RISK MANAGEMENT PLAN FOR TUZNUE (TRASTUZUMAB)

RMP version to be assessed as part of this application:

Market Authorization Applicant: Prestige Biopharma Belgium

RMP Version number: 1.0

Data lock point for this RMP: 25-May-2026

Date of final sign off: 15-Jul-2026

Rationale for submitting an updated RMP: This RMP has been updated in line with EPAR-RMP of Herceptin (trastuzumab) (version 24.0, DLP 24-Sep-2025) published by EMA on 02-Mar-2026

Summary of significant changes in this RMP: Significant changes have been made in the following sections: Part I, Part II, Part III, Part V, Part VI and Part VII (Annex-4, Annex-7 and Annex-9)

Details of the currently approved RMP:

Version	Approved with procedure	Date of approval (opinion date)
0.2	Centralised Procedure:(EMEA/H/C/006252)	19-Sep-2024

QPPV name: Paulina Majewska

QPPV signature: [redacted]

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1 PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Trastuzumab
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, monoclonal antibodies (L01FD01)
Marketing Authorisation Applicant	Prestige Biopharma Belgium
Medicinal product to which this RMP refers.	2
Invented name(s) in the European Economic Area (EEA)	Tuznue 150 mg powder for concentrate for solution for infusion Tuznue 420 mg powder for concentrate for solution for infusion
Marketing authorization procedure	Centralised
Brief description of the product:	**Chemical class:** Trastuzumab is a recombinant humanized Immunoglobulin G (IgG) 1 monoclonal antibody.
	Summary of mode of action: Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, trastuzumab-

	mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.
	Important information about its composition: **Tuznue 150 mg powder for concentrate for solution for infusion** One vial contains 150 mg of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures. **Tuznue 420 mg powder for concentrate for solution for infusion** One vial contains 420 mg of trastuzumab, a humanized IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures. The reconstituted Tuznue solution contains 21 mg/mL of trastuzumab.
Product Information	Tuznue Product Information (**Module 1.3.1**)
Indications in the EEA	**Current:** Tuznue (trastuzumab) is developed for the same indications for intravenous use for which Herceptin® is authorized in the European Union (EU) and internationally. It is indicated for the treatment of adult patients with HER2-positive cancer in the following indications:

[redacted]

	Breast cancer **Early Breast Cancer (EBC)** Tuznue is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC): • Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). • Following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel. • In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin. • In combination with neoadjuvant chemotherapy followed by adjuvant Tuznue therapy, for locally advanced (including inflammatory) disease or tumours >2 cm in diameter. **Metastatic Breast Cancer (MBC)** Tuznue is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC): • As monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone-receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments. • In combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

	• In combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease. • In combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab. **<u>Metastatic Gastric Cancer (MGC)</u>** • In combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease. • Tuznue should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC 2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used.
Dosage in the EEA	**Current**: Tuznue is for intravenous use. <u>Early Breast Cancer</u> *Three-weekly and weekly schedule* As a three-weekly regimen the recommended initial loading dose of Tuznue is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel

	following chemotherapy with doxorubicin and cyclophosphamide. Metastatic Breast Cancer *Three-weekly schedule* The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. *Weekly schedule* The recommended initial loading dose of Tuznue is 4 mg/kg body weight. The recommended weekly maintenance dose of Tuznue is 2 mg/kg body weight, beginning one week after the loading dose. *Administration in combination with docetaxel or paclitaxel* In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of trastuzumab and immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated. *Administration in combination with an aromatase inhibitor* In the pivotal trial (BO16216) trastuzumab and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration (for dose, see the SmPC for anastrozole or other aromatase inhibitors). Metastatic Gastric Cancer *Three-weekly Schedule* The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-

	weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose. *Breast cancer and gastric cancer* *Duration of treatment* Patients with MBC or MGC should be treated with Tuznue until progression of disease. Patients with EBC should be treated with Tuznue for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended.
Pharmaceutical form (s) and strengths	**Current**: Tuznue 150 mg powder for concentrate for solution for infusion Tuznue 420 mg powder for concentrate for solution for infusion The reconstituted solution contains 21 mg/mL of trastuzumab.
Is/will the product be subject to additional monitoring in the EU?	Yes

2 PART II: SAFETY SPECIFICATION

Reference medicinal product for Tuznue is Herceptin®.

Herceptin® has a published the Risk Management plan available on the EMA website[1]. Regarding safety concerns, no data are published on the CMDh website[2] either for Herceptin® in particular, or for trastuzumab in general.

3 PART II: MODULE SI – EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Not applicable.

Part II module SI is not required for new marketing authorization applications in the European Union for biosimilar medicinal products as specified in the Guideline on Good pharmacovigilance practices – Module V (EMA/838713/2011 Rev. 2).

4 PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies applicable to similar biological medicinal products and relevance to human usage:

Toxicity

Repeated-dose toxicity

The repeated dose toxicity study was conducted in female Cynomolgus monkeys. It is based on weekly intravenous infusion during 4 consecutive weeks, and to evaluate the reversibility, progression, or delayed appearance of any observed changes following a 4-week recovery period. Five groups of four or six female cynomolgus monkeys received either the vehicle (0.9% Sodium Chloride for Injection), Herceptin® or HD201 (Tuznue). There were no Herceptin® and HD201 related effects on clinical observations, body temperatures, body weight, electrocardiographs, food consumption, indirect blood pressures or ophthalmic evaluations. No meaningful differences were observed in haematology, coagulation, or clinical chemistry parameters. There were no Herceptin® or HD201 related effects on organ weights and microscopic evaluations of the terminal or recovery animals showed no adverse response to treatment. In general, the toxicologic

[1] https://www.ema.europa.eu/en/documents/rmp/herceptin-epar-risk-management-plan_en.pdf
2https://www.hma.eu/human-medicines/cmdh.html

responses to treatment with HD201 and Herceptin® in female cynomolgus monkeys were similar. There were no notable toxicological findings for either HD201 or Herceptin®, thus supporting the biosimilarity of HD201 to Herceptin®

Relevance to human usage: Yes

Discussion: No safety concerns were identified therefore supporting the use of Tuznue in the target population.

Reproductive toxicity

No reproductive toxicity studies were performed for HD201 as CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMA/CHMP/42832/05; EMA/CHMP/403543/2010) does not routinely require reproductive/ developmental toxicity studies for similar biological medicinal products, unless indicated by results of repeat-dose studies. According to Herceptin® SmPC, there was no evidence of reproductive toxicity in teratology, female fertility, or late gestational toxicity/placental transfer studies. Studies were undertaken in cynomolgus monkey at doses up to 25 times that of the weekly human maintenance dose of 2mg/kg of trastuzumab; and no evidence of impaired fertility has been revealed. Placental transfer of trastuzumab was observed during the early and late days of gestation of the foetal development period (days 20 to 50 and days 120 to 150, respectively).

