade 1 Increase of <4 stools/day; mild increase in ostomy output compared to baseline ⁶	27%	26%	28%
Grade 2 Increase of 4-6 stools/day; moderate increase in ostomy output compared to baseline ⁶	31%	33%	13%
Grade 3+ Grade 3 - Increase of ≥7 stools/day; severe increase in ostomy output compared to baseline; hospitalization indicated ⁶ Grade 4 - Life-threatening consequences; urgent intervention indicated ⁶ Grade 5 - Death ⁶	25%	20%	13%

- 0.3% of patients treated with ZIIHERA + tislelizumab + CT had a treatment-related Grade 5 diarrhea event in HERIZON-GEA-01⁷
- Incidence of Grade 3-4 diarrhea was higher with ZIIHERA + tislelizumab + CT in patients ≥65 years (32%) compared to patients <65 years (20%)¹
- In the pooled safety population (n=330) across clinical studies, fatal outcomes resulting from diarrhea occurred in 1.5% of patients who received ZIIHERA + tislelizumab + CT¹

Prophylactic loperamide, along with other management strategies, can help mitigate diarrhea.¹

*Five patients assigned to the ZIIHERA + tislelizumab + CT arm did not receive tislelizumab and are included in the ZIIHERA + CT arm.⁸
CT=chemotherapy.

Please see Important Safety Information on pages 8-10 and full [Prescribing Information](#), including **BOXED WARNINGS and **Medication Guide**.**

Most cases of diarrhea occurred early in treatment and typically resolved within 3 weeks⁸

Continue to monitor patients for diarrhea in subsequent treatment cycles.¹

	ZIIHERA + tislelizumab + CT* (n=294) ^{3,9}	ZIIHERA + CT* (n=305) ^{1,3,9}	Trastuzumab + CT (n=302) ^{3,9}
Median time to first onset of diarrhea (min-max)			
Any grade	7 days (1-341)	6 days (1-211)	10 days (1-488)
Grade ≥3	16 days (1-536)	11 days (1-512)	37 days (3-188)
Median duration of first diarrhea event			
Any grade	14 days (95% CI: 11-18)	17 days (95% CI: 13-20)	10 days (95% CI: 7-15)
Grade ≥3	8 days (95% CI: 7-9)	9 days (95% CI: 6-11)	9 days (95% CI: 6-12)
Diarrhea leading to discontinuation			
Any component	8%	5%	2%
ZIIHERA or trastuzumab	4%	1.6%	0.3%
Tislelizumab	3%	—	—

Discontinuation of ZIIHERA due to diarrhea was 4% with ZIIHERA + tislelizumab + CT and 1.6% with ZIIHERA + CT¹

Rates of treatment-emergent constipation were consistent across treatment arms (16%), suggesting that antidiarrheal prophylaxis did not result in more constipation with ZIIHERA.³

*Five patients assigned to the ZIIHERA + tislelizumab + CT arm did not receive tislelizumab and are included in the ZIIHERA + CT arm.⁸

CI=confidence interval; CT=chemotherapy.

It's vital to identify when to take action in response to the onset of diarrhea¹

Grade 1:

Increase of
<4
stools per day⁶

Grade 2:

Increase of
4 – 6
stools per day⁶

It's important to explain the risks of diarrhea to your patients, and how proactive management strategies can help support them.

If Grade 1 or 2 diarrhea occurs:

- No dosage modification is required for ZIIHERA¹
- Start loperamide at first loose stool¹
- Patients should be encouraged to increase intake of fluids¹
- Monitor for diarrhea throughout each treatment cycle¹
- Have patients contact their care team if they experience any diarrhea¹

The use of **additional antidiarrheal agents alongside loperamide may be recommended** when needed.¹



**Have patients log their bowel movements
in their ZIIHERA Journey Tracker**

Patients experiencing severe diarrhea may need dose modifications^{1*}

Before modifying the dose of ZIIHERA, evaluate, modify or discontinue drug(s) contributing to diarrhea in accordance with their respective prescribing information.¹

Grade 3:

Increase of
≥7
stools per day⁶

- Withhold ZIIHERA until severity of diarrhea improves to Grade ≤1¹
- Initiate or intensify appropriate medical therapy and monitor as clinically indicated¹
- Administer subsequent ZIIHERA treatment at the same dose level or consider a dose reduction¹
- For recurrent Grade 3 symptoms, withhold ZIIHERA treatment and ensure medical management has been optimized¹
 - Resume ZIIHERA treatment at a reduced dose after severity improves to Grade ≤1¹
- Permanently discontinue ZIIHERA for recurrent Grade 3 symptoms that last >3 days despite optimized medical management¹

