Product Monograph

Including Patient Medication Information

Pr ZIIHERA®

Zanidatamab for injection

Bi-specific antibody produced in Chinese Hamster Ovary (CHO) Cells through recombinant DNA technology

Powder for solution for intravenous infusion

300 mg of zanidatamab/vial

Antineoplastic

ZIIHERA, indicated for:

- the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as monotherapy,

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ZIIHERA please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html.

Jazz Pharmaceuticals Ireland Limited
5th Floor, Waterloo Exchange
Dublin, Ireland D04 EW57

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Importer:

Jazz Pharmaceuticals Canada Inc.
4080 Confederation Parkway, Suite 602
Mississauga, Ontario L5B 0G1

Control Number: 296499

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

Recent Major Label Changes

Not applicable.

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

ZIIHERA (zanidatamab for injection) is indicated for:

- the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as monotherapy (see 4.1 Dosing Considerations).

  The marketing authorisation with conditions is based on objective response rate and durability of response. An improvement in survival has not yet been established (see 14 Clinical Trials).

1.1. Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies suggests that use in the geriatric population is not associated with differences in safety or effectiveness. No dose adjustment is required in this population (see 7.1.4 Geriatrics).

2. Contraindications

ZIIHERA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

3. Serious Warnings and Precautions Box

- Embryo-Fetal Toxicity: Exposure to ZIIHERA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception (see 7 Warnings and Precautions, Reproductive Health, 7.1 Special Populations).

4. Dosage and Administration

4.1. Dosing Considerations

Patient Selection

Select patients for the treatment of unresectable locally advanced or metastatic HER2-positive BTC based on HER2 protein overexpression defined as a score of 3+ by immunohistochemistry (IHC) in tumour specimens.

Premedication

Administer premedication to all patients 30 to 60 minutes prior to each ZIIHERA infusion to reduce the risk of infusion-related reactions. Premedication is recommended to include a corticosteroid, antihistamine, and antipyretic (see 7 Warnings and Precautions, Infusion-Related Reactions).

4.2. Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended dose of ZIIHERA is 20 mg/kg, administered as an intravenous infusion once every 2 weeks (every 14 days) until disease progression or unacceptable toxicity. For infusion durations, see Table 5.

Dosage Adjustment

Dose modifications for left ventricular dysfunction

Assess left ventricular function at baseline and at regular intervals during treatment. The recommendations on dose modifications in the event of LVEF dysfunction are indicated in Table 1.

Table 1 – Dose Modifications for Left Ventricular Dysfunction

Left Ventricular Dysfunction (see 7 Warnings and Precautions)	Severity	Treatment Modification
	Absolute decrease of ≥16% points in LVEF from pre-treatment baseline or LVEF value below 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. • If LVEF has not recovered to within 15% points from baseline, permanently discontinue.
	Confirmed symptomatic congestive heart failure	• Permanently discontinue ZIIHERA.

Dose modifications for infusion-related reactions

Management of IRRs may require reduced infusion rate, dose interruption, or treatment discontinuation of ZIIHERA as described in Table 2 (see 7 Warnings and Precautions, Infusion-Related Reactions).

Table 2 – Dosage and Infusion Duration Modifications for Infusion-Related Reactions

Infusion related reactions (see 7 Warnings and Precautions)	**Severity**	**Treatment Modification**
	Mild (Grade 1)	• Reduce infusion rate by 50%. • Subsequent infusions should start at this reduced rate. • Infusion rate for subsequent ZIIHERA infusions may be increased gradually to the rate prior to symptoms, as tolerated.
	Moderate (Grade 2)	• Stop infusion immediately. • Treat with appropriate therapy. • Resume infusion at 50% of previous infusion rate once symptoms resolve. • For subsequent infusions, the infusion rate may be increased gradually to the rate prior to symptoms, as tolerated.
	Severe (Grade 3)	• Stop infusion immediately. • Promptly treat with appropriate therapy. • Do not restart the infusion during the same cycle even if signs and symptoms resolve. • Resume infusion at the next scheduled dose at 50% of the previous infusion rate once symptoms resolve. • Permanently discontinue for recurrent Grade 3 reactions.
	Life threatening (Grade 4)	• Stop infusion immediately. • Promptly treat with appropriate therapy. • Permanently discontinue.

Dose modifications for pneumonitis

Management of pneumonitis may require treatment discontinuation as described in Table 3.

Table 3 – Dose Modifications for Pneumonitis

Pneumonitis	**Severity**	**Treatment Modification**
	Confirmed Grade ≥2	• Permanently discontinue.

4.3. Reconstitution

Parenteral Products:

ZIIHERA vials are for single dose use only.

