ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ziihera 300 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 300 mg of zanidatamab.

After reconstitution, one vial contains 50 mg/mL of zanidatamab.

Zanidatamab is a humanised (IgG1) bispecific antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

White lyophilised cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ziihera as monotherapy is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy (for biomarker-based patient selection, see section 4.2).

4.2 Posology and method of administration

Ziihera must be initiated by a physician experienced in the diagnosis and treatment of patients with biliary tract cancer. It must be administered by a qualified healthcare professional, with appropriate resuscitation equipment available.

Patient selection
Patients treated with Ziihera for BTC should have documented HER2-positive tumour status, defined as a score of 3 + by immunohistochemistry (IHC) assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If a CE-marked IVD is not available, an alternate validated test should be used.

Posology
The recommended dose of Ziihera is 20 mg/kg, administered as an intravenous infusion every 2 weeks (every 14 days) until disease progression or unacceptable toxicity. For duration of infusion, see Table 4.

Premedications
Premedication should be administered 30 to 60 minutes prior to each infusion to prevent potential infusion related reaction. Premedication is recommended to include a corticosteroid, antihistamine, and antipyretic (see section 4.4).

Dose modifications for left ventricular dysfunction
Left ventricular function must be assessed at baseline and at regular intervals during treatment.
The recommendations on dose modifications in the event of left ventricular ejection fraction (LVEF) decrease are indicated in Table 1.

Table 1. Dose modifications for left ventricular dysfunction

Left ventricular dysfunction (see section 4.4)	Severity	Treatment modification
	Absolute decrease of ≥ 16% points in LVEF from pre-treatment baseline	• Withhold treatment 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.
	LVEF value below 50% and absolute decrease of ≥ 10% points below pre-treatment baseline	

Dose modifications for infusion related reactions
Management of infusion related reaction (IRRs) may require reduced infusion rate, dose interruption, or treatment discontinuation as described in Table 2.

Table 2. Dose and infusion duration modifications for infusion-related reactions

Infusion related reactions (see sections 4.4 and 4.8)	Severity	Treatment modification
	Mild (Grade 1)	• Reduce infusion rate by 50%. • Subsequent infusions should start at this reduced rate. • Infusion rate for subsequent infusions may be increased gradually to the rate prior to symptoms, as tolerated.
	Moderate (Grade 2)	• Hold infusion immediately. • Treat with appropriate therapy. • Resume infusion at 50% of previous infusion rate once symptoms resolve. • Infusion rate for subsequent infusions may be increased gradually to the rate prior to symptoms, as tolerated.
	Severe (Grade 3)	• Hold infusion immediately. • Promptly treat with appropriate therapy. • Resume infusion at the next scheduled dose at 50% of previous infusion rate once symptoms resolve. • Permanently discontinue for recurrent Grade 3 symptoms.
	Life threatening (Grade 4)	• Hold 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 (see section 4.4)	Severity	Treatment modification
	Confirmed Grade ≥ 2	• Permanently discontinue.

Missed dose
If a patient misses a dose of Ziihera, the scheduled dose should be administered as soon as possible. The administration schedule should be adjusted to maintain a 2-week interval between doses.

Special populations

Renal impairment
Dose adjustments are not required for patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min estimated using the CKD-EPI). Zanidatamab has not been evaluated in patients with severe renal impairment and patients with end-stage renal disease with or without dialysis. However, due to minor involvement of renal processes in the clearance of zanidatamab, no dose adjustment is recommended for patients with renal impairment as no difference in exposure is expected (see section 5.2).

Hepatic impairment
Dose adjustments are not required for patients with 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). Zanidatamab has not been evaluated in patients with moderate (total bilirubin > 1.5 to ≤ 3 ULN and any AST) to severe (total bilirubin > 3 ULN and any AST) hepatic impairment. However, due to minor involvement of hepatic processes in the clearance of zanidatamab, no dose adjustment is recommended for patients with hepatic impairment as no difference in exposure is expected (see section 5.2).