Grade 4:

Life-threatening consequences⁶

- Permanently discontinue ZIIHERA¹

Dose modifications¹

Patient weight: <70 kg

**Every
2 weeks**

1200 mg

900 mg

**Every
3 weeks**

1800 mg

1400 mg



STARTING DOSE

DOSE REDUCTION

Patient weight: ≥70 kg

**Every
2 weeks**

1600 mg

1200 mg

**Every
3 weeks**

2400 mg

1800 mg

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

*Diarrhea requiring dosage reduction occurred in 10% of patients who received ZIIHERA + tislelizumab + CT and 11% of patients who received ZIIHERA + CT.¹

CT=chemotherapy.

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.**

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. 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.

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.

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.

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.

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.

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%.

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.

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 LVD was 6.0 months (range: 1.4 to 15.0 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.

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.

Adverse Reactions

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%).

IMPORTANT SAFETY INFORMATION (CONT'D)

Adverse Reactions (cont'd)

Permanent discontinuation of ZIIHERA occurred in 10% of patients. Adverse reactions that resulted in permanent discontinuation of ZIIHERA in $\geq 1\%$ of patients included ejection fraction decreased (2.0%), IRR (1.6%), and diarrhea (1.6%).

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

Pediatric Use

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

Geriatric Use

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.

References: 1. ZIIHERA (zanidatamab-hrii) Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2026. 2. Elimova E, Ajani J, Burris H, et al. Zanidatamab plus chemotherapy as first-line treatment for patients with HER2-positive advanced gastro-oesophageal adenocarcinoma: primary results of a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2025;26(7):847-859. doi:10.1016/S1470-2045(25)00287-6. Supplementary appendix. 3. Elimova E, Rha SY, Shitara K, et al. Characterization and management of gastrointestinal adverse events with zanidatamab + chemotherapy $\pm$ tislelizumab in first-line HER2-positive locally advanced or metastatic gastroesophageal adenocarcinoma: analysis from HERIZON-GEA-01. Presented at: American Society of Clinical Oncology Annual Meeting; May 29-June 2, 2026; Chicago, IL. 4. National Cancer Institute. *Eating Hints: Before, during, and after cancer treatment*. Bethesda, MD: U.S. Department of Health & Human Services, National Institutes of Health; 2022. 5. Elimova E, Rha SY, Shitara K, et al. Characterization and management of gastrointestinal (GI) adverse events (AEs) with zanidatamab + chemotherapy (CT) $\pm$ tislelizumab in first-line (1L) HER2-positive (HER2+) locally advanced or metastatic gastroesophageal adenocarcinoma (mGEA): Analysis from HERIZON-GEA-01. *J Clin Oncol.* 2026;44(16_suppl):4042. doi:10.1200/JCO.2026.44.16_suppl.4042 6. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, 2017. Accessed April 2, 2026. dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v5-5x7.pdf 7. Shitara K, Elimova E, Liu T, et al. Zanidatamab with and without tislelizumab in HER2-positive gastroesophageal cancer. *N Engl J Med.* 2026;394(20):2002-2014. doi:10.1056/NEJMoa2517729. Supplementary appendix. 8. Shitara K, Elimova E, Liu T, et al. Zanidatamab with and without tislelizumab in HER2-positive gastroesophageal cancer. *N Engl J Med.* 2026;394(20):2002-2014. doi:10.1056/NEJMoa2517729 9. Data on File—REF-24123. Jazz Pharmaceuticals, Inc.

AIM TO HELP PATIENTS MITIGATE DIARRHEA



Anticipate

Recognize that diarrhea may occur.

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

Encourage patients to increase oral intake of fluids and to notify their care team if diarrhea or uncontrolled symptoms occur.¹

Intervene

Identify when to take action in response to the onset of diarrhea.

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

Evaluate the severity and progression of diarrhea to guide treatment modification.¹

Manage

Monitor, adjust, or discontinue treatment to mitigate severe diarrhea.

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

Prophylaxis and active monitoring can help you take early action in managing your patients' diarrhea¹



Have patients log their symptoms in their ZIIHERA Journey Tracker

BID=twice daily.

Please see additional Important Safety Information on pages 8-10 and full [Prescribing Information](#), including **BOXED WARNINGS and **Medication Guide**.**