ZIIHERA must be reconstituted with sterile water for injection and subsequently diluted with

0.9% sodium chloride or 5% dextrose for infusion.

Aseptic technique must be used for reconstitution and dilution of ZIIHERA.

- Calculate the recommended dose of ZIIHERA based on the patient's weight to determine the number of vials needed.
- Remove the vial(s) from the refrigerator and allow to reach room temperature.
- Reconstitute each vial with 5.7 mL of sterile water for injection to obtain a concentration of 50 mg/mL in an extractable volume of 6.0 mL (see Table 4).
- Swirl the vial gently until completely dissolved. Do not shake. Reconstitution should take no more than 10 minutes.
- Allow the reconstituted vial to settle to allow bubbles to dissipate.
- Visually inspect the reconstituted solution for particulate matter and discolouration. The reconstituted product should be colourless to light yellow, clear to slightly opalescent solution that is essentially free of particles. Discard the reconstituted vial if any discolouration 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 or in a refrigerator (2°C to 8°C) (see 11 Storage, Stability, and Disposal).

Table 4 – Reconstitution

Vial Size	Volume of Diluent To Be Added to Vial	Approximate Available Volume	Concentration Per mL
20 mL	5.7 mL	6.0 mL	50 mg/mL

Instructions for Dilution

- Withdraw the necessary volume for the calculated dose from each vial.
- Slowly add the necessary dose volume to an appropriate size infusion bag containing 0.9% sodium chloride or 5% dextrose. The final concentration of the diluted solution should be between 0.4 mg/mL and 6.0 mg/mL.
- Gently invert the infusion bag to mix. Do not shake.
- The solution for infusion must be a clear, colourless solution with no visible particles. If particulate matter or discolouration is identified, the solution must be discarded.
- Discard any unused portion left in the vial(s).
- Use the infusion solution immediately upon dilution or store the infusion solution at room temperature for up to 12 hours or in the refrigerator (2°C to 8°C) for up to 24 hours. These storage times start from the time of reconstitution (see 11 Storage, Stability, and Disposal).
- Compatibility with intravenous administration materials and the diluted ZIIHERA 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 c-polymer, polycarbonate (PC), polyisoprene (PI), polyester, polypropylene (PP), polytetrafluoroethylene (PTFE), silicone and stainless steel (SS).

4.4. Administration

- Administer ZIIHERA as an intravenous infusion with a 0.2 or 0.22 micron filter.
- Do not administer by intravenous push or as a rapid single bolus injection.
- Do not co-administer ZIIHERA and other intravenous drugs concurrently within the same intravenous line.

Table 5 – Recommended ZIIHERA Infusion Durations

Dose	Infusion Duration
First and Second	120 to 150 minutes
Third and Fourth	90 minutes, if previous infusions were well-tolerated
Subsequent	60 minutes, if previous infusions were well-tolerated

4.5. Missed Dose

If a patient misses a dose of ZIIHERA, administer the scheduled dose as soon as possible. Adjust the administration schedule to maintain a 2-week interval between doses.

5. Overdose

In clinical studies, the maximum tested dose has been 30 mg/kg. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment initiated if required.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 6 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Intravenous infusion	Powder for Solution 300 mg zanidatamab	Polysorbate 20, sodium succinate anhydrous (disodium succinate), succinic acid, sucrose, water for injection

Contains less than 1 mmol sodium (23 mg) per dose, essentially 'sodium-free'.

Description

Each carton of ZIIHERA contains two single-dose 20 mL Type I glass vials with a chlorobutyl stopper and a flip-off cap.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

Therapy with ZIIHERA should be initiated under supervision of a physician experienced in the treatment of cancer patients.

Cardiovascular

Left Ventricular Dysfunction

Decreases in LVEF have been reported with drugs that block HER2 activity, including ZIIHERA (see 8 Adverse Reactions). Assess LVEF prior to initiation of ZIIHERA and at regular intervals during treatment. Withhold or permanently discontinue ZIIHERA based on the severity of the adverse reaction (see Table 1 Dose Modifications for Left Ventricular Dysfunction).

The safety of ZIIHERA has not been established in patients with a baseline ejection fraction that is below 50% or a history of clinically significant cardiac disease.

Driving and Operating Machinery

ZIIHERA may have minor influence on the ability to drive and use machines. Fatigue has been reported with the use of ZIIHERA. Therefore, caution is recommended when driving or operating machines. Patients experiencing infusion-related symptoms should be advised not to drive or use machines until symptoms resolve completely.

Immune

Infusion-Related Reactions

ZIIHERA can cause infusion-related reactions (IRRs) (see 8 Adverse Reactions). Prior to each dose of ZIIHERA, administer pre-medications to reduce the risk of IRRs (see 4.1 Dosing Considerations).