Relevance to human usage: Yes

Discussion: The use of trastuzumab should be avoided during pregnancy unless potential benefit for the mother outweighs the potential risk to the foetus. Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab and for 7 months after treatment has concluded.

Genotoxicity

No genotoxicity studies were performed for HD201 as CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMA/CHMP/42832/05; EMA/CHMP/403543/2010) does not routinely require genotoxicity/ mutagenicity studies for similar biological medicinal products, unless indicated by results of repeat-dose studies. Although not studied, according to Herceptin® SmPC, trastuzumab is not genotoxic.

Carcinogenicity

No carcinogenicity studies were performed for HD201 as CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMA/CHMP/42832/05; EMA/CHMP/403543/2010) does not routinely require carcinogenicity studies for similar biological medicinal products, unless indicated by results of repeat-dose studies. According to Herceptin® SmPC, no long-term carcinogenicity studies have been performed to establish the carcinogenic potential of Herceptin®.

Local tolerance

Local tolerance assessment was performed as part of the 4-week repeated-dose toxicity study in female cynomolgus monkey. No significant effects or differences were observed between HD201 and Herceptin®.

Relevance to human use: Yes

Discussion: No safety concerns were identified therefore supporting the use of Tuznue in the target population.

Safety pharmacology

Separate comparative safety pharmacology studies were not conducted as safety endpoints were incorporated in female cynomolgus monkey repeat-dose toxicity study. These endpoints included clinical observations, ECG, blood pressure, and respiration rate. There were no treatment-related changes noted on these parameters. This approach is in line with the Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMENCHMP/ BMWP/42832/2005 Rev. l) and CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies (EMNCHMP/BMWP/403543/2010). Moreover, no clinical signs or histopathological findings suggestive of central nervous system effects were noted in the 4 week repeat-dose toxicity study in female cynomolgus monkeys.

5 PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

Tuznue is being developed by Prestige Biopharma Limited as a biosimilar product to Herceptin®. The reference product Herceptin® is authorized in the EU both as a formulation for intravenous infusion and as a formulation for subcutaneous administration. Tuznue (HD201) is presented as a single use 20 ml vial containing 150 mg or a single use 50 ml vial containing 420mg Trastuzumab for intravenous administration. Tuznue as a biosimilar of Herceptin® is being developed to be used in the same indications as the approved reference product which are the treatment of adult patients with HER2-positive early breast cancer, metastatic breast cancer and metastatic gastric cancer.

The PK similarity of Tuznue was demonstrated in a 3-arm Phase 1 PK similarity study TROIKA-1 and the efficacy and safety similarity was demonstrated in the pivotal confirmatory Phase 3 TROIKA study.

TROIKA-I, a 3-arm, Phase I, PK similarity study was conducted in healthy male subjects to demonstrate equivalent PK properties of HD201, EU-Herceptin® and US-Herceptin®. Each eligible subject was randomised (1:1:1) to receive a single dose of HD201, EU- or US-Herceptin® as an IV infusion (6 mg/kg) over 90-minutes. The primary objective of the study was to demonstrate the equivalent pharmacokinetic (PK) properties of HD201 EU- and US-Herceptin® following a single IV infusion and the secondary objectives were to assess the safety, tolerability, immunogenicity and additional PK parameters of HD201, EU- and US-Herceptin®. A total of 105 healthy male volunteers, 18 to 55 years of age were randomly assigned to one of the 3 treatment arms (35 in each treatment arm).

TROIKA was a Phase III, randomised, double-blind, parallel group, equivalence, multicentre study conducted in female patients with HER2-positive early breast cancer (EBC), randomised (1:1) to receive chemotherapy with either HD201 or EU-Herceptin® in the neoadjuvant setting. Patients eligible for enrolment in the study were female patients 18 years or older with stage II and stage III unilateral operable early breast cancer. Stratification factors included hormone receptor status, clinical stage of disease, and geographic location. Patients received 8 cycles of HD201 or EU-Herceptin® in combination with chemotherapy (4 cycles of docetaxel IV 75 mg/m^2, followed by 4 cycles of epirubicin IV 75 mg/m^2 and cyclophosphamide IV 500 mg/m^2). After administration of the final neoadjuvant study drug dose, surgery was performed within 3-8 weeks and, patients continued with adjuvant HD201, or EU-Herceptin® monotherapy for 10 additional cycles to complete a total of 1 year of HER2-directed therapy, with a follow up period of 2 years after last dose of study drug.

[redacted]

A total of 625 patients were screened in this study from 19 February 2018 to 21 September 2018. Of the 625 screened patients, 503 were randomised and a total of 502 patients were exposed to study medication, 250 patients to Tuznue and 252 to EU-Herceptin®. Patients received treatment as per protocol, an initial infusion of 8 mg/kg of HD201 or EU-Herceptin® followed by a maintenance infusion of 6 mg/kg every 3 weeks.

TROIKA clinical study exposure data is presented below including safety data for both neoadjuvant and adjuvant treatment phases with HER2-positive early breast cancer patients.

Table 2 Study duration of exposure

Duration of exposure	Tuznue		Herceptin®	
	Patient (n)	Person time (weeks)	Patient (n)	Person time (weeks)
Duration ≤ 12 weeks	5	21.00	5	29.86
12 weeks < Duration ≤ 24 weeks	1	18.00	4	75.86
24 weeks < Duration ≤ 36 weeks	7	182.43	3	91.57
36 weeks < Duration ≤ 48 weeks	9	384.43	4	168.00
48 weeks < Duration ≤ 54 weeks	3	154.71	5	252.43
54 weeks < Duration ≤ 60 weeks	160	9313.14	176	10271.29
60 weeks < Duration ≤ 66 weeks	60	3709.86	49	3034.57
66 weeks > Duration	5	337.57	6	410.00
Total	250	14121.14	252	14333.58

Table 3 Age group (TROIKA)

Age group	Tuznue		Herceptin®	
	Patient (n)	Person time (weeks)	Patient (n)	Person time (weeks)
18 ≤ Age ≤ 64	210	11898.14	212	12155.43
65 ≤ Age ≤ 74	35	1945.86	32	1740.86
75< Age	5	277.14	8	437.29
Total	250	14121.14	252	14333.58

Table 4 Ethnic origin (TROIKA)

Ethnic Origin	Tuznue		Herceptin®	
	Patient (n)	Person time (weeks)	Patient (n)	Person time (weeks)
Caucasian	226	12796.14	228	12991.29
Asian	24	1325.00	24	1342.29
Total	250	14121.14	252	14333.58

6 PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

6.1 SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Important exclusion criteria in phase III clinical study (TROIKA) are provided in Table 5

Table 5 Important Exclusion criteria in phase III clinical study (TROIKA) in the Development Programme

