Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

TRASTUZUMAB 150mg (Lyophilized powder in vial)
TRASTUZUMAB 440mg (Lyophilized powder in vial)

2. Qualitative and quantitative composition

Each vial contains: trastuzumab 150mg
Each vial contains: trastuzumab 440mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Lyophilized Powder for concentrate for solution for intravenous infusion.

4. Clinical particulars

4.1 Therapeutic indications

Breast Cancer Metastatic breast cancer Trastuzumab is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer: 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 metastatic breast cancer, not previously treated with Trastuzumab. Early breast cancer Trastuzumab is indicated for the treatment of adult patients with HER2 positive early breast cancer: - 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 Trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter. Trastuzumab should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. Metastatic Gastric Cancer Trastuzumab 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-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease. Trastuzumab should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used.

4.1 Posology and method of administration

HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1). Trastuzumab treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4), and should be administered by a healthcare professional only.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed. trastuzumab intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only.

Switching treatment between trastuzuma bintravenous and trastuzumab subcutaneous formulations and vice versa, using the three-weekly (q3w) dosing regimen, was investigated in study MO22982 (see section 4.8).

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is trastuzumab and not another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan).

Posology

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 trastuzumab is 4 mg/kg body weight. The recommended weekly maintenance dose of trastuzumab is 2 mg/kg body weight, beginning one week after the loading dose.

Administration in combination with paclitaxel or docetaxel

In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of Trastuzumab (for dose, see the Summary of Product Characteristics (SmPC) for paclitaxel or docetaxel) 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).

Early breast cancer

Three-weekly and weekly schedule

As a three-weekly regimen the recommended initial loading dose of trastuzumab is 8 mg/kg body weight. The recommended maintenance dose of trastuzumab 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.

See section 5.1 for chemotherapy combination dosing.

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 Trastuzumab until progression of disease.

Patients with EBC should be treated with trastuzumab for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended (see section 5.1).

Dose reduction

No reductions in the dose of trastuzumab were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time. Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

If left ventricular ejection fraction (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 has declined further, or if symptomatic congestive heart failure (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.

Missed doses

If the patient has missed a dose of Trastuzumab by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of Trastuzumab by more than one week, a re-loading dose of trastuzumab should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent trastuzumab maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively.

Special populations

Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Paediatric population

There is no relevant use of Trastuzumab in the paediatric population.

Method of administration

Trastuzumab loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus. trastuzumab intravenous infusion should be administered by a

health-care provider prepared to manage anaphylaxis and an emergency kit should be available. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms (see sections 4.4 and 4.8). Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

For instructions on reconstitution of trastuzumab intravenous formulation before administration, see section 6.6.

4.2 Contraindications

Hypersensitivity to trastuzumab, murine proteins, or to any of the

excipients listed in section 6.1

Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.3 Special warnings and precautions for use

Raceability

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

HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures (see section 5.1).

Currently no data from clinical trials are available on re-treatment of patients with previous exposure to Trastuzumab in the adjuvant setting**.**

Cardiac dysfunction

General considerations

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 Herceptin 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 (see section 4.8). 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 (see section 5.2). 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.

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.

Metastatic breast cancer

trastuzumab and anthracyclines should not be given concurrently in combination in the MBC setting.

Patients with MBC who have previously received anthracyclines are also at risk of cardiac dysfunction with Trastuzumab treatment, although the risk is lower than with concurrent use of Trastuzumab and anthracyclines.

Early breast cancer

For patients with EBC, 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. In patients who receive anthracycline-containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of trastuzumab, or longer if a continuous decrease of LVEF is observed.

Patients with history of myocardial infarction (MI), angina pectoris requiring medical treatment, history of or existing CHF (NYHA Class II – IV), LVEF of < 55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant EBC pivotal trials with Herceptin and therefore treatment cannot be recommended in such patients.

Adjuvant treatment

Trastuzumab and anthracyclines should not be given concurrently in combination in the adjuvant treatment setting.