Monitor patients for signs and symptoms of IRRs during administration and as clinically indicated after completion of infusion. Have appropriate emergency medicine and equipment to treat IRRs available for immediate use, and manage IRRs based on severity (see Table 2 Dosage and Infusion Duration Modifications for Infusion-Related Reactions).

Reproductive Health

Pregnancy Testing

A pregnancy test should be performed before initiating treatment with ZIIHERA in female patients of childbearing potential to exclude pregnancy (see 7.1.1 Pregnancy).

Contraception

Advise patients to avoid becoming pregnant while receiving ZIIHERA. Female patients of childbearing potential must use an effective method of contraception while receiving ZIIHERA and for 4 months following the last dose of ZIIHERA (see 7.1.1 Pregnancy).

- **Fertility**

  Fertility studies have not been performed with ZIIHERA.

Respiratory

Pneumonitis

Pneumonitis has been reported with medicinal products that block HER2 activity, including ZIIHERA (see 8 Adverse Reactions). Patients should be monitored for signs and symptoms of pneumonitis. In the event of confirmed Grade ≥2 pneumonitis, treatment should be permanently discontinued (see Table 3 Dose Modifications for Pneumonitis).

7.1. Special Populations

7.1.1. Pregnancy

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 post-marketing reports of another HER2-directed antibody, use during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. ZIIHERA is not recommended for use during pregnancy.

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 (see 7 Warnings and Precautions, Reproductive Health).

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 standards of care.

7.1.2. Breastfeeding

It is not known whether ZIIHERA is secreted in human milk, or what effect it has on a breastfed child or milk production.

A decision should be made whether to discontinue breast-feeding or to discontinue treatment, taking into account the benefit of breast-feeding for the child, any potential adverse effects on the breastfed child and the benefit of ZIIHERA therapy for the woman. This consideration should also take into account the ZIIHERA washout period of 4 months (see 10.3 Pharmacokinetics).

7.1.3. Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Geriatrics (≥ 65 years of age): Of the 87 patients with BTC, treated with ZIIHERA 20 mg/kg, 48.3% were 65 years or older and 4.6% were 75 years or older. Evidence from clinical studies suggests that use in the geriatric population is not associated with differences in overall safety and effectiveness, therefore no dose adjustment is required (see 1.2 Geriatrics).

8. Adverse Reactions

8.1. Adverse Reaction Overview

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

- Embryo-Fetal Toxicity (see 3 Serious Warnings and Precautions Box and 7 Warnings and Precautions)
- Left Ventricular Dysfunction (see 7 Warnings and Precautions)
- Infusion-Related Reactions (see 7 Warnings and Precautions)
- Pneumonitis (see 7 Warnings and Precautions)

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Previously treated, unresectable, locally advanced or metastatic HER2-positive biliary tract cancer (BTC)

The safety of ZIIHERA was evaluated in the HERIZON-BTC-01 study, which included 87 patients (Cohorts 1 and 2) with previously treated, unresectable, locally advanced or metastatic HER2-positive BTC. All patients had received at least one prior gemcitabine-containing chemotherapy regimen (see 14 Clinical Trials). Patients received ZIIHERA at 20 mg/kg administered intravenously once every 2 week cycle until disease progression or unacceptable toxicity. Among the 87 patients who received ZIIHERA, 43.7% were exposed for 6 months or longer and 23% were exposed for greater than one year.

The most commonly reported adverse reactions (≥20% of patients) were diarrhea (46%), infusion-related reaction (33.3%), abdominal pain (26.4%), anemia (25.3%), fatigue (24.1%), alanine aminotransferase increased (19.5%) and aspartate aminotransferase increased (19.5%).

Serious adverse reactions occurred in 52.9% of patients. The most frequent serious adverse reactions (≥2% of patients) were jaundice cholestatic, pneumonia, cholangitis, biliary obstruction, sepsis, obstruction gastric, diarrhea, alanine aminotransferase increased, fatigue, bacteremia and jaundice. There were 3 patients with fatal adverse reactions including hepatic failure, hematemesis and multiple organ dysfunction syndrome (one patient for each event).

Permanent discontinuation due to an adverse reaction occurred in 2.3% of patients. Adverse reactions which resulted in permanent discontinuation included ejection fraction decreased (1.1%) and pneumonitis (1.1%).