Elderly population
No dose adjustment is required in patients aged 65 years and over (see section 5.2).

Paediatric population
Children under the age of 18 were not included in the clinical trials. Hence, the safety, efficacy and pharmacokinetics of zanidatamab have not been established in this population.

Method of administration
Ziihera is administered by intravenous infusion. It must not be administered by intravenous push or as a rapid single bolus injection.

The diluted solution for infusion must have a final concentration of 0.4 to 6 mg/mL zanidatamab.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Table 4. Recommended infusion durations

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

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Embryo-foetal toxicity, pregnancy and contraception
Based on the mechanism of action, zanidatamab may cause foetal harm when administered to a pregnant woman. In post-marketing reports of other HER2-directed antibodies, use during pregnancy resulted in cases of oligohydramnios manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death (see section 4.6).

Patients should be advised to avoid becoming pregnant while receiving Ziihera. A pregnancy test should be performed before initiating treatment to exclude pregnancy.

Female patients of childbearing potential should use an effective method of contraception while receiving Ziihera and for 4 months following the last dose (see section 4.6).

Left ventricular dysfunction
Decreases in LVEF have been reported with medicinal products that block HER2 activity, including zanidatamab. LVEF should be assessed prior to initiation of Ziihera by echocardiogram or multigated acquisition (MUGA) scan and at regular intervals during treatment to ensure that LVEF is within normal limits. If the LVEF declines and has not improved, or has declined further at the subsequent assessment, Ziihera should be discontinued as recommended in Table 1 (see section 4.2).

Zanidatamab has not been studied in patients with a pre-treatment LVEF value of < 50%; history of myocardial infarction or unstable angina within 6 months; troponin levels consistent with myocardial infarction, or clinically significant cardiac disease such as ventricular arrhythmia requiring therapy, uncontrolled hypertension, or any history of symptomatic congestive heart failure (CHF).

Infusion related reactions
Ziihera can cause infusion related reactions (IRRs) (see section 4.8). Premedications should be administered prior to each dose , to reduce the risk of IRRs (see section 4.2).

Patients should be monitored for signs and symptoms of IRRs during administration and as clinically indicated after completion of infusion. Appropriate emergency medicine and equipment to treat IRRs should be available for immediate use, and IRRs should be managed as recommended in Table 2 (see section 4.2).

Pneumonitis
Pneumonitis has been reported with medicinal products that block HER2 activity, including Ziihera. Pneumonitis has been reported in 0.4% of 233 patients treated with Ziihera 20 mg/kg intravenously as a single agent in clinical studies. Patients should be monitored for signs and symptoms of pneumonitis. In the event of confirmed Grade ≥2 pneumonitis, treatment should be permanently discontinued (see section 4.2).

Excipients with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Polysorbate 20
This medicinal product contains 0.63 mg of polysorbate 20 in each vial, which is equivalent 0.105 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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 PK of concomitant medicines.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females
To exclude pregnancy, women of childbearing potential should undergo pregnancy testing before initiation of Ziihera.

Based on the mechanism of action, zanidatamab may cause embryo-foetal harm when administered during pregnancy. Female patients should use effective contraception during treatment with Ziihera and for 4 months following the last dose.

Pregnancy
Based on the mechanism of action, zanidatamab may cause foetal harm when administered to a pregnant woman. There are no human or animal data on the use of zanidatamab in pregnancy. In post-marketing reports of other HER2-directed antibodies, use during pregnancy resulted in cases of oligohydramnios manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Ziihera is not recommended for use during pregnancy or in women of childbearing potential not using contraception. Patients should be advised on potential risks to the foetus.

Women who received Ziihera during pregnancy or within 4 months prior to conception should be monitored for oligohydramnios. If oligohydramnios occurs, foetal testing that is appropriate for gestational age and consistent with local standard of care should be performed.