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when trastuzumab was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. In one of the 3 pivotal studies conducted in which a median follow-up of 5.5 years was available (BCIRG006) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed in patients who were administered Trastuzumab concurrently with a taxane following anthracycline therapy up to 2.37% compared to approximately 1% in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and Herceptin).

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low LVEF (<55%) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal

products. In patients receiving Trastuzumab after completion of adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Trastuzumab and a body mass index (BMI) >25 kg/m^2.

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment Trastuzumab should be used concurrently with anthracyclines only in chemotherapy-naive patients and only with low-dose anthracycline regimens i.e. maximum cumulative doses of doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2.

If patients have been treated concurrently with a full course of low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials (MO16432 and BO22227).

In the pivotal trial MO16432, Trastuzumab was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2).

The incidence of symptomatic cardiac dysfunction was 1.7% in the drug arm.

The pivotal trial BO22227 was designed to demonstrate non-inferiority of treatment with trastuzumab subcutaneous formulation versus treatment with trastuzumab intravenous formulation based on co-primary PK and efficacy endpoints (trastuzumab C_{trough} at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively) (See Section 5.1. of Trastuzumab subcutaneous formulation SmPC). In the pivotal trial BO22227, Trastuzumab was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m^2); at a median follow-up exceeding 70 months, the incidence of cardiac failure/congestive cardiac failure was 0.3% in the Trastuzumab intravenous arm.

Clinical experience is limited in patients above 65 years of age.

Infusion-related reactions (IRRs) and hypersensitivity

Serious IRRs to trastuzumab infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported (see section 4.8). 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 (see section 4.2). These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of 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 (see section 4.3).

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the Trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Pulmonary events

pulmonary events have been reported with the use of Trastuzumab in the post-marketing setting (see section 4.8). These events have occasionally been fatal. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. These events may occur as part of an infusion-related reaction or with a delayed onset. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Trastuzumab (see section 4.3). Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

4.4 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. Clinically significant interactions between trastuzumab and the concomitant medicinal products used in clinical trials have not been observed.

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents

Pharmacokinetic data from studies BO15935 and M77004 in women with HER2-positive MBC suggested that exposure to paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) was not altered in the presence of trastuzumab (8 mg/kg or 4 mg/kg IV loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w IV, respectively).

However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite was unclear.

Data from study JP16003, a single-arm study of trastuzumab (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m2 IV) in Japanese women with HER2- positive MBC, suggested that concomitant administration of Trastuzumab had no effect on the single dose pharmacokinetics of docetaxel. Study JP19959 was a sub study of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer to study the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab. The results of this sub study suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Trastuzumab.

Pharmacokinetic data from Study H4613g/GO01305 in patients with metastatic or locally advanced inoperable HER2-positive cancer suggested that trastuzumab had no impact on the PK of carboplatin.

Effect of antineoplastic agents on trastuzumab pharmacokinetics

By comparison of simulated serum trastuzumab concentrations after monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2- positive MBC (study JP16003) no evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetics of trastuzumab was found.

Comparison of PK results from two Phase II studies (BO15935 and M77004) and one Phase III study (H0648g) in which patients were treated concomitantly with Trastuzumab and paclitaxel and two Phase II studies in which trastuzumab was administered as monotherapy (W016229 and MO16982), in women with HER2-positive MBC indicates that individual and mean trastuzumab trough serum concentrations varied within and across studies but there was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab. Comparison of trastuzumab PK data from Study M77004 in which

women with HER2-positive MBC were treated concomitantly with Trastuzumab, paclitaxel and doxorubicin to trastuzumab PK data in studies where the drug was administered as monotherapy (H0649g) or in combination with anthracycline plus cyclophosphamide or paclitaxel (Study H0648g), suggested no effect of doxorubicin and paclitaxel on the pharmacokinetics of trastuzumab.

Pharmacokinetic data from Study H4613g/GO01305 suggested that carboplatin had no impact on the PK of trastuzumab.

The administration of concomitant anastrozole did not appear to influence the pharmacokinetics of trastuzumab.

