SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

- Trastuzumab (Hertraz™) for Injection – 150 mg/Vial (Multiple Use Vial)
- Trastuzumab (Hertraz™) for Injection – 440 mg/Vial (Multiple Use Vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

150 mg multi-dose vials and 440 mg multi-dose vial containing powder for concentrate for solution for intravenous infusion. Reconstituted Hertraz™ concentrate contains 21 mg/mL of trastuzumab, a humanized IgG1 monoclonal antibody expressed in Chinese hamster ovary cells.

For a full list of excipients, (see section 6.1).

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for intravenous infusion.
White to pale yellow lyophilized powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer

Metastatic breast cancer:

Hertraz™ 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.

Early breast cancer*:*

Hertraz™ 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) (see section 5.1).

- 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 Hertraz™ therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Hertraz™ 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 (see sections 4.4 and 5.1).

***Metastatic gastric cancer**:*

Hertraz™ 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 gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Hertraz™ should only be used in patients with metastatic gastric cancer (MGC) 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 (see sections 4.4 and 5.1).

4.2 Posology and method of administration

HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1). Hertraz™ 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 is being administered to the patient, as prescribed. Hertraz™ should be administered via an intravenous infusion only and is not intended for subcutaneous administration.

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

As per the published literature on another trastuzumab product, in the pivotal trials, 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

As per the published literature on another trastuzumab product, in the pivotal trial from day 1 trastuzumab and anastrozole were administered. There were no restrictions on the relative timing of trastuzumab and anastrozole at administration.

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

As per the published literature on another trastuzumab product, 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 ejection fraction (EF) 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 misses 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 given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses (weekly regimen: 2 mg/ kg; three-weekly regimen: 6 mg/kg respectively) should then be given according to the previous schedule.

If the patient misses a dose of trastuzumab by more than one week, a re-loading dose of trastuzumab should be given over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg). Subsequent trastuzumab maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should then be given (weekly regimen: every week; three-weekly regimen every 3 weeks) from that point.

Special populations

Dedicated pharmacokinetic studies in older people and those with renal or hepatic impairment have not been carried out. As per the published literature on another trastuzumab product, 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

Hertraz™ loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus. Only a healthcare provider should administer Hertraz™ intravenous infusion Preparations 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.

4.3 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.

4.4 Special warnings and precautions for use

HER2 testing must be performed in a specialized laboratory having trained and qualified personnel which can ensure adequate validation of the testing procedures (see section 5.1).

The below narrated data is from published literature

Cardiac dysfunction

General considerations

As per the published literature, 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 (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 on another Trastuzumab product. 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 27 weeks after stopping trastuzumab. In case, 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.

During trastuzumab therapy if symptomatic cardiac failure develops, 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 trastuzumab 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.

As per the published literature on another trastuzumab product, an increase in the incidence of symptomatic and asymptomatic cardiac events was observed in patients with EBC when trastuzumab 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 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 trastuzumab).

As per the published literature on another trastuzumab product, 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.

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

As per the published literature on another trastuzumab product, experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials.

Trastuzumab was administered concurrently with neoadjuvant chemotherapy that contained three cycles of an doxorubicin (cumulative dose 180 mg/m^2) The incidence of symptomatic cardiac dysfunction was low in the Trastuzumab arms (up to 1.7 %).

In patients above 65 years of age clinical experience is limited.

Infusion-related reactions, (IRRs) and hypersensitivity

As per the published literature, serious IRRs to trastuzumab infusion that have been reported infrequently include dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema (see section 4.8). Premedication 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

As per the published literature on another trastuzumab product, with the use of trastuzumab in the post-marketing setting severe pulmonary events have been reported (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.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. As per the published literature on another trastuzumab product, clinically significant interactions with the concomitant medication used in clinical trials have not been observed

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents
As per published literature on another trastuzumab product, Pharmacokinetic data from studies 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.

As per published literature on another trastuzumab product data, 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. As per published literature on another trastuzumab product, a clinical study 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.

As per published literature on another trastuzumab product, pharmacokinetic data from Study 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 trastuzumab monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2- positive MBC no evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetics of trastuzumab was found.