Breast-feeding
It is not known whether zanidatamab is excreted in human milk, or what effect it has on a breast-fed 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 and the benefit of Ziihera therapy for the woman. This consideration should also take into account the washout period of 4 months (see section 5.2).

Fertility
Fertility studies have not been performed with zanidatamab.

4.7 Effects on ability to drive and use machines

Zanidatamab has minor influence on the ability to drive and use machines. Fatigue has been reported with the use of Ziihera. Therefore, patients should be advised to use caution when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
The pooled safety population of Ziihera reflects exposure in 233 patients who were administered Ziihera 20 mg/kg intravenously as a single agent in two single-arm trials. Among 233 patients who

received Ziihera, 39% were exposed for 6 months or longer, and 17% were exposed for greater than one year.

From the pooled data, serious adverse reactions were observed in 8.2% of patients. The most frequent serious adverse reactions were diarrhoea (1.7%) and fatigue (1.3%).

The most common adverse reactions observed in the pooled data were diarrhoea (48.5%), infusion related reaction (30.5%), fatigue (26.2%), anaemia (21.9%) and rash (21.5%).

The safety of Ziihera in adult patients with BTC (N=87) was evaluated in Study 203, an open-label, multi-cohort, multicenter trial.

In Study 203 (N=87), serious adverse reactions occurred in 16.1% of patients. The most frequent serious adverse reactions were diarrhoea (2.3%), fatigue (2.3%), and alanine aminotransferase increased (2.3%).

The most common adverse reactions in Study 203 (N=87) were diarrhoea (46%), infusion related reaction (33.3%), abdominal pain (26.4%), anaemia (25.3%) and fatigue (24.1%).

Tabulated list of adverse reactions

Unless otherwise stated, the frequencies of adverse reactions are based on all-cause adverse event frequencies identified in 233 patients exposed to Ziihera at 20 mg/kg administered intravenously as a single agent in two single-arm trials.

Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 5. Adverse reactions in patients receiving Ziihera as monotherapy reported in the pooled safety population (N=233)

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very common	Anaemia*
Metabolism and nutrition disorders	Very common	Decreased appetite
Cardiac disorders	Common	Ejection fraction decreased*
Gastrointestinal disorders	Very common	Diarrhoea*
		Abdominal pain[a]
		Nausea
		Vomiting
Hepatobiliary disorders	Very common	Alanine aminotransferase increased*
		Aspartate aminotransferase increased*
Skin and subcutaneous tissue disorders	Very common	Rash[b]
General disorders and administration site conditions	Very common	Fatigue[c]

Injury, poisoning and procedural complications	Very common	Infusion related reaction*
Respiratory, thoracic and mediastinal disorders	Uncommon	Pneumonitis

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

[b] Rash includes dermatitis acneiform, rash, rash maculo-papular, rash pruritic, and urticaria.

[c] Fatigue includes asthenia, fatigue, and malaise.

* See "Description of selected adverse reactions" below

Description of selected adverse reactions in the pooled safety population (N=233)

Diarrhoea
Diarrhoea was reported in 48.5% of patients who received Ziihera. 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 diarrhoea in 1.3% of patients and was held or delayed in 2.6% of patients. There were no discontinuations of treatment due to diarrhoea.
Infusion related reactions
Infusion related reactions (IRRs) were reported in 30.5% of patients who received Ziihera. Grade 3 reported event incidence in patients was 0.4%, Grade 4 and Grade 5 events were not observed. Median time to first onset was 1 day and median time to resolution was 1 day. Ziihera infusion was interrupted in 25.3% of patients and discontinued in 0.4% of patients due to IRRs (see section 4.4).

Anaemia
Anaemia was reported in 21.9% of patients who received Ziihera. Grade 3 reported event incidence in patients was 9.9%, Grade 4 was 0.4% and no Grade 5 events were observed. Median time to first onset was 42 days and median time to resolution was 14 days. Ziihera infusion was held or delayed in 0.4% of patients and there were no other actions taken with Ziihera due to anaemia.