4.5 Fertility, pregnancy, and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment with Trastuzumab and for 7 months after treatment has concluded (see section 5.2).

Pregnancy

Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab intravenous formulation and have revealed no evidence of impaired fertility or harm to the foetus. Placental transfer of trastuzumab during the early (days 20–50 of gestation) and late (days 120–150 of gestation) foetal development period was observed. It is not known whether Trastuzumab can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, Trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving trastuzumab. 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 the drug or within 7 months following the last dose of Trastuzumab, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

A study conducted in Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Trastuzumab intravenous formulation from days 120 to 150 of pregnancy demonstrated that trastuzumab is secreted in the milk postpartum. The exposure to trastuzumab in utero and the presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known

whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during Trastuzumab therapy and for 7 months after the last dose.

Fertility

There is no fertility data available.

4.6 Effects on ability to drive and use machines.

Trastuzumab has a minor influence on the ability to drive or use machines (see section 4.8). Dizziness and somnolence may occur during treatment with Trastuzumab (see section 4.8). Patients experiencing infusion-related symptoms (see section 4.4) should be advised not to drive and use machines until symptoms abate.

4.7 Undesirable effects

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

The adverse reactions that have been reported in association with the use of Trastuzumab alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting in are listed by system organ class and frequency. Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to

System organ class	Frequency	Adverse reaction
Infections and infestations	Very common	Infection, Nasopharyngitis
	Common	Neutropenic sepsis, Cystitis, Herpes zoster Influenza, Sinusitis, Skin infection, Rhinitis, Upper respiratory tract infection, Urinary tract infection, Erysipelas, Cellulitis, Pharyngitis
	Uncommon	Sepsis
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Not known	Malignant neoplasm progression, Neoplasm progression
Blood and lymphatic system disorders	Very common	Febrile neutropenia, Anaemia, Neutropenia, White blood cell count decreased/leukopenia, Thrombocytopenia

	Not known	Hypoprothrombinemia, Immune thrombocytopenia
Hypoprothrombinemia, Immune thrombocytopenia	Common	**Hypersensitivity**
	Not known	+Anaphylactic reaction, +Anaphylactic shock
Metabolism and nutrition disorders	Very common	Weight decreased/Weight loss, Anorexia
	Not known	Hyperkalaemia
Psychiatric disorders	**Very common**	**Insomnia**
	Common	Anxiety, Depression, Thinking abnormal
Nervous system disorders	Very common	Tremor, Dizziness, Headache, Paraesthesia, Dysgeusia
	Common	Peripheral neuropathy, Hypertonia, Ataxia Somnolence
	Rare	Paresis
	Not known	Brain oedema
Eye disorders	Very common	Conjunctivitis, Lacrimation increased
	Common	Dry eye
	Not known	Papilloedema, Retinal haemorrhage
Ear and labyrinth disorders		**Deafness**
Cardiac disorders	**Very common**	Blood pressure decreased, 1 Blood pressure increased, 1 Heart beat irregular, 1 Palpitation, 1 Cardiac flutter, Ejection fraction decreased*
	Common	+Cardiac failure (congestive), +1 Supraventricular tachyarrhythmia, Cardiomyopathy
	Uncommon	Pericardial effusion
	Not known	Cardiogenic shock, Pericarditis, Bradycardia Gallop rhythm present
Vascular disorders	Very common	**Hot flush**
	Common	1 Hypotension, Vasodilatation
Respiratory, thoracic and mediastinal disorders	Very common	Wheezing, +Dyspnoea, Cough, Epistaxis Rhinorrhoea
	Common	Pneumonia, Asthma, Lung disorder, +Pleural effusion
	Rare	Pneumonitis
	Not known	Pulmonary fibrosis, +Respiratory distress +Respiratory failure, +Lung infiltration, +Acute pulmonary oedema, +acute respiratory distress syndrome, +Bronchospasm, +Hypoxia, +Oxygen saturation decreased,