As per published literature on another trastuzumab product, comparison of PK results from two Phase II studies and one Phase III study in which patients were treated concomitantly with trastuzumab and paclitaxel and two Phase II studies in which trastuzumab was administered as monotherapy, 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 a study in which women with HER2-positive MBC were treated concomitantly with trastuzumab, paclitaxel and doxorubicin to trastuzumab PK data in studies where trastuzumab was administered as monotherapy or in combination with anthracycline plus cyclophosphamide or paclitaxel, suggested no effect of doxorubicin and paclitaxel on the pharmacokinetics of trastuzumab.

Pharmacokinetic data 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.

4.6 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 at least 7 months after treatment has concluded.

Pregnancy

As per the published literature on another trastuzumab product, 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.

As per the published literature on another trastuzumab product, 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 trastuzumab or within 7 months following the last dose of trastuzumab, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

As per the published literature on another trastuzumab product, a study conducted in lactating cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Trastuzumab intravenous formulation demonstrated that trastuzumab is secreted in the milk. 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 in public literature.

4.7 Effects on ability to drive and use machines

As per the published literature, Trastuzumab has no or negligible influence on the ability to drive or use machines. However, patients experiencing infusion-related symptoms (see section 4.4) should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile:

As per the published literature, amongst the most serious and/or common adverse reactions reported in trastuzumab usage to date are cardiac dysfunction, infusion-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

Tabulated list of adverse reactions:

In this section, the following categories of frequency have been used:

- very common (≥1/10),
- common (≥1/100 to <1/10),
- uncommon (≥1/1,000 to <1/100),
- rare (≥1/10,000 to <1/1,000),
- very rare (<1/10,000),
- not known (cannot be estimated from the available data).

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

As per the published literature, presented in **Table 1** are adverse reactions that have been reported in association with the use of intravenous trastuzumab alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting.

All the terms included are based on the highest percentage seen in pivotal clinical trials.

Table 1: Undesirable Effects

System organ class	Adverse reaction	Frequency
Infections and infestations	Infection	Very common
	Nasopharyngitis	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Herpes zoster	Common
	Influenza	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Erysipelas	Common
	Cellulitis	Common
	Pharyngitis	Common
	Sepsis	Uncommon
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile neutropenia	Very common
	Anaemia	Very common
	Neutropenia	Very common
	White blood cell count decreased/leukopenia	Very common
	Thrombocytopenia	Very common
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Immune system disorders	Hypersensitivity	Common
	[+]Anaphylactic reaction	Not known
	[+]Anaphylactic shock	Not known
Metabolism and nutrition disorders	Weight decreased/Weight loss	Very common
	Anorexia	Very common
	Hyperkalaemia	Not known
Psychiatric disorders	Insomnia	Very common
	Anxiety	Common
	Depression	Common
	Thinking abnormal	Common

System organ class	Adverse reaction	Frequency
Nervous system disorders	[1]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common
	Dysgeusia	Very common
	Peripheral neuropathy	Common
	Hypertonia	Common
	Somnolence	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and labyrinth disorders	Deafness	Uncommon
Cardiac disorders	1 Blood pressure decreased	Very common
	1 Blood pressure increased	Very common
	1 Heart beat irregular	Very common
	1Palpitation	Very common
	1Cardiac flutter	Very common
	Ejection fraction decreased*	Very common
	+Cardiac failure (congestive)	Common
	+1Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis	Not known
	Bradycardia	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very common
	+1 Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	+1Wheezing	Very common
	+Dyspnoea	Very common
	Cough	Very common
	Epistaxis	Very common
	Rhinorrhoea	Very common
	+Pneumonia	Common
	Asthma	Common
	Lung disorder	Common
	+Pleural effusion	Common
	Pneumonitis	Rare
	+Pulmonary fibrosis	Not known
	+Respiratory distress	Not known
	+Respiratory failure	Not known

System organ class	Adverse reaction	Frequency
	+Lung infiltration	Not known
	+Acute pulmonary oedema	Not known
	+Acute respiratory distress syndrome	Not known
	+Bronchospasm	Not known
	+Hypoxia	Not known
	+Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known
	Pulmonary oedema	Not known
	Interstitial lung disease	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Pancreatitis	Common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular injury	Common
	Hepatitis	Common
	Liver tenderness	Common
	Jaundice	Rare
	Hepatic failure	Not known
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	[1] Swelling face	Very common
	Alopecia	Very common
	Nail disorder	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Acne	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	[1]Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common

System organ class	Adverse reaction	Frequency
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck Pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Mucosal inflammation	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Contusion	Common

+ 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

Description of selected adverse reactions

Cardiac dysfunction

As per the published literature, congestive heart failure, NYHA class II - IV is a common adverse reaction associated with the use of trastuzumab and has been associated with a fatal outcome (see section 4.4). Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with trastuzumab (see section 4.4).