Criterion	Reason for exclusion	Is it to be included as missing information?	Rationale
Bilateral, multicentric or metastatic, breast cancer with exception of supraclavicular nodes	Exclude confounding factors associated with bilateral, multicentric or metastatic breast cancer in order to perform appropriate assessment of IMP	No	Tuznue is indicated for patients presenting HER2-positive metastatic breast cancer. Exclusion from study does not apply to target population
Serious pulmonary illness and other severe acute or chronic medical or psychiatric condition	Treatment with Trastuzumab is contraindicated in patients with severe dyspnoea at rest	No	Use of Tuznue is contraindicated in patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy. Risk of severe dyspnoea is classified as an important identified risk
Serious cardiac illness that would preclude the use of Trastuzumab such as history of documented congestive heart failure, LVEF < 50% angina pectoris requiring anti-anginal medication, evidence of transmural infarction	Patients receiving treatment with trastuzumab are at an increased risk of developing heart failure and cardiac dysfunction. These events have been observed in patients receiving Trastuzumab in	No	Warnings and precautions regarding use of Tuznue in patients with cardiac illness, treatment in such conditions is not recommended. Risk of cardiac dysfunction is classified as an important identified risk

[redacted]

[redacted]

Criterion	Reason for exclusion	Is it to be included as missing information?	Rationale
on ECG, uncontrolled hypertension, clinically significant valvular disease and high-risk uncontrolled arrythmias	monotherapy or in combination with Paclitaxel or Docetaxel		
Known history of active hepatitis B, active hepatitis C or HIV infection (by patient declaration)	Patients with these viral infections may not be able to tolerate myelosuppressive chemotherapy and are at increased risk of infectious complications associated with myelosuppression	No	Exclusion from study does not apply to target population. Assessment of patient fitness for chemotherapy is routine oncology practice
Known hypersensitivity to the IMPs, non-IMPs or any of the ingredients or excipients of the IMPs or non-IMPs or murine proteins	Treatment with Trastuzumab is contraindicated in patients with hypersensitivity to trastuzumab, murine proteins or to any of the excipients	No	Use of Tuznue is contraindicated in patients with hypersensitivity. Risk of hypersensitivity is classified as an important identified risk
Lactating or pregnant women Women of childbearing potential including women who had	Post-marketing practice with Herceptin® revealed cases of foetal renal growth and/or function impairment in association with	No	Women of childbearing potential should prevent pregnancy by using adequate contraceptive methods. Treatment with Tuznue during pregnancy should be

Criterion	Reason for exclusion	Is it to be included as missing information?	Rationale
menopause onset within 2 years prior to randomization	oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving the reference product Herceptin®		avoided during pregnancy unless potential benefit for the mother outweighs potential risk for the foetus. Women should be advised on the possible harm treatment with Tuznue could cause to the foetus

6.2 SIV.2 Limitations to detect adverse reactions in the clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with long latency, or those caused by prolonged or cumulative exposure. The total number of patients exposed to Tuznue in the TROIKA trial is 250 and it is unlikely to detect rare and very rare adverse reactions in study populations included in clinical development programmes. According to CIOMS definition of adverse drug reactions, rare adverse reactions occur with frequency greater than 1 in 1000 and equal or less than 10 000. A much greater number of patients should be exposed to Tuznue to detect rare and idiosyncratic adverse reactions. Such number could only be reached during the post-marketing authorisation period. Moreover, as a biosimilar of Herceptin®, safety profile of the reference product will be similar to Tuznue.

Patients in the TROIKA study have received 18 cycles of treatment during a period of 54 weeks. Adverse drug reactions requiring prolonged or cumulative exposure greater than 54 weeks will not be detected during the clinical programme. A 5-year follow-up of patients treated with reference product Herceptin® has been conducted, and no new safety signals were detected.

6.3 SIV.3 Limitations in respect to populations typically under- represented in clinical trial development programmes

Table 6 Exposure of special populations included or not included in clinical trial development programme

Type of special population	Exposure
Pregnant women	Trastuzumab is not recommended to be administered during pregnancy therefore pregnant women were not included in the clinical development programme.
Breastfeeding women	No available data supports use of Trastuzumab during breastfeeding, potential harm it may cause to the foetus is unknown therefore breastfeeding women were not included in the clinical development programme.
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in clinical development programme

Patients with renal impairment	Not included in clinical development programme
Patients with cardiovascular impairment	Not included in clinical development programme
Patients with respiratory impairment	Not included in clinical development programme
Patients with a disease severity different from the inclusion criteria in the clinical trial population	Not applicable
Immunocompromised patients	Not included in clinical development programme
Population with relevant different ethnic origin	The patients exposed to Tuznue in TROIKA trial were mainly Caucasian (n = 226) and fewer patients from Asian region (n = 24) were included compared to Caucasian patients
Subpopulations carrying known and relevant genetic polymorphisms.	Not applicable
Other	
Male patients	Not included in the clinical development programme
Children	Not included in the clinical development programme
Elderly[3]	The number of elderly patients exposed were 40.

[3] Elderly considered >65 years old.

7 PART II: MODULE SV–POST-AUTHORISATION EXPERIENCE

No sales data available.

8 PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

No data from clinical trials are available, however, use of Tuznue is limited to hospital settings and potential misuse for illegal purposes and/or abuse would not be expected.

9 PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

9.1 SVII.1. Identification of safety concerns in the initial RMP submission

9.2 SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

9.2.1.1 SVII.1.1.1 Identified Risks

Adverse reactions with clinical consequences, even serious, but considered to be acceptable in relation to the severity of the indication treated include the following: asthenia, fatigue, arthralgia, alopecia, diarrhoea, rash, headache, nausea (see descriptions below). All these events are recognized ADRs of trastuzumab and are included in SmPC Section 4.8.

- **Asthenia**
- **Fatigue**

In the TROIKA trial, asthenia was reported in 27.2 % of patients receiving HD201 and 26.2% of patients receiving Herceptin®, fatigue was reported in 24.8% of patients receiving HD201 and 26.6% of patients receiving Herceptin®. In the context of patients suffering from recognized indications for Tuznue: early breast cancer, metastatic breast cancer and/or metastatic gastric cancer, both asthenia and fatigue are usual concerns not representing signs of medication toxicity.

- **Arthralgia**

In the TROIKA trial, arthralgia was reported in 16% of patients receiving HD201 and 12.3% of patients receiving Herceptin®. Although frequent, the clinical impact of the risk on patients is considered acceptable in relation to the severity of the indication treated.

- **Alopecia**

In the TROIKA trial, alopecia was reported in 80.8% of patients receiving HD201 and 79.4% of patients receiving Herceptin®. Although frequent, alopecia is a known risk that does not impact the risk-benefit profile.

- **Diarrhoea**
- **Nausea**
- **Rash**
- **Headache**

Diarrhoea, nausea, rash and headache are identified risks of trastuzumab; however, these risks can be adequately managed through labelling and are not considered important risks.