ALT increased
ALT increased was reported in 12.4% of patients who received Ziihera. Grade 3 reported event incidence in patients was 1.7%, Grade 4 was 0.4% and no Grade 5 events were observed. Median time to first onset was 78 days and median time to resolution was 16 days. Ziihera infusion was held or delayed in 7 patients (3%) and there were no other actions taken with Ziihera due to ALT increased.

AST increased
AST increased was reported in 11.6% of patients who received Ziihera. Grade 3 reported event incidence in patients was 1.3%, Grade 4 was 0.9% and no Grade 5 events were observed. Median time to first onset was 87 days and median time to resolution was 15 days. Dose of Ziihera was held or delayed in 6 patients (2.6%) and there were no other actions taken with Ziihera due to AST increased.

Left ventricular dysfunction
Decreases in LVEF have been reported with medicinal products that block HER2 activity, including Ziihera. Twelve events of LVEF decreased were observed in 10 patients (4.3%) and one of these events was considered serious. Grade 3 reported event incidence in patients was 1.3%, Grade 4 and Grade 5 events were not observed. Median time to first onset was 171 days and median time to resolution was 27 days. The dose of Ziihera was reduced in 1 patient (0.4%), was held or delayed in 5 patients (2.1%)and was discontinued in 2 patients (0.9%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The maximum tolerated dose of zanidatamab has not been determined. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, HER2 (Human Epidermal Growth Factor Receptor 2) inhibitors, ATC code: L01FD07

Mechanism of action
Zanidatamab is a dual HER2-targeted bispecific antibody that simultaneously binds extracellular domains 2 and 4 on separate HER2 monomers (binding in trans). Binding of zanidatamab with HER2 results in internalization leading to a reduction of the receptor on the 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 tumour cell death.

Immunogenicity
The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADA) in the studies described below with incidence of ADA in other studies.

ADA were rarely detected. Zanidatamab is categorised as a low-risk molecule to elicit an immune response on the basis of assessment of the immunogenicity risk factors and the low incidence of ADAs observed to date across the clinical studies (1.6% [3 of 183 evaluable participants] and 1.2% [1 of 85 evaluable participants] in Study 101 and Study 203, respectively). No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited.

Cardiac electrophysiology
The relationship between time-matched zanidatamab serum concentrations and ΔQTcF measurements was evaluated based on data obtained during treatment with zanidatamab from participants in Study 101. The C-QT analysis dataset included measurements of QTcF from 179 out of the 192 participants enrolled in Study 101. Zanidatamab has no effect on QTc interval and there was no relationship between zanidatamab exposure and change in QTc interval.

Clinical efficacy and safety
The efficacy of Ziihera was evaluated in Cohort 1 (N=62) of ZWI-ZW25-203 (Study 203), 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 experienced disease progression after or developed intolerance to the most recent prior therapy, and whose tumour tested HER2-positive (IHC 3+).

Patients received Ziihera every 2 weeks at a dose of 20 mg/kg intravenously. It 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%), oxaliplatin (16%), 5-fluoruracil (39%), and PD-1 or PD-L1 inhibitor (26%). The median overall survival (OS) in the IHC3+ population was 18.1 months (95% CI: 12.2, 22.9). The median duration of study follow-up in the IHC3+ population was 34.0 months.

Efficacy results are summarised in Table 6.

Table 6. Efficacy results in Study 203

Efficacy parameter*	**N=62**
Confirmed objective response rate (cORR)	
n % (95% CI)	32 51.6 (38.6, 64.5)
Complete response, n (%)	3 (4.8)
Partial response, n (%)	29 (46.8)
Duration of response (DOR)	**N=32**
Median †, months (95% CI)	14.9 (7.4, 24.0)

*Assessed by independent central review

†Based on Kaplan-Meier estimate

LPLV = Last patient last visit 11 July 2024

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ziihera in all subsets of the paediatric population in biliary tract cancer (see section 4.2 for information on paediatric use).