		Laryngeal oedema, Orthopnoea, Pulmonary oedema, Interstitial lung disease
Gastrointestinal disorders	Very common	Diarrhoea, Vomiting, Nausea, 1 Lip swelling Abdominal pain, Dyspepsia, Constipation Stomatitis
	Common	Haemorrhoids, Dry mouth
Hepatobiliary disorders	Common	Hepatocellular injury, Hepatitis, Liver tenderness
	Rare	Jaundice
	Not known	Hepatic failure
Skin and subcutaneous tissue disorders	Very common	Erythema, Rash, 1 Swelling face, Alopecia Nail disorder, Palmar-plantar erythrodysaesthesia syndrome
	Uncommon	Urticaria
	Common	Acne, Dry skin, Ecchymosis, Hyperhydrosis Maculopapular rash, Pruritus, Onychoclasis Dermatitis
	Not known	Angioedema
Musculoskeletal and connective tissue disorders	Very common	**Arthralgia**
	common	1Muscle tightness Myalgia
	Uncommon	Arthritis, Back pain, Bone pain, Muscle spasms Neck Pain, Pain in extremity
Renal and urinary disorders	Common	**Renal disorder**
	Not known	Glomerulonephritis membranous, Glomerulonephropathy, Renal failure
Pregnancy, puerperium and perinatal conditions	Not known	Oligohydramnios, Renal hypoplasia, Pulmonary hypoplasia
Reproductive system and breast disorders	Common	Breast inflammation/mastitis
General disorders and administration site conditions	Very common	Asthenia, Chest pain, Chills, Fatigue, Influenza-like symptoms, Infusion related reaction, Pain, Pyrexia, Mucosal inflammation, Peripheral oedema
	Common	Malaise, Oedema
Injury, poisoning and procedural complications C	Common	**Confusion**

+ Denotes adverse reactions that have been reported in association with a fatal outcome.
1 Denotes adverse reactions that are reported largely in association with Infusion-related reactions. Specific percentages for these are not available.
* Observed with combination therapy following anthracyclines and combined with taxanes

4.8 Overdose

There is no experience with overdose in human clinical trials. Single doses of Trastuzumab alone greater than 10 mg/kg have not been

administered in the clinical trials. Doses up to this level were well tolerated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Cardiac Electrophysiology The effects of Trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumours. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum Trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumours.

Pharmacokinetic properties

The pharmacokinetics of Trastuzumab was evaluated in a pooled population pharmacokinetic (PK) model analysis of 1,582 subjects with primarily breast cancer and metastatic gastric cancer (MGC) receiving intravenous Trastuzumab. Total Trastuzumab clearance increases with decreasing concentrations due to parallel linear and non-linear elimination pathways.

Although the average Trastuzumab exposure was higher following the first cycle in breast cancer patients receiving the three-weekly schedule compared to the weekly schedule of Trastuzumab, the average steady-state exposure was essentially the same at both dosages. The average Trastuzumab exposure following the first cycle and at steady state as well as the time to steady state was higher in breast cancer patients compared to MGC patients at the same dosage; however, the reason for this exposure difference is unknown. Additional predicted Trastuzumab exposure and PK parameters following the first Trastuzumab cycle and at steady state exposure are described in below tables respectively. Population PK based simulations indicate that following discontinuation of Trastuzumab, concentrations in at least 95% of breast cancer and MGC patients will decrease to approximately 3% of the population predicted steady-state trough serum concentration (approximately 97% washout) by 7 months

Population Predicted Cycle 1 PK Exposures (Median with 5th – 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC0-21days (µg.day/mL)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	29.4 (5.8 - 59.5)	178 (117 - 291)	1373 (736 - 2245)
	MGC	274	23.1 (6.1 - 50.3)	132 (84.2 - 225)	1109 (588 - 1938)
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	37.7 (12.3 - 70.9)	88.3 (58 - 144)	1066 (586 - 1754)

Population Predicted Steady State PK Exposures (Median with 5th - 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	$C_{min,ss}$ [a] (µg/mL)	$C_{max,ss}$ [b] (µg/mL)	$AUC_{ss,0\text{-}21\ days}$ (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	47.4 (5 -115)	179 (107 - 309)	1794 (673 -3618)	12	0.173 -0.283
	MGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 -2875)	9	0.189 -0.337

a Steady-state trough serum concentration of Trastuzumab
b Maximum steady-state serum concentration of Trastuzumab

5.2 Preclinical safety data

Not applicable

5.3. Pharmaceutical particulars

5.4 List of excipients

L-histidine hydrochloride monohydrate

L-histidine

α,α-trehalose dihydrate

polysorbate 20

5.3 Incompatibilities

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

Do not dilute with glucose solutions since these cause aggregation of the protein.