9.3 SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

9.3.1.1 SVII.1.2.1 Important Identified Risks

Cardiac dysfunction

Risk-benefit impact: Cardiac dysfunction or failure has been commonly reported in clinical trials involving trastuzumab and scientific literature, which is also reflected in the SmPC of Herceptin®. Patient treated with trastuzumab are at increased risk of CHF or asymptomatic cardiac dysfunction and clinical outcomes ranging from mild to fatal have been reported in association with trastuzumab-based therapies. These events have been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on therapy without additional clinical cardiac events. However, caution should be exercised in treating patients with increased cardiac risk, e.g., hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age. Cardiological assessment can be considered.

Cardiotoxicity meets the definition of important safety concern as the risk does require special risk management activities to further minimize them in clinical practice, as the risk associated with cardiotoxicity can be potentially life-threatening.

Infusion-related reactions (IRRs)

Risk-benefit impact: The risk of infusion-related reaction is included in Section 4.8 of Herceptin® SmPC and it is stated that approximately 40 % of patients who are treated with trastuzumab will experience some form of infusion-related reaction. Although events of infusion-related reactions are generally nonserious, in rare cases, these reactions are associated with hypersensitivity reactions culminating in a fatal outcome.

Infusion-related reactions (IRRs) are mostly mild to moderate reactions and have been very commonly reported in clinical trials and scientific literature. IRRs such as shortness of breath, low or high blood pressure, wheezing, or skin rash may occur within 2 to 3 hours of the start of the first infusion and majority of patients experience resolution of symptoms. Other relatively uncommon serious reactions include dyspnoea, hypotension, wheezing, bronchospasm and respiratory distress.

The SmPC for Herceptin® indicates that patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction.

Infusion-related reactions meets the definition of important safety concern as the risk does require special risk management activities to further minimize them in clinical practice, as the risk associated with IRRs can be potentially life-threatening.

Oligohydramnios

Risk-benefit impact: The use of trastuzumab in pregnancy has limited data available, especially regarding effects on human pregnancies. However, oligohydramnios are severe complications, usually associated with abnormal foetal outcomes, such as intrauterine growth retardation, post-maturity syndrome, lung hypoplasia, soft tissue deformities, and foetal distress in labour, and may be fatal. A specific pregnancy follow-up form has been implemented to collect additional maternal and foetal/infant information on all reports of women exposed to trastuzumab and pregnancy must be avoided during and for 7 months after trastuzumab treatment.

Oligohydramnios meets the definition of important safety concern as the risk does require special risk management activities to further minimize them in clinical practice as it is associated with risks to foetal development and therefore may have a significant impact on an individual patient.

9.3.1.2 SVII1.2.2 Missing Information

Safety of 75mg/m^2 vs 100mg/m^2 docetaxel dose

Risk-benefit impact: The consequence of concomitant treatment of Tuznue and docetaxel dose greater than 75 mg/m^2 has not yet been specifically studied. However, according to the SmPC for docetaxel, administration of 100 mg/m^2 in combination with trastuzumab is indicated for the treatment of breast cancer. Undesirable effects relating to haematotoxicity such as neutropenia may be more likely when using greater dose of docetaxel than was used during clinical trials.

Safety of docetaxel 75 mg/m^2 versus 100 mg/m^2 meets the definition of missing information as there is no experience in of using Tuznue with docetaxel doses greater than 75 mg/m^2.

10 SVII.2. New safety concerns and reclassification with a submission of an updated RMP

"Infusion-related reactions (IRRs)" previously classified as important identified risk has been updated as "Administration-Related Reactions" to the list of safety concerns.

"Safety of 75 mg/m2 vs 100 mg/m2 docetaxel dose" previously classified as missing information has been removed from the list of safety concerns.

Reasons for the reclassification/removal to the list of safety concerns:

List of safety concerns for Tuznue has been updated in line with the Reference Medicinal Product (Herceptin) EPAR-RMP (version 24.0, DLP: 24 September 2025) published by EMA on 02-Mar-2026.

11 SVII.3. Details of important identified risks, important potential risks, and missing information

11.1 SVII.3.1. Presentation of important identified risks and important potential risks

11.2 SVII.3.1.1 Important Identified Risks

CARDIAC DYSFUNCTION

Potential mechanisms:

- There may be a feedback loop involving neuregulin and ErbB2 (as a co-receptor) as part of a cell (myocyte) survival pathway.
- Trastuzumab may block or alter cell survival signalling.
- Trastuzumab may down-regulate ErbB2 and thereby prevent cell survival signalling.
- Cardiac physiological stress or damage can be exacerbated by trastuzumab.

Evidence source(s) and strength of evidence:

MBC, First-line HER2-positive

The incidence of symptomatic CHF (grades 3 or 4) for non-trastuzumab containing regimens:

- Without anthracyclines: 0.3% to 1% (Slamon et al 2001, Johnston et al 2009).
- With anthracyclines> 3% to 4.7% (Slamon et al 2001. O'brien et al 2004).

For Trastuzumab containing regimens:

- Without anthracyclines: 2% to 4% (Slamon et al 2001, Seidman 2002).

- With anthracyclines: 16% (Slamon et al 2001).

MBC, Second-line HER2-positive

Based on three lapatinib studies, the incidence of symptomatic CHF (grades 3 or 4) was < 1% for non-trastuzumab containing regimens (Blackwell et al. 2012; Capri et al. 2010; Burstein et al. 2003) In a pooled analysis of 3689 lapatinib patients enrolled in clinical trials, the incidence of symptomatic cardiac toxicity by prior treatment was:

- Anthracyclines: 0.5%
- Trastuzumab: 0.1%
- Neither anthracyclines nor trastuzumab: 0.1%

EBC, HER2- positive

Based on data from three randomised controlled trials the incidence of symptomatic CHF (grades 3 or 4) was:

- For trastuzumab containing regimens: 0.8% to 3.8% (Costa et al 2010)
- For non-trastuzumab containing regimens: 0% to 0.9% (Costa et al 2010)

Advanced Gastric cancer

A randomised trial reported 1.1% incidence of decreased LVEF (unspecified criteria) among HER2-positive patients with advanced gastric cancer not treated with trastuzumab (Van Cutsem et al 2009).

The evidence of the above-mentioned risk is derived from Herceptin® RMP. Tuznue is a biosimilar of Herceptin®, therefore the strength of the evidence is consistent with the strength of evidence included in Herceptin® RMP.