Dosage interruptions due to an adverse reaction occurred in 25.3% of patients. Adverse reactions requiring dosage interruption were infusion-related reaction (25.3%) and extravasation (1.1%). Dose reductions due to an adverse reaction occurred in 3.4% of patients. The adverse reactions which led to a dose reduction included diarrhea (2.3%), nausea (1.1%) and weight decreased (1.1%). Dose hold/delay due to an adverse reaction occurred in 42.5% of patients. The most common adverse reactions (≥5% of patients) which led to a dose hold/delay included diarrhea (5.7%), alanine aminotransferase increased (5.7%) and aspartate aminotransferase increased (5.7%).

Table 7 lists adverse events which were reported in ≥10% of patients. The adverse events, frequencies derived from all treatment-emergent adverse events, irrespective of the investigator's assessment of causality, reported in this patient population.

Table 7 – Adverse Events (≥10% Incidence) in Patients with Previously-treated, Unresectable Locally Advanced or Metastatic HER2-Positive BTC who Received ZIIHERA as Monotherapy in HERIZON-BTC-01

System Organ Class /Adverse Event Preferred Term *	ZIIHERA N=87	
	All Grades n (%)	Grades ≥3 n (%)
Blood and lymphatic system disorders		
Anemia	22 (25.3)	11 (12.6)
Cardiac Disorder		
Ejection fraction decreased	11 (12.6)	3 (3.4)
Gastrointestinal disorders		
Diarrhea	40 (46)	7 (8)
Abdominal pain[a]	23 (26.4)	1 (1.1)
Nausea	14 (16.1)	1 (1.1)
Vomiting	14 (16.1)	1 (1.1)
General disorders and administration site conditions		
Fatigue[b]	21 (24.1)	3(3.4)
Pyrexia	14 (16.1)	0 (0)
Injury, poisoning and procedural complications		
Infusion-related reaction	29 (33.3)	1 (1.1)
Investigations		
Alanine aminotransferase increased	17 (19.5)	5 (5.7)
Aspartate aminotransferase increased	17 (19.5)	4 (4.6)

System Organ Class /Adverse Event Preferred Term *	ZIIHERA N=87	
	All Grades n (%)	Grades ≥3 n (%)
Weight decreased	12 (13.8)	0 (0)
Blood bilirubin increased	10 (11.5)	2 (2.3)
Blood alkaline phosphatase increased	9 (10.3)	4 (4.6)
Metabolism and nutrition disorders		
Decreased appetite	13 (14.9)	0 (0)
Hypokalemia	11 (12.6)	5 (5.7)
Skin and subcutaneous tissue disorders		
Rash[c]	16 (18.4)	0 (0)
Pruritus	11 (12.6)	0 (0)
Vascular Disorders		
Hypertension	10 (11.5)	6 (6.9)

*Graded per CTCAE version 5

[a] Abdominal pain includes Abdominal pain and Abdominal pain upper

[b] Fatigue includes Asthenia and Fatigue

[c] Rash includes Acne, Dermatitis, Dermatitis acneiform, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash pruritic, Rash pustular, and Urticaria

Additional Information on Selected Adverse Reactions in the pooled safety population (N=233)

The selected adverse reactions described below are based on the pooled safety population that reflects exposure in 233 patients administered ZIIHERA 20 mg/kg intravenously once every 2 weeks as a single agent in two single-arm, open-label studies (ZWI-ZW25-101 and HERIZON-BTC-01), which enrolled 109 patients with biliary tract cancer, and 124 patients with other cancers. Among the 233 patients who received ZIIHERA, 39% were exposed for 6 months or longer, and 18% were exposed for greater than one year.

Diarrhea

Diarrhea was reported in 48.5% of patients who received ZIIHERA. The Grade 3 reported event incidence in patients was 5.2%, Grade 4 and Grade 5 events were not observed. Median time to first onset was 10 days and median time to resolution was 3 days. The dose of ZIIHERA was reduced due to diarrhea in 1.3% of patients and was held or delayed in 1.3% of patients. There were no discontinuations of treatment due to diarrhea.

Infusion-related reactions

Infusion related reaction (IRR) was reported in 30.5% of patients who received ZIIHERA. A Grade 3 event was reported in one patient (0.4%). No Grade 4 or 5 events were reported. The median time to the onset of the event from the first dose was 1 day. All events resolved. No event led to dose

reduction of ZIIHERA. Infusion was interrupted due to the event in 25.3% of patients and discontinued in 1 patient (0.4%) (see 7 Warnings and Precautions, Infusion-Related Reactions).

Left ventricular dysfunction

Thirteen events of LVEF decreased were observed in 10 (4.3%) patients; two of these events were considered serious. The Grade 3 reported event incidence in patients was 1.3%; no Grade 4 or Grade 5 events were observed. Median time to first onset was 170.5 days and median time to resolution was 27 days. The dose of ZIIHERA was reduced in 1 (0.4%) patient, delayed in 5 (2.1%) patients and ZIIHERA was discontinued in 2 (0.9%) patients (see 7 Warnings and Precautions, Left Ventricular Dysfunction).