Conditional marketing authorisation

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Zanidatamab PK exhibited non-linear 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 geometric mean accumulation indices based on C_{trough} at steady state was approximately 2.7 for the 20 mg/kg once every 2 weeks zanidatamab dose level. The observed zanidatamab exposure and PK parameters following the first administration in the first cycle and steady state, based on the available sampling scheme, are described in Table 7.

The pharmacokinetics of zanidatamab following intravenous infusion in participants with HER2 expressing cancers was evaluated in a population pharmacokinetic model analysis from 279 participants. From the PopPK analysis, participants with BTC were predicted to have a typical CL of 0.0115 L/h, a typical Vc of 3.51 L, a typical Vp of 3.95 L, and an estimated $t_{1/2}$ of approximately 21 days. Based on the estimated $t_{1/2}$, it would take approximately 3.5 months (i.e., 5 half-lives) to reach steady state following multiple dose administration of zanidatamab.

Table 7. Study 203: Pharmacokinetic parameters (geometric mean [percent coefficient of variation]) of zanidatamab following the first administration of zanidatamab at 20 mg/kg Q2W in cycle 1 and steady-state in BTC patients

Cycle	C_{max} (µg/mL)	C_{trough} (µg/mL)	$AUC_{0\text{-}tau}$ (days*µg/mL)
Cycle 1 N=19	455 (16.3)	68.3 (42.9)	2280 (22.7)
Cycle 4 or later (steady-state) N=8	600 (22.2)	178 (29.6)	3980 (22.5)

Abbreviations: $AUC_{0\text{-}tau}$ = area under the curve during the dosing interval; C_{max} = maximum concentration; C_{trough} = trough concentration; Q2W = once every 2 weeks

Note: Cycle 1 and Cycle 4 are referred to as "first dose" and "steady-state", respectively; these terms are interchangeable.

Absorption
Ziihera is administered as an intravenous infusion.

Distribution
Following intravenous dosing, zanidatamab undergoes biphasic elimination from the circulation. Based on population pharmacokinetic analysis, participants with HER2 amplified BTC were predicted to have a typical Vc of 3.51 L and a typical Vp of 3.95 L.

Elimination
Based on population pharmacokinetic analysis, participants with BTC were predicted to have a typical CL of 0.0115 L/h and an estimated $t_{1/2}$ of approximately 21 days for zanidatamab administered at 20 mg/kg every 2 weeks at steady-state.

Specific populations
Based on population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of zanidatamab were observed based on age (24 to 88 years), sex, race (White, Black, Asian), and body weight (35.4 kg to 128 kg).

Renal impairment
Based on population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of zanidatamab were observed based on mild and moderate renal impairment (eGFR 30 to 89 mL/min estimated using the CKD-EPI). The pharmacokinetics of zanidatamab in patients with severe renal impairment and end-stage renal disease with or without hemodialysis is unknown. However, as IgG monoclonal antibodies are not primarily cleared via renal pathways, a change in renal function is not expected to influence zanidatamab exposure.

Hepatic impairment
Based on population pharmacokinetics analysis, no clinically significant differences in the pharmacokinetics 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 pharmacokinetics of zanidatamab in patients with moderate (total bilirubin > 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin >3 ULN and any AST) is unknown. However, as IgG monoclonal antibodies are not primarily cleared via hepatic pathways, a change in hepatic function is not expected to influence zanidatamab exposure.

5.3 Preclinical safety data

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

Genotoxicity
Studies have not been conducted to evaluate the mutagenic potential of zanidatamab.

Repeat-dose toxicity
Zanidatamab was generally well tolerated in a 13-week repeat dose toxicity study in cynomolgus monkeys dosed once weekly (intravenous) at dose levels resulting in exposure margins up to at least 10 times the exposure in human patients. Non-severe, transient, non-dose dependent treatment-related soft or watery faeces was observed at clinically relevant exposure. In some, but not all animals, soft or watery faeces correlated with non-severe changes in blood urea nitrogen and blood albumin levels. From day 22, BUN was generally increased (up to 45%) and albumin levels tended to be decreased (up to 12%) throughout the dosing phase. However, these values were not dosed-related and remained within historical control ranges.