Characterization of the risk:

<table>
<tr><th>Identified Risk</th><th colspan="3">CARDIAC DYSFUNCTION</th></tr>
<tr><td rowspan="5">Frequency with 95% CI</td><td colspan="3">Incidence of Cardiac dysfunctions from Phase III study (entire treatment period)</td></tr>
<tr><td></td><td>Tuznue (N = 250)</td><td>Herceptin® (N = 252)</td></tr>
<tr><td>Subjects with treatment-related* TEAEs, N1 (%) [95% CI]</td><td>55 (22.0%) [17.0; 27.7]</td><td>57 (22.6%) [17.6; 28.3]</td></tr>
<tr><td>Number of treatment-related* TEAEs, n</td><td>83</td><td>79</td></tr>
<tr><td>Exposure (PY)</td><td>270.6</td><td>274.7</td></tr>
<tr><td>TEAE Rate/ 100 PY [95% CI]</td><td>30.67 [24.43; 38.02]</td><td>28.76 [22.77; 35.84]</td></tr>
</table>

CI = Confidence Interval, N = Number of subjects within the treatment group, N1 = Number of subjects with an event, n = number of events, PY = Patient-Year, TEAE = Treatment Emergent Adverse Event
% = Subject incidence = N1/N x 100
*Possibly, probably, or definitely related to study treatment

Incidence of Cardiac dysfunctions from Phase III study, by type of Cardiac dysfunction (entire treatment period)

MedDRA (V21.0) PT	Tuznue (N = 250) N1 (%)	Herceptin® (N = 252) N1 (%)
Any treatment-related* TEAEs	55 (22.0%)	57 (22.6%)
Ejection fraction decreased	19 (7.6%)	17 (6.7%)
Electrocardiogram abnormal	7 (2.8%)	3 (1.2%)
Electrocardiogram repolarisation abnormality	5 (2.0%)	5 (2.0%)
Dyspnoea	6 (2.4%)	3 (1.2%)
Tachycardia	4 (1.6%)	5 (2.0%)
Sinus Tachycardia	2 (0.8%)	6 (2.4%)
Bundle Branch block right	3 (1.2%)	4 (1.6%)
Left ventricular dysfunction	5 (2.0%)	2 (0.8%)
Oedema peripheral	1 (0.4%)	4 (1.6%)
Dilation atrial	1 (0.4%)	3 (1.2%)
Left ventricular hypertrophy	2 (0.8%)	2 (0.8%)
Palpitations	2 (0.8%)	2 (0.8%)
Cardiomyopathy	2 (0.8%)	1 (0.4%)
Defect conduction intraventricular	1 (0.4%)	2 (0.8%)
Left atrial dilation	2 (0.8%)	1 (0.4%)
Sinus bradycardia	3 (1.2%)	0 (0.0%)
Supraventricular extrasystoles	0 (0.0%)	3 (1.2%)
Ventricular dyssynchrony	2 (0.8%)	1 (0.4%)
Atrial enlargement	1 (0.4%)	1 (0.4%)
Left atrial enlargement	1 (0.4%)	1 (0.4%)
Left ventricular dilatation	1 (0.4%)	1 (0.4%)
Arrhythmia	1 (0.4%)	0 (0.0%)
Arrhythmia supraventricular	1 (0.4%)	0 (0.0%)
Atrial tachycardia	0 (0.0%)	1 (0.4%)
Atrioventricular block	1 (0.4%)	0 (0.0%)
Atrioventricular block first degree	0 (0.0%)	1 (0.4%)
Bradycardia	1 (0.4%)	0 (0.0%)

Cardiac aneurysm	0 (0.0%)	1 (0.4%)
Cardiac failure	1 (0.4%)	0 (0.0%)
Cardiac failure chronic	1 (0.4%)	0 (0.0%)
Cardiac septal hypertrophy	0 (0.0%)	1 (0.4%)
Cardiomegaly	1 (0.4%)	0 (0.0%)
Chest pain	1 (0.4%)	0 (0.0%)
Cytotoxic cardiomyopathy	0 (0.0%)	1 (0.4%)
Right atrial dilatation	0 (0.0%)	1 (0.4%)
Right atrial enlargement	0 (0.0%)	1 (0.4%)
Sinus arrhythmia	0 (0.0%)0	1 (0.4%)
Supraventricular tachycardia	0 (0.0%)	1 (0.4%)
Ventricular extrasystoles	1 (0.4%)	0 (0.0%)
Wandering pacemaker	0 (0.0%)	1 (0.4%)

N = Number of subjects within the treatment group, N1 = Number of subjects with an event; PT = Preferred term
% = Subject incidence = N1/N x 100
*Possibly, probably, or definitely related to study treatment

Incidence of Cardiac dysfunctions from post-treatment follow-up period; (PTAS), by type of Cardiac dysfunction

MedDRA (V21.0) PT	**Tuznue (N = 234) N 1 (%)**	**Herceptin® N = 242 N1 (%)**
Any treatment-related* PTAE	10 (4.3%)	12 (5.0%)
Ejection fraction decreased	2 (0.9%)	2 (0.8%)
Electrocardiogram abnormal	2 (0.9%)	2 (0.8%)
Bundle branch block right	2 (0.9%)	1 (0.4%)
Electrocardiogram repolarization abnormality	0 (0.0%)	3 (1.2%)
Left ventricular dysfunction	2 (0.9%)	1 (0.4%)
Atrial enlargement	0 (0.0%)	2 (0.8%)
Supraventricular extrasystoles	0 (0.0%)	2 (0.8%)
Cardiac aneurysm	0 (0.0%)	1 (0.4%)
Cardiomegaly	0 (0.0%)	1 (0.4%)
Defect conduction intraventricular	0 (0.0%)	1 (0.4%)
Left atrial dilatation	0 (0.0%)	1 (0.4%)
Left atrial enlargement	1 (0.4%)	0 (0.0%)
Left ventricular hypertrophy	1 (0.4%)	0 (0.0%)

	Metabolic cardiomyopathy: 1 (0.4%) / 0 (0.0%) Sinus arrhythmia: 1 (0.4%) / 0 (0.0%) Sinus bradycardia: 0 (0.0%) / 1 (0.4%) Ventricular dyssynchrony: 1 (0.4%) / 0 (0.0%)
Seriousness / outcomes	**Seriousness and outcomes of Cardiac dysfunctions from Phase III study (entire treatment period)**

	Tuznue (N = 250) N1 (%), n	**Herceptin® (N = 252) N1 (%), n**
Serious treatment-related* TEAEs	1 (0.4%), 1	1 (0.4%), 1
Outcomes		
Recovered/ resolved	0	0
Recovered/ resolved with sequelae	1 (0.4%), 1	1 (0.4%), 1
Did not recover	0	0
Fatal	0	0

N = Number of subjects within the treatment group, N1 = Number of subjects with an event, n = number of events, TEAE = Treatment Emergent Adverse Event
% = Subject incidence = N1/N x 100
*Possibly, probably, or definitely related to study treatment

Overall, there were two serious TEAEs related to cardiac dysfunction in patients treated with Tuznue and Herceptin®. Of the two events reported, there was one event of cardiac failure (chronic) in one patient treated with HD201, and one event of cytotoxic cardiomyopathy in one patient treated with Herceptin®. Both patients who experienced serious cardiac dysfunction recovered from the event with sequelae.