Pneumonitis

One event of Grade 3 pneumonitis was reported in 1 (0.4%) patient who received ZIIHERA. Grade 4 and Grade 5 events were not observed. Time to first onset was 223 days. The dose of ZIIHERA was held and discontinued in 1 (0.4%) patient (see 7 Warnings and Precautions, Pneumonitis).

8.3 Less Common Clinical Trial Adverse Reactions

The following clinically important adverse events were reported in less than 10% of patients with locally advanced unresectable or metastatic BTC who received ZIIHERA as monotherapy in HERIZON-BTC-01:

Cardiac disorders: atrial fibrillation

Gastrointestinal disorders: obstruction gastric, stomatitis, enteritis, hematochezia, melena, ascites, hematemesis

Immune system disorders: drug hypersensitivity

Infections and infestations: sepsis, bacteremia, pneumonia

Investigations: blood lactate dehydrogenase increased, platelet count decreased, neutrophil count decreased, blood creatinine increased

Metabolism and nutrition disorders: hyperglycemia, hypoalbuminemia

Nervous system disorders: peripheral motor neuropathy, peripheral sensory neuropathy

Respiratory, thoracic and mediastinal disorders: dyspnea, pleural effusion

Skin and subcutaneous tissue disorders: palmar-plantar erythrodysesthesia syndrome

Vascular disorders: hypotension

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

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

Table 8 –Laboratory Abnormalities (≥20%) that worsened from Baseline in patients with Unresectable Locally Advanced or Metastatic HER2-Positive BTC who Received ZIIHERA in HERIZON-BTC-01

Laboratory Abnormalities*	ZIIHERA N=87	
	All Grades (%)	Grades 3-4 (%)
Hematology		
Hemoglobin decreased	88.5	14.9
Lymphocyte count decreased	46.5	7.0
Platelet count decreased	29.1	1.2
White blood cell count decreased	24.4	1.2
Neutrophil count decreased	22.1	2.3
Chemistry		
Blood lactate dehydrogenase increased	54.1	0
Blood albumin decreased	55.8	0
Aspartate aminotransferase increased	46.5	9.3
Alanine aminotransferase increased	45.3	8.1
Blood alkaline phosphatase increased	43.0	5.8
Blood sodium decreased	38.4	14.0
Blood potassium decreased	34.9	5.8
Blood calcium decreased	26.7	1.3
Blood bilirubin increased	25.6	8.1
Blood uric acid increased	22.4	0
Blood creatinine increased	22.1	1.2

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range: 75 – 87).
*Graded per CTCAE version 5.

8.5. Post-Market Adverse Reactions

Not available.

9. Drug Interactions

9.2. Drug Interactions Overview

No dedicated clinical studies evaluating the drug interaction potential of zanidatamab have been conducted. Zanidatamab is an antibody that is not expected to impact the cytochrome P450 enzymes. Also, zanidatamab is not known to target mechanisms related to proinflammatory cytokines or any mechanism related to proinflammatory cytokines that may impact the pharmacokinetics of concomitant medicines.

9.3. Drug-Behaviour Interactions

The interaction of ZIIHERA with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4. Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

ZIIHERA is a HER2-targeted bispecific antibody that binds to two extracellular sites on HER2. Binding of zanidatamab to HER2 results in internalization leading to a reduction of the receptor on the tumour cell surface. Zanidatamab induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms result in tumour growth inhibition and cell death *in vitro* and *in vivo*.

10.2. Pharmacodynamics

Cardiac Electrophysiology:

Zanidatamab does not have a clinically relevant prolongation effect on QTc interval at 20 mg/kg once every 2 weeks (Q2W) in participants with locally advanced (unresectable) and/or metastatic HER2-expressing cancers.

Exposure-Response Analyses:

The exposure-response relationships are unknown.

10.3. Pharmacokinetics

Zanidatamab pharmacokinetics (PK) exhibited nonlinear kinetics with more rapid clearance (CL) at low doses ranging from 5 to 30 mg/kg. Following the first dose, the geometric mean zanidatamab C_{max} was dose proportional with increasing doses, while total systemic exposure ($AUC_{0-\infty}$) was greater than dose proportional with increasing doses.

The PK of zanidatamab following intravenous infusion in participants with HER2 expressing cancers was evaluated in a population pharmacokinetic (popPK) model analysis from 279 participants. Based on the estimated half-life ($t_{1/2}$) of 21 days using popPK, it would take approximately 3.5 months (i.e., 5 half-lives) to reach steady state following multiple dose administration of zanidatamab. The mean (SD) C_{trough} accumulation ratio of zanidatamab 20 mg/kg Q2W in BTC patients at steady state was 3.35 (1.25).