5.4 Shelf life

36 months

5.5 Special precautions for storage:

Stored at 2°C to 8°C prior to reconstitution and protected from light. Keep out of reach of children. Vials should not be used beyond the expiration date stamped on the vial, the reconstitution drug solution should be used immediately and any unused portion must be discarded. DO NOT FREEZE THE DRUG THAT HAS BEEN RECONSTITUTED. The drug solution for infusion diluted in bags/bottles containing 0.9% Sodium Chloride for injection, USP, may be stored 2°C to 8°C (36°F to 46°F) for up to 24hours prior to use.

Shelf-life of the reconstituted solution 440 mg/150 mg (Multi-dose use vials)

Reconstituted solution made with bacteriostatic water for injection for 440 mg/150 mg vials of Transtuzumab, as supplied, are stable for 28 days when refrigerated at 2°C to 8°C. The reconstituted solution contains preservative and is therefore suitable for multiple uses. Any remaining reconstituted solution should be discarded after 28 days.

Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product The infusion solution (0.9% sodium chloride solution) containing the reconstituted product is physically and chemically stable for 48 hours (do not store above 30°C). From a microbiological point of view, the Trastuzumab infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibilities of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

5.6 Nature and contents of container

150 mg is supplied in 15 mL USP type 1 glass vial closed with a elastomeric Chlorobutyl rubber stopper and sealed with 20 mm flip off seal. The 150 mg vial is provided with 10 mL bacteriostatic water for injection (containing 1.1 % Benzyl alcohol as preservative) for

reconstitution. 7.2 mL BWFI to be used for reconstitution. 440mg is supplied in 50 mL USP type 1 glass vial closed with a elastomeric Chlorobutyl rubber stopper and sealed with 20 mm flip off seal. The 440 mg vial is provided with 20 mL bacteriostatic water for injection (1 vials of 20 mL each, containing 1.1 % Benzyl alcohol as preservative) for reconstitution. 20 mL BWFI to be used for reconstitution. Each carton contains one vial and BWFI.

5.7 Special precautions for disposal and other handling:

Appropriate aseptic technique should be used. Use of other reconstitution solvents should be avoided. The reconstitution details are given in the table below. Reconstitution Details of 150mg and 440 mg Vial (Multi-dose Use)

Type of Vial (multi-dose use)	RECONSTITUTION	TRASTUZUMAB MG/ML	PH
150mg	7.2mL of BWFI (Containing 1.1% benzyl alcohol)	21	6.0
440mg	20mL of BWFI (Containing 1.1% benzyl alcohol)	21	6.0

BWFI: Bacteriostatic Water for Injection.

6 Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Hetero Biopharma Limited,

Sy. No. 458 (part),

TSIIC-Formulation SEZ,

Polepally Village, Jadcherla Mandal

Mahaboobnagar District– 509 301,

Telangana State, India.

Manufacturing site address:

Unit-III
M/s. Hetero Biopharma Limited,
Sy. No. 458 (Part),
TSIIC-Formulation SEZ,
Polepally (Village),
Jadcherla (Mandal)
Mahaboobnagar (District) – 509 301,
Telangana State, India.
Tel: +91-8542-227500
Email id: contact.hbl@heterodrugs.com

7 Marketing authorization number
CTD10748

8 Date of first registration
21/05/2023

9 **Date of revision of the text:**
13/09/2023

10 **Dosimetry:**
Not Applicable

11 **Instructions for Preparation of Radiopharmaceuticals:**
Not Applicable