Severity

Severity of Cardiac dysfunctions from Phase III study (entire treatment period)

Severity of treatment-related* TEAEs	**Tuznue (N = 250) N1 (%)**	**Herceptin® (N = 252) N1 (%)**
Grade 1 (Mild)	34 (13.6%)	32 (12.7%)
Grade 2 (Moderate)	16 (6.4%)	24 (9.5%)
Grade 3 (Severe)	5 (2.0%)	1 (0.4%)
Grade 4 (Life-threatening)	0	0
Grade 5 (Fatal)	0	0

N = Number of subjects within the treatment group, N1 = Number of subjects with an event
% = Subject incidence = N1/N x 100
For incidence of subjects, the maximal severity of any cardiac dysfunction is reported
*Possibly, probably, or definitely related to study treatment

Risk factors and risk groups:

In a systematic review and meta-analysis 27 clinical factors were identified to be associated with risk of incident Heart failure (HF) in 15 observational studies in unselected community populations which followed 456,850 participants over 4-29 years. The strongest independent associations for incident HF were coronary artery disease (HR=2.94; 95% CI 1.36 to 6.33), diabetes mellitus (HR=2.00; 95% CI 1.68 to 2.38), age (HR (per 10 years)=l.80; 95% CI 1.13 to 2.87) followed by hypertension (HR=l.61; 95% CI 1.33 to 1.96), smoking (HR=l.60; 95% CI 1.45 to 1.77), male gender (HR= 1.52; 95% CI 1.24 to 1.87) and body mass index (HR (per 5 kg/m2)= 1.15; 95% CI 1.06 to 1.25). Atrial fibrillation (HR= 1.88; 95% CI 1.60 to 2.21), left ventricular hypertrophy (HR=2.46; 95% CI 1.71 to 3.53) and valvular heart disease (HR=l.74; 95% CI 1.07 to 2.84) were also strongly associated with incident HF but were not examined in sufficient papers to provide pooled hazard estimates

Preventability:

Patients treated with trastuzumab are at increased risk for developing CHF (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death. In addition, caution should be exercised in treating patients with increased cardiac risk, e.g., hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age.

All candidates for treatment with trastuzumab, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. A careful risk-benefit assessment should be made before deciding to treat with trastuzumab.

Trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment based on population pharmacokinetic analysis of all available data. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction.

If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients, cardiac function should be monitored during treatment (e.g., every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g., every 6-8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of trastuzumab therapy has been seen.

The safety of continuation or resumption of trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. If LVEF percentage drops ≥10 points from baseline and to below 50%, treatment should be suspended, and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic CHF has developed, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Impact on risk-benefit of the product:

If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued on therapy without additional clinical cardiac events.

Furthermore, as a biosimilar of Herceptin®, Tuznue has shown to have comparable safety profile to Herceptin® and the benefit-risk balance of Herceptin® is positive for the identified risk of cardiac dysfunctions.

Public health impact:

The safety concern of cardiac dysfunction does not have a potential public health impact.

ADMINISTRATION-RELATED REACTIONS

Potential mechanism:

The potential mechanism of administration-related reactions, which is also described hypersensitivity reaction has not been clearly established. However, Calogiuri et al. 2009 hypothesize that such reactions (to monoclonal antibodies in general) are attributable to Beta-type reactions: immediate and delayed hypersensitivity; Gamma type reactions: over-reactions or depression of the immune functions like the immunodeficit, autoimmune or allergic phenomena; but that other mechanisms such as specific release of cytokines, might also be involved.

Evidence source(s) and strength of evidence:

Not applicable.

Characterization of the risk:

Identified Risk: ADMINISTRATION-RELATED REACTIONS

Frequency with 95% CI

Incidence of Administration-Related Reactions from Phase III study (entire treatment period)

	Tuznue (N = 250)	Herceptin® (N = 252)
Subjects with treatment-related* TEAEs, N1 (%) [95% CI]	48 (19.2%) [14.5; 24.6]	43 (17.1%) [12.6; 22.3]
Number of treatment-related* TEAEs, n	99	114
Exposure (PY)	270.6	274.7
TEAE Rate/100 PY [95% CI]	36.58 [29.73; 44.54]	41.50 [34.23; 49.85]

CI = Confidence Interval, N = Number of subjects within the treatment group, N1 = Number of subjects with an event, n = number of events, PY = Patient-Year, TEAE = Treatment Emergent Adverse Event
% = Subject incidence = N1/N x 100
*Possibly, probably, or definitely related to study treatment

Incidence of Administration-Related Reactions from Phase III study (entire treatment period), by type of Administration-Related Reactions

MedDRA (V21.0) PT	Tuznue (N = 250) N1 (%)	Herceptin® (N = 252) N1 (%)
Any treatment-related* TEAEs	48 (19.2%)	43 (17.1%)
Rash	17 (6.8%)	9 (3.6%)
Nausea	7 (2.8%)	17 (6.7%)
Headache	5 (2.0%)	7 (2.8%)

Identified Risk	ADMINISTRATION-RELATED REACTIONS

Dyspnoea	6 (2.4%)	3 (1.2%)
Tachycardia	4 (1.6%)	5 (2.0%)
Rash maculo-papular	4 (1.6%)	3 (1.2%)
Vomiting	2 (0.8%)	5 (2.0%)
Erythema	1 (0.4%)	5 (2.0%)
Conjunctivitis	3 (1.2%)	2 (0.8%)
Pruritus	2 (0.8%)	3 (1.2%)
Stomatitis	1 (0.4%)	3 (1.2%)
Infusion related reaction	1 (0.4%)	2 (0.8%)
Pyrexia	2 (0.8%)	1 (0.4%)
Dermatitis	2 (0.8%)	0 (0.0%)
Dermatitis allergic	1 (0.4%)	1 (0.4%)
Flushing	1 (0.4%)	1 (0.4%)
Hand dermatitis	1 (0.4%)	1 (0.4%)
Bronchospasm	1 (0.4%)	0 (0.0%)
Chills	0 (0.0%)	1 (0.4%)
Conjunctivitis allergic	0 (0.0%)	1 (0.4%)
Dermatitis acneiform	0 (0.0%)	1 (0.4%)
Drug eruption	1 (0.4%)	0 (0.0%)
Eczema	1 (0.4%)	0 (0.0%)
Face oedema	0 (0.0%)	1 (0.4%)
Hypersensitivity	0 (0.0%)	1 (0.4%)
Rash erythematous	0 (0.0%)	1 (0.4%)
Rash pruritic	0 (0.0%)	1 (0.4%)
Skin exfoliation	0 (0.0%)	1 (0.4%)
Swelling face	0 (0.0%)	1 (0.4%)
Urticaria	0 (0.0%)	1 (0.4%)

N = Number of subjects within the treatment group, N1 = Number of subjects with an event, PT = Preferred term
% = Subject incidence = N1/N x 100
*Possibly, probably, or definitely related to study treatment

Incidence of Administration-Related Reactions from post-treatment follow-up period; (PTAS) by type of Administration-Related Reactions

MedDRA (V21.0) PT	Tuznue N = 234 N1 (%)	Herceptin® N = 242 N1 (%)
Any treatment-related* TEAEs	0 (0%)	1 (0.4%)
Dyspnoea	0 (0.0%)	0 (0.0%)
Headache	0 (0.0%)	0 (0.0%)
Pruritis	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	1 (0.4%)
Rash macular	0 (0.0%)	0 (0.0%)

Seriousness/ outcomes

Seriousness and outcomes of Administration-Related Reactions from Phase III study (entire treatment period)

	Tuznue (N = 250) N1 (%), n	Herceptin® (N = 252) N1 (%), n
Serious treatment-related* TEAEs	0	1 (0.4%), 1
Outcomes		
Recovered/ resolved	0	1 (0.4%), 1

Identified Risk	**ADMINISTRATION-RELATED REACTIONS**

Recovered/ resolved with sequelae	0	0
Did not recover	0	0
Fatal	0	0

N = Number of subjects within the treatment group, N1 = Number of subjects with an event, n = number of events, TEAE = Treatment Emergent Adverse Event
% = Subject incidence = N1/N x 100
*Possibly, probably, or definitely related to study treatment

There was one serious TEAE related to infusion site reactions and hypersensitivity. One patient treated with Herceptin® experienced hypersensitivity, in which the patient recovered with medical treatment.