Developmental and reproductive toxicity
Reproductive and developmental toxicity studies have not been conducted with zanidatamab. However, antibodies that bind to HER2 have been observed to cause severe embryo-foetal toxicity. Fertility studies have not been performed with zanidatamab. In a 13-week repeat-dose toxicity study in cynomolgus monkeys dosed once weekly (intravenous) at dose levels resulting in exposure margins up to at least 10-times the exposure in human patients, zanidatamab had no effect on male and female reproductive organs when evaluated by organ weights and histopathology.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20 (E432)
Disodium succinate
Succinic acid (E363)
Sucrose
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years.

Reconstituted solution
Chemical and physical in-use stability of reconstituted solution has been demonstrated for up to 6 hours at room temperature (18 °C to 24 °C) and up to 24 hours at 2 °C to 8 ºC.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should not exceed 4 hours at room temperature (18 ºC to 24 ºC) or in the refrigerator (2 ºC to 8 ºC).

Diluted solution
Chemical and physical in-use stability of the diluted solution has been demonstrated for up to 24 hours at room temperature (18 °C to 24 °C) and at 2 ºC to 8 ºC.

From a microbial point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions are the responsibility of the user and should not exceed 12 hours at room temperature (18 °C to 24 °C) or 24 hours in the refrigerator at 2 ºC to 8 ºC. These storage times start from the time of reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).

Do not freeze.

For storage conditions after reconstitution and dilution of the product, see section 6.3.

6.5 Nature and contents of container

20 mL Type I glass vial with a chlorobutyl stopper and flip-off cap.

Each pack contains either 1 vial or 2 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ziihera must be reconstituted with sterile water for injections and subsequently diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose for infusion.

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

Reconstitution

- 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 them to reach room temperature.
- Reconstitute each vial with 5.7 mL of sterile water for injections to obtain a concentration of 50 mg/mL in an extractable volume of 6 mL.
- Gently swirl the vial until complete dissolution. 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 discoloration. The reconstituted product should be a colourless to light yellow, clear to slightly opalescent solution that is essentially free of particles. Discard the reconstituted vial if any discoloration or particulate matter is observed.

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 sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose for infusion. The final concentration of the diluted solution should be between 0.4 mg/mL and 6 mg/mL.
- Mix the diluted solution by gentle inversion. Do not shake.
- The solution for infusion must be a clear, colourless solution with no visible particles. If particulate matter or discoloration is identified, the solution must be discarded.
- Compatibility with intravenous administration materials and the diluted Ziihera solution has been demonstrated in the following materials:
    - Intravenous bag: polyvinyl chloride (PVC), polyolefin (PO), ethyl vinyl acetate (EVA), polypropylene (PP) and ethylene-propylene copolymer.
    - Infusion sets: polyvinyl chloride/ bis (2-ethylhexyl) phthalate (PVC/DEHP), polyurethane (PUR), polyethylene-lined (PE-lined) acrylonitrile-butadiene-styrene (ABS).
    - Inline filters: polyethersulfone solution filter (PES), polyvinylidene fluoride air filter (PVDF).

- Closed system transfer devices: acrylonitrile-butadiene-styrene (ABS), acrylic copolymer, polycarbonate (PC), polyisoprene (PI), polyester polypropylene (PP), polytetrafluoroethylene (PTFE), silicone and stainless steel (SS).

Administration

- Administer Ziihera as an intravenous infusion with a 0.2 or 0.22 micron filter.
- Do not co-administer Ziihera and other intravenous medicinal products concurrently through the same intravenous line.

Disposal

Ziihera vials are for single dose use only.