The observed zanidatamab PK parameters following single and multiple dose administration in HERIZON-BTC-01 are described in Table 9.

Table 9 – Summary of pharmacokinetic parameters of zanidatamab following single and multiple administration at 20 mg/kg Q2W in BTC patients.

Cycle	C_{max} (mcg/mL)	C_{trough} (mcg/mL)	AUC_{0-tau} (days*mcg/mL)	Linear CL (L/h)	Vd (L)
Single Dose N=87	414.256 (86.404)	72.987 (30.839)	2058.029 (554.546)	0.0110 (0.00370)	8.16 (3.23)
Steady-State N=87	638.651 (151.067)	224.733 (89.905)	4680.317 (1476.033)		

Data based on popPK analysis presented as mean (SD).
Abbreviations: AUC_{0-tau} = area under the curve during the dosing interval; CL = clearance; SD= standard deviation; Vd= Volume of Distribution; C_{max} = maximum concentration; C_{trough} = trough concentration; Q2W = once every 2 weeks.
Note: PPK model includes linear CL as well as nonlinear elimination with Km = 8.92 µg/mL and V_{max} = 4.37 µg/mL/day.

Absorption

Zanidatamab is administered via the intravenous route and therefore is expected to be immediately and completely bioavailable.

Distribution

Following intravenous dosing, zanidatamab undergoes biphasic elimination from the circulation. The mean (SD) volume of distribution of zanidatamab is approximately 8.16 (3.23) L based on the popPK analysis.

Metabolism

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

Elimination

Based on popPK analysis, participants with BTC were predicted to have a typical CL of 0.0110 L/h (0.00370) and an estimated $t_{1/2}$ of approximately 21 days for zanidatamab administered at 20 mg/kg every 2 weeks at steady-state.

Special populations and conditions

Based on popPK analysis, no clinically significant differences in the PK of zanidatamab were observed based on age (24 to 88 years), sex, race (White, Black, Asian), tumour size (12-313 mm), HER2 expression (0 to 3+ by IHC), soluble HER2 extracellular domain (ECD) concentration, and body weight (35.4 kg to 128 kg).

- **Hepatic Insufficiency:** Based on popPK analysis, no clinically significant differences in the PK of zanidatamab were observed based on mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin between 1 and 1.5 times ULN and any AST). The PK of zanidatamab in patients with moderate (total bilirubin >1.5 to ≤ 3 ULN and any AST) or severe hepatic (total bilirubin > 3 ULN and any AST) is unknown.
- **Renal Insufficiency:** Based on popPK analysis, no clinically significant differences in the PK of zanidatamab were observed based on mild and moderate renal impairment (eGFR 30 to 89 mL/min estimated using the CKD-EPI). The PK of zanidatamab in patients with severe renal impairment and end-stage renal disease with or without hemodialysis is unknown.

10.4. Immunogenicity

All therapeutic proteins have the potential for immunogenicity.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

There is insufficient information to characterize the anti-drug antibody response to zanidatamab and the effects of anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety or efficacy.

11. Storage, Stability, and Disposal

Store unopened vials in the original carton at 2°C to 8°C. Do not freeze.

Reconstituted solution

From a microbiological point of view, the reconstituted solution should be used immediately. If not used immediately, in-use storage times should not exceed 4 hours at room temperature or in the refrigerator (2°C to 8°C).

Diluted solution

From a microbial point of view, the product should be used immediately. If not used immediately, in-use storage time should not exceed 12 hours at room temperature or 24 hours in the refrigerator at 2°C to 8°C. These storage times start from the time of reconstitution.

Discard any portion of the reconstituted solution that remains unused.

12. Special Handling Instructions

Aseptic technique must be used for reconstitution and dilution of ZIIHERA.

Do not freeze the product (see 11 Storage, Stability, and Disposal).

Part 2: Scientific Information

13. Pharmaceutical Information

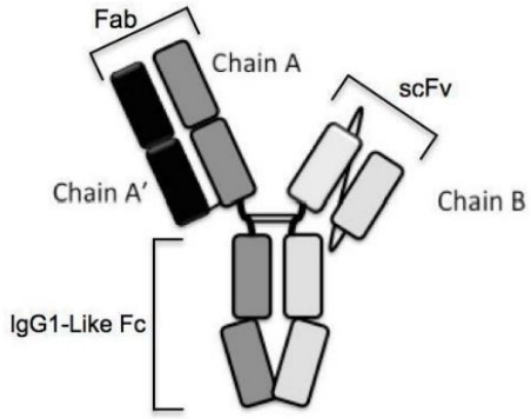
Drug Substance

Non-proprietary name of the drug substance(s): zanidatamab

Chemical name: recombinant bispecific antibody recognizing HER2

Molecular formula and relative molecular mass: $C_{5553}H_{8545}N_{1482}O_{1726}S_{36}$ (aglycosylated; all cysteines disulfide bonded); 127,718.4 Da (for the predominant G0F/G0F glycoform)

Structure:



Abbreviations: Fab = Fragment antigen-binding; Fc = Fragment crystallizable; IgG1 = immunoglobulin G antibody isotype 1; scFv = Single-chain variable fragment

Physicochemical properties: ZIIHERA is a lyophilized white powder.

