DOSING AND ADMINISTRATION GUIDE FOR ZIIHERA

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

For 2L treatment of adults with unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC)[1]

YOUR GUIDE TO:

- ZIIHERA DOSING SCHEDULE
- PREPARATION AND ADMINISTRATION
- DOSAGE MODIFICATIONS AND LABORATORY ABNORMALITIES

2L=second-line; HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry.

INDICATION

ZIIHERA (zanidatamab-hrii) 50 mg/mL for Injection for IV 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-approved test.

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

IMPORTANT SAFETY INFORMATION

WARNING: 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 Warning.

ZIIHERA IS A SINGLE INFUSION EVERY 2 WEEKS[1]

Recommended administration time: decrease over time to 60 minutes[1]

The recommended dosage of ZIIHERA is 20 mg/kg, administered as an intravenous (IV) infusion once every 2 weeks until disease progression or unacceptable toxicity.[1]

Infusion Duration[1]

1st 2nd	3rd 4th	5th
120-150 minutes	90 minutes, if previous infusions were well-tolerated	60 minutes, if previous infusions were well-tolerated

- Premedicate all patients 30 to 60 minutes prior to each dose of ZIIHERA to reduce the risk of infusion-related reactions[1]
  - Administer acetaminophen, an antihistamine and a corticosteroid[1]
- Individual weight-based dosing, no loading dose, and shorter infusion sessions, if previous infusions were well-tolerated[1]
- Do not co-administer ZIIHERA and other IV drugs through the same IV line[1]
- 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]
- Permanently discontinue ZIIHERA in patients who cannot tolerate 15 mg/kg[1]

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity

ZIIHERA can cause fetal harm when administered to a pregnant woman. 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 during treatment with ZIIHERA and for 4 months following the last dose of ZIIHERA.

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ZIIHERA PREPARATION AND ADMINISTRATION

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Administer only as an intravenous infusion after ZIIHERA is reconstituted and diluted.[1]

RECONSTITUTION[1]

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 final 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. 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 8ºC [36°F to 46ºF])

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS AND PRECAUTIONS (CONT'D)

Left Ventricular Dysfunction

ZIIHERA can cause decreases in left ventricular ejection fraction (LVEF). LVEF declined by >10% and decreased to <50% in 4.3% of 233 patients. Left ventricular dysfunction (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). LVD resolved in 70% of patients.

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 below 50%.

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ZIIHERA PREPARATION AND ADMINISTRATION (CONT'D)

DILUTION[1]

- Withdraw the necessary volume for the calculated dose from each vial
- 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 of the diluted solution between 0.4 mg/mL and 6 mg/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

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Infusion-Related Reactions

ZIIHERA can cause infusion-related reactions (IRRs). 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. IRRs occurred on the first day of dosing in 28% of patients; 97% of IRRs resolved within one day.

Prior to each dose of ZIIHERA, administer premedications 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.

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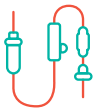
DILUTION[1] (CONT'D)

Compatibility with IV administration materials and the infusion solution has been demonstrated in the following materials:

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 (PES) solution filter, polyvinylidene fluoride (PVDF) air filter

Closed System Transfer devices: Acrylonitrile-butadiene-styrene (ABS), acrylic co-polymer, polycarbonate (PC), polyisoprene (PI), polyester, polypropylene (PP), polytetrafluoroethylene (PTFE), silicone and stainless steel (SS)

ADMINISTRATION[1]

- Administer ZIIHERA as an IV infusion with a 0.2 or 0.22 micron filter
- Do not administer as an IV push or bolus
- Do not co-administer ZIIHERA and other IV drugs through the same IV line

IV=intravenous.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Infusion-Related Reactions (cont'd)

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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DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS[1]

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]

	Severity	Treatment Modification
Left Ventricular Dysfunction (LVD)	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 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	Mild (Grade 1)	• Reduce 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)	• 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

IMPORTANT SAFETY INFORMATION (CONT'D)
WARNINGS AND PRECAUTIONS (CONT'D)
Diarrhea
ZIIHERA can cause severe diarrhea.

Please see additional Important Safety Information throughout and full Prescribing Information, including BOXED Warning.

	Severity	Treatment Modification
Diarrhea	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 dose reduction to 15 mg/kg • For recurrent Grade 3 symptoms, withhold ZIIHERA treatment and ensure medical management has been optimized ◦ Resume ZIIHERA treatment at a reduced dose of 15 mg/kg 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

IRR=infusion-related reaction; LVEF=left ventricular ejection fraction.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Diarrhea (cont'd)

Diarrhea was reported in 48% of 233 patients treated in clinical studies, including Grade 3 (6%) and Grade 2 (17%). If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Withhold or permanently discontinue ZIIHERA based on severity.

ADVERSE REACTIONS

Serious adverse reactions occurred in 53% of 80 patients with unresectable or metastatic HER2-positive BTC 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.

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DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS[1] (CONT'D)

	Severity	Treatment Modification
Pneumonitis	Confirmed Grade ≥2	• Permanently discontinue ZIIHERA
Other Adverse Reactions (excluding LVD, IRR, Diarrhea, and Pneumonitis)	Mild/Moderate (Grades 1 or 2)	• No dose 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 to 15 mg/kg 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

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%), infusion-related reaction (35%), abdominal pain (29%), and fatigue (24%).

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LABORATORY ABNORMALITIES

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Laboratory abnormalities (≥30%) that worsened from baseline in patients receiving ZIIHERA (N=80)[1]*†

Laboratory Abnormalities	ZIIHERA	
	All Grades (%)	Grades 3-4 (%)
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

*Analysis includes 62 patients with HER2 IHC 3+ and 18 patients with HER2 IHC 2+ who received ZIIHERA in HERIZON-BTC-01.[1]

†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.[1]

HER2=human epidermal growth factor receptor 2; IHC=immunohistochemistry; IRR=infusion-related reaction; LVD=left ventricular dysfunction; LVEF=left ventricular ejection fraction.

IMPORTANT SAFETY INFORMATION (CONT'D)

USE IN SPECIFIC POPULATIONS

Pediatric Use

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

Geriatric Use

Of the 80 patients who received ZIIHERA for unresectable or metastatic HER2-positive BTC, 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.

No overall differences in safety or efficacy were observed between these patients and younger adult patients.

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IMPORTANT SELECT DOSING AND ADMINISTRATION INFORMATION FOR ZIIHERA

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- Administer acetaminophen, an antihistamine and a corticosteroid[1]

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Do not co-administer ZIIHERA and other intravenous (IV) drugs through the same IV line[1]

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Please refer to the full Prescribing Information for ZIIHERA for complete dosing and administration information.

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INDICATION

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Reference: 1. ZIIHERA (zanidatamab-hrii) Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2024.

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