Discard any portion of the reconstituted solution that remains unused.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals Ireland Ltd
5th Floor, Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1931/001
EU/1/25/1931/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 June 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

WuXi Biologics Co. Ltd.
108 Meiliang Road
Mashan, Binhu
Wuxi, 214092, China

Name and address of the manufacturer responsible for batch release
Jazz Pharmaceuticals Ireland Ltd
5th Floor, Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines webportal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of zanidatamab in the treatment of adults with unresectable locally advanced or metastatic HER2-positive biliary tract cancer previously treated with at least one prior line of systemic therapy, the MAH should submit the results of the ongoing open-label phase III randomised clinical study JZP598-302 to evaluate the efficacy and safety of zanidatamab plus standard-of-care therapy versus standard-of-care therapy alone for advanced HER2-positive biliary tract cancer.	30 September 2029

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ziihera 300 mg powder for concentrate for solution for infusion
zanidatamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 300 mg of zanidatamab.

After reconstitution, one vial of 6 mL solution contains 50 mg/mL of zanidatamab.

3. LIST OF EXCIPIENTS

Also contains: polysorbate 20 (E432), disodium succinate, succinic acid (E363), sucrose, and water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.

1 vial
2 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals Ireland Ltd
5th Floor, Waterloo Exchange
Waterloo Road
Dublin 4
D04 E5W7
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1931/001
EU/1/25/1931/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ziihera 300 mg powder for concentrate
zanidatamab

2. METHOD OF ADMINISTRATION

IV use after reconstitution and dilution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ziihera 300 mg powder for concentrate for solution for infusion
zanidatamab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ziihera is and what it is used for
2. What you need to know before you are given Ziihera
3. How you will be given Ziihera
4. Possible side effects
5. How to store Ziihera
6. Contents of the pack and other information

1. What Ziihera is and what it is used for

How Ziihera works
Ziihera is a medicine that contains the active substance zanidatamab. Zanidatamab is a bispecific antibody that attaches itself to a specific protein or antigens on cancer cells. It recognises 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 zanidatamab attaches to the HER2 on cancer cells, it slows or stops the cancer cells from growing and may kill them.

What Ziihera is used for
Ziihera is used in adults with biliary tract cancer, a cancer of the structures that store and transport bile. It is used when the cancer:
- has high levels of the HER2 protein on its surface (also known as 'HER2-positive');
- cannot be removed by surgery (unresectable) and has spread to nearby tissues (locally advanced) or other parts of the body (metastasised); and
- has returned or worsened after previous chemotherapy treatment.

2. What you need to know before you are given Ziihera

You must not be given Ziihera

- If you are allergic to zanidatamab or any of the other ingredients of this medicine (listed in section 6).

If you are not sure if you are allergic, talk to your doctor or nurse before you are given Ziihera.

Warnings and precautions

Talk to your doctor or nurse before you are given Ziihera, or during treatment, if you have any of the following symptoms before or during treatment with Ziihera:

- 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 decreased left ventricular ejection fraction, a condition where your heart cannot pump blood well enough. Your doctor will check your heart function before starting treatment with Ziihera. See section 4 “Serious side effects” for more details about signs of heart problems to look out for.

Infusion reactions
Ziihera is given by a drip into a vein (intravenous infusion). Reactions to the infusion 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. See section 4 “Serious side effects” for more details about infusion reactions to look out for during the infusion and thereafter.

Children and adolescents
Ziihera is not recommended in children or adolescents. It has not been tested in this age group.

Other medicines and Ziihera
Tell your doctor or nurse if you are taking, have recently taken, or might take any other medicines.

Pregnancy and breast-feeding
Before starting treatment, you must tell your doctor or nurse if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.

Ziihera may harm the unborn baby. Your doctor will advise you about the risks of taking Ziihera for your baby while you are pregnant or breast-feeding. If you are able to get pregnant, you should use effective contraception (birth control) during treatment and for 4 months after stopping Ziihera treatment. Talk to your doctor about the best contraception for you. Tell your doctor straight away if you get pregnant during treatment with Ziihera or during the 4 months after stopping treatment.