14. Clinical Trials

14.1. Clinical Trials by Indication

Previously-treated Unresectable Locally Advanced or Metastatic HER2-positive (IHC 3+) Biliary Tract Cancer

Table 10 – Summary of Patient Demographics for Clinical Trials in Biliary Tract Cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (range)	Sex
HERIZON-BTC-01	Phase 2, multicentre, open-label, single-arm	20 mg/kg, intravenously, every 2 weeks	N = 62	64 years (38 to 79 years)	55% female

The efficacy of ZIIHERA was evaluated in Cohort 1 (n=62) of HERIZON-BTC-01, a multicentre open-label single arm trial of patients with locally advanced unresectable or metastatic biliary tract cancer who received at least one prior gemcitabine-containing systemic chemotherapy regimen for advanced disease, and whose tumour tested HER2-positive (IHC 3+) at a central laboratory. Patients were required to have adequate cardiac function (defined as LVEF ≥ 50%).

Patients received ZIIHERA once every 2 weeks at a dosage of 20 mg/kg intravenously. ZIIHERA was administered until disease progression or unacceptable toxicity. The major efficacy outcome measures were confirmed objective response rate (cORR) and duration of response (DoR) as determined by an independent central review (ICR) according to Response Evaluation Criteria in Solid Tumours (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. 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. Forty percent of patients had received more than one prior line of therapy for metastatic or locally advanced disease. The most commonly received prior treatments, other than gemcitabine, included: cisplatin (76%), fluoropyrimidine-based (32%), PD-1 or PD-L1 inhibitor (26%), and oxaliplatin (16%).

The efficacy results are summarized in Table 11.

Table 11 – Efficacy Results in HERIZON-BTC-01

Efficacy Parameter*	**ZIIHERA N=62**
Confirmed Objective Response Rate (cORR)	
n % (95%, CI)	32 51.6 (38.6, 64.5)
Complete response, n (%)	2 (3.2)
Partial response, n (%)	30 (48.4)
Duration of Response (DOR)[ǂ]	**N=32**
Median, months (95% CI)	14.9 (7.4, NE)

*Assessed by independent central review
[ǂ]Based on Kaplan-Meier estimate
NE = not estimable
Data cut off 28 July 2023

16. Non-Clinical Toxicology

General toxicology: In a 13-week repeat-dose toxicity study of cynomolgus monkeys, ZIIHERA induced non-severe and transient treatment-related soft or watery feces at intravenous doses of up to 150 mg/kg weekly.

Genotoxicity: Studies have not been conducted to evaluate mutagenic potential of ZIIHERA.

Carcinogenicity: Studies have not been conducted to evaluate the carcinogenic potential of ZIIHERA.

Reproductive and developmental toxicology: Reproductive and developmental toxicity studies have

not been conducted with ZIIHERA. Fertility studies have not been performed with ZIIHERA. In a repeat-dose toxicity study of cynomolgus monkeys, ZIIHERA had no effect on male and female reproductive organs through 13 weeks of treatment with doses of up to 150 mg/kg weekly.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr **ZIIHERA®**

Zanidatamab for injection

This patient medication information is written for the person who will be taking **ZIIHERA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **ZIIHERA**, talk to a healthcare professional.

Serious warnings and precautions box

ZIIHERA can cause harm to your unborn baby. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with ZIIHERA.

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

What ZIIHERA is used for:

For the following indication(s) ZIIHERA has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- ZIIHERA is used to treat adults with a type of cancer known as 'biliary tract cancer' (BTC) when:
  - it has high levels of a protein known as 'HER2-positive' BTC, and
  - it has spread to nearby tissues (locally advanced), or to other parts of the body (metastasized) or
  - the cancer has returned or worsened after previous chemotherapy treatment or you were not able to continue your prior treatment.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How ZIIHERA works:

ZIIHERA is a type of medicine that contains the active substance zanidatamab, which is a 'bispecific' antibody that attaches itself to specific proteins or antigens on cancer cells. It recognizes and attaches

to a protein called “human epidermal growth factor receptor 2” (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When ZIIHERA attaches to the HER2 receptor on cancer cells, it may slow or stop the cancer cells from growing or may kill them.