Severity

Severity of Administration-Related Reactions from Phase III study (entire treatment period)

Severity of treatment-related* TEAEs	Tuznue (N = 250) N1 (%)	Herceptin® (N = 252) N1 (%)
Grade 1 (Mild)	29 (11.6%)	21 (8.3%)
Grade 2 (Moderate)	19 (7.6%)	21 (8.3%)
Grade 3 (Severe)	0	1 (0.4%)
Grade 4 (Life-threatening)	0	0
Grade 5 (Fatal)	0	0

N = Number of subjects within the treatment group, N1 = Number of subjects with an event
% = Subject incidence = N1/N x 100
For incidence of subjects, the maximal severity of any infusion related reaction is reported
*Possibly, probably, or definitely related to study treatment

Risk factors and risk groups:

There are currently no reliable predictors of patients who may or may not be susceptible to administration-related reactions to trastuzumab. However, patients who are experiencing dyspnoea at rest due to complications of advanced malignancy or co-morbidities, may be at greater risk of severe reactions including fatal outcomes.

Preventability:

Pre-medication may be used to reduce risk of occurrence of these events. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued, or the rate of infusion slowed, and the patient should be monitored until resolution of all observed symptoms. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Most patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal

outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

Impact on risk-benefit of the product:

Administration-Related Reactions are mostly mild to moderate reactions; they can be minimized by the preventive measures outlined above. Furthermore, as a biosimilar of Herceptin®, Tuznue has shown to have comparable safety profile to Herceptin® and the benefit-risk balance of Herceptin® is positive for the identified risk of IRRs.

Public health impact:

The safety concern of administration-related reactions does not have a potential public health impact as monitoring and treatment of administration-related reactions forms part of routine oncology clinical practice.

OLIGOHYDRAMNIOS

Potential mechanism:

Bader et al. hypothesized that Trastuzumab may have a direct effect on the function of HER2 receptors in the foetal kidney, leading to reduce cell proliferation and restriction of foetal kidney function in vivo. This hypothesis was confirmed in Pharmacovigilance surveillance (Bader et al 2007).

Evidence source(s) and strength of evidence:

Stoll et al reviewed 225,669 consecutive pregnancies and births and observed that 0.99/1000 pregnancies were complicated by oligohydramnios. However, since there is no accepted standard definition of oligohydramnios, incidence has been estimated as being between 0.4 % and 1 % of pregnancies.

Characterization of the risk

Frequency:

No cases were reported in clinical trials related to the Oligohydramnios.

Severity and nature of risk:

No cases were reported in clinical trials related to the Oligohydramnios.

Background incidence/prevalence:

Oligohydramnios is a complication which occurs in approximately 4.5% of all pregnancies, severe forms manifest in 0.7% of pregnancies.

Risk factors and risk groups:

There are no reliable indicators of patients who may or may not be at risk.

Preventability:

Women of childbearing potential should be advised to use effective contraception during treatment with trastuzumab and for 7 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with trastuzumab, or if a patient becomes pregnant while receiving trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable.

Impact on risk-benefit of the product:

The risk of oligohydramnios is adequately described in the current labelling documents with appropriate risk minimisation measures. A specific pregnancy follow-up form has been implemented to collect additional maternal and foetal/infant information on all reports of pregnant women exposed to trastuzumab.

As a biosimilar of Herceptin®, Tuznue has shown to have comparable safety profile to Herceptin® and the benefit-risk balance of Herceptin® is positive for the identified risk of oligohydramnios.

Public health impact:

The percentage of pregnancies complicated by oligohydramnios in patients exposed to trastuzumab is higher than that seen in the population unexposed to trastuzumab; however, this does not take into account previous or concurrent chemotherapy or radiotherapy and given the small number of pregnancies reported in the trastuzumab exposed population, there is only very limited, if at all, potential public health impact (Herceptin® RMP version 21.0).

11.3 SVII.3.2. Presentation of the missing information

Not applicable.

12 PART II: MODULE SVIII – SUMMARY OF SAFETY CONCERNS

Table 7 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Cardiac dysfunction • Administration-Related Reactions • Oligohydramnios
Important potential risks	• None
Important Missing information	• None

13 PART III: PHARMACOVIGILANCE PLAN

13.1 III.1: Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concerns mentioned in the "Module SVIII - Summary of the safety concerns".

13.2 III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are foreseen for Tuznue.

13.3 III.3 Summary table of additional pharmacovigilance activities

No additional pharmacovigilance activities are foreseen for Tuznue.

14 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Tuznue has been developed as a biosimilar of Herceptin®. The clinical studies performed during clinical development programme of Tuznue have demonstrated bioequivalence and biosimilarity of Tuznue to Herceptin®. As currently, no post-authorization efficacy studies are required by competent authorities, none are planned for Tuznue.

15 PART V: RISK MINIMISATION MEASURES

15.1 V.1 ROUTINE RISK MINIMISATION MEASURES

Table 8 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified risk - Cardiac dysfunction	**Routine risk communication:** SmPC Section 4.2: Posology and Method of Administration SmPC Section 4.4 Special warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for monitoring to identify patients who develop cardiac dysfunction are included in Section 4.4 of SmPC. Clinical recommendation for managing LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.2 of SmPC. **Other risk minimisation measures beyond the Product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine.
Important identified risk - Administration-Related Reactions.	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Guidance on observation period after administration has been adequately captured in Section 4.2 of SmPC. **Other risk minimisation measures beyond the Product information:** Pack size: Each carton contains one vial.

Safety concern	Routine risk minimisation activities
	Legal Status: Tuznue is a prescription only medicine.
Important Identified risk - Oligohydramnios	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy, and lactation **Routine risk minimisation activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Tuznue or if a patient becomes pregnant while receiving Tuznue or within 7 months following last dose of Tuznue, close monitoring by a multidisciplinary team is desirable. This has been adequately covered in Section 4.6 of SmPC. **Other risk minimisation measures beyond the Product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine.