It is not known if Ziihera passes into breast milk. 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. Your doctor will consider the benefits of breast-feeding for your child and the benefits to you of taking this medicine.

Driving and using machines
You may feel tired after receiving Ziihera. If this happens, do not drive or use any tools or machines.

Ziihera contains sodium
Ziihera contains less than 1 mmol of sodium (23 mg) per dose unit, that is to say it is essentially sodium-free.

Ziihera contains polysorbate 20
Ziihera contains 0.63 mg of polysorbate 20 in each vial, which is equivalent to 0.105 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How you will be given Ziihera

Ziihera will be given to you by a doctor or nurse in a hospital or clinic.

- It is given by a drip into a vein (intravenous infusion) once every two weeks.
- The amount of medicine you are given depends on your weight and will be calculated by your doctor.
- The duration of the infusion may differ 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 your disease responds to treatment,
    - how well you tolerate the treatment.
- Before each infusion, your doctor/nurse may give you some medicines to help prevent infusion reactions. These may include antihistamines (medicines to reduce allergic reactions), corticosteroid (medicines that treat pain and inflammation) and antipyretics (medicines to reduce fever) and will be given to you 30-60 minutes before you are given the infusion.

If you miss an appointment
If you forget or miss your appointment to receive Ziihera, make another appointment with your doctor or nurse as soon as possible.

If you stop receiving Ziihera
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.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Tell your doctor if you get any side effects, including those not listed in the leaflet.

Some side effects may be serious. Tell a doctor or nurse straight away, if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- Infusion reactions. Reactions can either be mild or more severe. Symptoms may include feeling sick (nausea), fever, chills, feeling tired, headache, loss of appetite, joint and muscle pains, and hot flashes.

Common (may affect up to 1 in 10 people)
- Ejection fraction decreased. This medicine may cause heart problems that reduce your heart's ability to pump blood. Symptoms of this include feeling short of breath, cough, feeling tired, swelling of ankles or legs, irregular heartbeat, sudden weight gain, feeling dizzy, or loss of consciousness.

Other side effects

The frequency and severity of side effects may vary with the dose you receive. Talk to your doctor or nurse if you get any of the following:

Very common (may affect more than 1 in 10 people)
- diarrhoea
- belly (abdominal) pain
- feeling sick (nausea)
- vomiting
- feeling tired (fatigue)
- decreased appetite
- rash

- low levels of red blood cells (anaemia), as shown in blood tests
- abnormal liver function, as shown in blood tests

Uncommon (may affect up to 1 in 100 people)
- Chest symptoms such as a dry cough or breathlessness (pneumonitis)

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 are being treated with Ziihera.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ziihera

Ziihera will be stored by the healthcare professionals at the hospital or clinic where you receive treatment. The following information is intended for healthcare professionals.

- Keep this medicine out of the sight and reach of children.
- 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 ºC – 8 ºC). Do not freeze.
- The diluted solution should be used immediately after preparation.

Medicines should not be disposed of via wastewater. Your pharmacist will throw away any medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ziihera contains
- The active substance is zanidatamab.
- One vial of powder for concentrate for solution for infusion contains 300 mg of zanidatamab. After reconstitution one vial of 6 mL solution contains 50 mg/mL of zanidatamab.
- The other ingredients are polysorbate 20 (E432), disodium succinate, succinic acid (E363), sucrose, and water for injections (see section 2).

What Ziihera looks like and contents of the pack

Ziihera is a white lyophilised powder supplied in a glass vial with a stopper and flip-off cap.

One carton contains 1 or 2 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Jazz Pharmaceuticals Ireland Ltd
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Dublin 4
D04 E5W7
Ireland
Tel: +353 1 968 1631
Email: medinfo-int@jazzpharma.com

This leaflet was last revised in:

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.