The ingredients in ZIIHERA are:

Medicinal ingredient(s): zanidatamab

Non-medicinal ingredients: Polysorbate 20, sodium succinate anhydrous (Disodium succinate), succinic acid, sucrose, water for injection

ZIIHERA comes in the following dosage form(s):

One vial of powder contains 300 mg of zanidatamab.
After reconstitution one single-dose vial contains 50 mg/mL of zanidatamab.

Do not use ZIIHERA if:

- you are allergic to zanidatamab or to any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZIIHERA. Talk about any health conditions or problems you may have, including if you:

- are feeling short of breath, cough, feeling tired, swelling of ankles or legs, irregular heartbeat, sudden weight gain, feeling dizzy, or loss of consciousness. These may be symptoms of a condition where your heart cannot pump blood well enough (decreased left ventricular ejection fraction). Your doctor will check your heart function before starting treatment with ZIIHERA.
- are pregnant or breast-feeding, if you think you may be pregnant, or if you and your partner are planning to have a baby.
    - Tell your doctor immediately if you get pregnant during treatment with ZIIHERA or during the 4 months after stopping treatment.
    - Ask your doctor if you can breast-feed during treatment with ZIIHERA and for 4 months following treatment, as it may be harmful to the child.

Other warnings you should know about:

- **Infusion reactions**
  Infusion reactions can happen. Your doctor or nurse will monitor you for side effects during and after your infusion as needed. If you get any serious reaction, your doctor may stop treatment with ZIIHERA.
- **Contraception**
  ZIIHERA may harm the unborn baby. You should use effective contraception during treatment with this medicine and for 4 months after stopping treatment. Talk to your doctor about the best contraception for you.
- **Driving and using machines**
  You may feel tired after receiving ZIIHERA. If this happens, do not drive or use any tools or machines.
- **Children and adolescents**
  ZIIHERA is not recommended in children or adolescents, as it has not been tested in this age group.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take ZIIHERA:

ZIIHERA will be given to you by a healthcare professional in a hospital or clinic.

Usual dose:

- ZIIHERA is given by a drip into a vein (intravenous infusion) once every two weeks.
- The amount of medicine you are given is dependent upon your weight and will be decided by your doctor.
- The length of time the infusion will last may be different for the first dose and later doses depending on how well you tolerate receiving the infusions.
- The number of infusions you will be given depends on how you respond to treatment and how well you tolerate the treatment.
- Before each infusion your healthcare professional may give you some medicines to help prevent infusion reactions.

Do not stop treatment with this medicine without talking to your doctor first. It is important that you are given all the infusions that have been recommended by your treatment team.

Overdose:

If you think you, or a person you are caring for, have taken too much ZIIHERA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you forget or miss your appointment to receive ZIIHERA, make another appointment with your healthcare professional as soon as possible.

Possible side effects from using ZIIHERA:

These are not all the possible side effects you may have when taking ZIIHERA. If you experience any side effects not listed here, tell your healthcare professional.

Very common (may affect more than 1 in 10 people)

- diarrhea
- stomach pain
- feeling sick nausea
- being sick vomiting
- feeling tired
- decreased appetite
- rash
- low levels of red blood cells count – shown in blood tests (anemia)
- abnormal liver function – shown in blood tests

If you get any of the above side effects after treatment with ZIIHERA, you should talk to your doctor straight away and tell them that you have previously been treated with ZIIHERA.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking the/this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
Very common			
Reactions related to the infusion of the medicine. Symptoms that can either be mild or more severe: feeling sick (nausea), fever, chills, feeling tired, headache, loss of appetite, joint and muscle pains, and hot flashes		X	X
Common			
Heart problems: feeling short of breath, cough, feeling tired, swelling of ankles or legs, irregular heartbeat, sudden weight gain, feeling dizzy, or loss of consciousness		X	X
Uncommon			
Lung problems (pneumonitis): Chest symptoms such as a dry cough or breathlessness or other new or worsening breathing problems as these may be symptoms of a lung problem		X	X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

ZIIHERA will be stored by the healthcare professionals at the hospital or clinic where you receive your treatment. The storage details are as follows:

- Do not use ZIIHERA after the expiry date which is stated on the carton and vial label after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C to 8°C). Do not freeze.
- Store vials in the original carton.
- The diluted solution should be used immediately after preparation.

If you want more information about ZIIHERA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.jazzpharma.com; or by calling 1-800-520-5568.

This leaflet was prepared by Jazz Pharmaceuticals Ireland Limited.

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