15.2 V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described above are sufficient to manage the safety concern of the medicinal product.

15.3 V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 9 – Summary table of pharmacovigilance activities and risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Important Identified risk - Cardiac dysfunction	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for monitoring to identify patients who develop cardiac dysfunction are included in Section 4.4 of SmPC.	**Routine pharmacovigilance activities beyond adverse events reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	Clinical recommendation for managing LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.2 of SmPC. **Other risk minimisation measures beyond the Product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine. **Additional risk minimisation measures**: None	
Important identified risk - Administration-Related Reactions	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Guidance on observation period after administration has been adequately captured in Section 4.2 of SmPC. **Other risk minimisation measures beyond the Product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse events reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important Identified risk - Oligohydramnios	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy, and lactation **Routine risk minimisation activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Tuznue or if a patient becomes pregnant while receiving	**Routine pharmacovigilance activities beyond adverse events reporting and signal detection:** None. **Additional pharmacovigilance activities:** None

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	Tuznue or within 7 months following last dose of Tuznue, close monitoring by a multidisciplinary team is desirable. This has been adequately captured in Section 4.6 of SmPC. **Other risk minimisation measures beyond the Product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine. **Additional risk minimisation measures:** None	

16 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Tuznue 150 mg and 420 mg powder for concentrate for solution for infusion (Trastuzumab)

This is a summary of the Risk Management Plan (RMP) for Tuznue 150 mg and 420 mg powder for concentrate for solution for infusion (Trastuzumab). Hereinafter, referred to as Tuznue. The RMP details important risks of Tuznue, how these risks can be minimized, and how more information will be obtained about Tuznue's risks and uncertainties (missing information).

Tuznue's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tuznue should be used.

This summary of the RMP for Tuznue should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Tuznue's RMP.

16.1 I. The Medicine and What It Is Used for

Tuznue is authorized for the treatment of adult patients with HER2-positive metastatic breast cancer, early breast cancer and metastatic gastric cancer (see SmPC for the full indication). It contains trastuzumab as the active substance and it is given by intravenous route.

Further information about the evaluation of Tuznue’s benefits can be found in Tuznue’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage https://www.ema.europa.eu/en/medicines/human/EPAR/tuznue

16.2 II. Risk Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Tuznue, together with measures to minimize such risks and the proposed studies for learning more about Tuznue’s risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.

- Important advice on the medicine's packaging; The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures form *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

16.3 II.A List of Important Risks and Missing Information

Important risks of Tuznue are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tuznue. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

Table 10 – Important risks and missing information

List of important risks and missing information	
Important identified risks	• Cardiac dysfunction • Administration-Related Reactions • Oligohydramnios
Important potential risks	• None
Important Missing information	• None

16.4 II.B Summary of Important Risks

Table 11 – Summary of Important Risks

Important Identified Risk- Cardiac dysfunction	
Evidence for linking the risk to the medicine	**MBC, First-line HER2-positive** The incidence of symptomatic CHF (National Cancer Institute-Common Toxicity Criteria [NCI-CTC] Grades 3 or 4) for Non-trastuzumab containing regimens: • Without anthracyclines: 0.3 % to 1 % • With anthracyclines: 3 % to 4.7 % Trastuzumab containing regimens: • Without anthracyclines: 2 % to 4 % • With anthracyclines: 16 % **MBC, Second-line HER2-positive** Based on three lapatinib studies, the incidence of symptomatic CHF (Grades 3 or 4) was< 1 % for non-trastuzumab containing regimens. In a pooled analysis of 3,689 lapatinib patients enrolled in clinical trials, the incidence of symptomatic cardiac toxicity by prior treatment was: • Anthracyclines: 0.5 %. • Trastuzumab: 0.1 %. • Neither anthracyclines nor trastuzumab: 0.1 %. **EBC, HER2-positive** Based on data from three randomised controlled trials the incidence of symptomatic CHF (grades 3 or 4) was: - For trastuzumab containing regimens: 0.8% to 3.8% - For non-trastuzumab containing regimens: 0% to 0.9% **Advanced Gastric Cancer** A recent randomised trial reported a 1.1 % incidence of decreased LVEF (unspecified criteria) among HER2-positive patients with advanced gastric cancer not treated with trastuzumab.

Risk factors and risk groups	Patient treated with trastuzumab are at increased risk of CHF or asymptomatic cardiac dysfunction. Caution should be exercised in treating patients with increased cardiac risk, e.g., hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age, smoking and body mass index.
Risk minimisation measures	**Routine risk communication:** SmPC Section 4.2 Posology and method of administration SmPC Section 4.4 Special warnings and Precautions for Use SmPC Section 4.8 Undesirable effects. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for monitoring to identify patients who develop cardiac dysfunction are included in Section 4.4 of SmPC. Clinical recommendation for managing LVEF decreases that are associated with the cardiac dysfunction has been adequately covered in Section 4.2 of SmPC. **Other risk minimisation measures beyond the Product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine. **Additional risk minimisation measures:** None
Important Identified Risk - Administration-Related Reactions	
Evidence for linking the risk to the medicine.	Not applicable

Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not be susceptible to administration-related reactions to trastuzumab. However, patients who are experiencing dyspnoea at rest due to complications of advanced malignancy or co-morbidities, may be at greater risk of severe reactions including fatal outcomes.
Risk minimisation measures	**Routine risk communication:** SmPC Section 4.2 Posology and Method of Administration SmPC Section 4.4 Special warnings and Precautions for Use SmPC Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Guidance on observation period after administration has been adequately captured in Section 4.2 of SmPC. **Other risk minimisation measures beyond the Product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine. **Additional risk minimisation measures:** None
Important Identified Risk - Oligohydramnios	
Evidence for linking the risk to the medicine.	Stoll et al reviewed 225,669 consecutive pregnancies and births and observed that 0.99/1000 pregnancies were complicated by oligohydramnios. However, since there is no accepted standard definition of oligohydramnios, incidence has been estimated as being between 0.4 % and 1 % of pregnancies.
Risk factors and risk groups	There are no reliable indicators of patients who may or may not be at risk.

Risk minimisation measures	**Routine risk communication**: SmPC Section 4.6 Fertility, pregnancy, and lactation. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** If a pregnant woman is treated with Tuznue or if a patient becomes pregnant while receiving Tuznue or within 7 months following last dose of Tuznue, close monitoring by a multidisciplinary team is desirable. This has been adequately captured in Section 4.6 of SmPC. **Other risk minimisation measures beyond the Product information:** Pack size: Each carton contains one vial. Legal Status: Tuznue is a prescription only medicine. **Additional risk minimisation measures:** None

16.5 II.C Post-Authorisation Development Plan

16.5.1.1 II.C.1 Studies which are conditions of the marketing authorization.

There are no studies which are conditions of the marketing authorization or specific obligation of Tuznue.

16.5.1.2 II.C.2 Other studies in post-authorization development plan.

There are no studies required for Tuznue.