As per the published literature on another trastuzumab product, in 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (specifically symptomatic Congestive Heart Failure) was similar in patients who were administered chemotherapy alone (i.e. did not receive trastuzumab) and in

patients who were administered trastuzumab sequentially to a taxane (0.3-0.4 %). The rate was highest in patients who were administered trastuzumab concurrently with a taxane (2.0 %). In the neoadjuvant setting, the experience of concurrent administration of trastuzumab and low dose anthracycline regimen is limited (see section 4.4).

When trastuzumab was administered after completion of adjuvant chemotherapy NYHA class III-IV heart failure was observed in 0.6 % of patients in the one-year arm after a median follow-up of 12 months. After a median follow-up of 8 years the incidence of severe CHF (NYHA III & IV) following 1 year of trastuzumab therapy (combined analysis of the two trastuzumab treatment arms) was 0.8 %, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6 %.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50 % after the event) was evident for 71.4 % of trastuzumab-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5 % of trastuzumab-treated patients. Approximately 17% of cardiac related events occurred after completion of trastuzumab.

As per the published literature on another trastuzumab product, in the pivotal metastatic trials of intravenous trastuzumab, the incidence of cardiac dysfunction varied between 9 % and 12 % when it was combined with paclitaxel compared with 1 % – 4 % for paclitaxel alone. For monotherapy, the rate was 6 % – 9 %. The highest rate of cardiac dysfunction was seen in patients receiving trastuzumab concurrently with anthracycline/cyclophosphamide (27 %), significantly higher than for anthracycline/cyclophosphamide alone (7 % – 10 %). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2 % in patients receiving trastuzumab and docetaxel, compared with 0 % in patients receiving docetaxel alone. Most of the patients (79 %) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF.

Infusion reactions, allergic-like reactions and hypersensitivity

As per the published literature, it is estimated that approximately 40 % of patients who are treated with trastuzumab will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity (NCI-CTC grading system) and tend to occur earlier in treatment, i.e. during infusions one, two and three and lessen in frequency in subsequent infusions. Reactions include chills, fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache (see section 4.4). The rate of infusion-related reactions of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy.

Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of trastuzumab (see section 4.4) and have been associated with a fatal outcome.

Anaphylactoid reactions have been observed in isolated cases.

Haematotoxicity

As per the published literature, febrile neutropenia occurred very commonly. Commonly occurring adverse reactions included anemia, leukopenia, thrombocytopenia and neutropenia. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Pulmonary events

As per the published literature, severe pulmonary adverse reactions occur in association with the use of trastuzumab and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency (see section 4.4).

Immunogenicity

According to the published literature, in the neoadjuvant-adjuvant EBC treatment setting, 8.1 % (24/296) of patients treated with trastuzumab intravenous developed antibodies against trastuzumab (regardless of antibody presence at baseline).

Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 24 trastuzumab intravenous patients.

The clinical relevance of these antibodies is not known; nevertheless, the pharmacokinetics, efficacy (determined by pathological Complete Response [pCR]) and safety determined by occurrence of administration related reactions (ARRs) of trastuzumab intravenous did not appear to be adversely affected by these antibodies.

There are no immunogenicity data available for trastuzumab in gastric cancer.

Change of treatment between the formulations of Trastuzumab intravenous and Trastuzumab subcutaneous and vice versa

According to the published literature, switching between the trastuzumab intravenous and trastuzumab subcutaneous formulation with a primary objective to evaluate patient preference for either intravenous or the subcutaneous route of trastuzumab administration. In this trial, 2 cohorts (one using subcutaneous formulation in vial and one using subcutaneous formulation in administration system) were investigated using a 2-arm, cross-over design with 488 patients being randomized to one of two different three-weekly trastuzumab treatment sequences (IV [Cycles 1-4]→ SC [Cycles 5-8], or SC [Cycles 1-4]→ IV [Cycles 5-8]). Patients were either naïve to trastuzumab IV treatment (20.3%) or pre-exposed to trastuzumab IV (79.7%). For the sequence IV→SC (SC r vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre-switching (Cycles 1-4) and post-switching (Cycles 5-8) as 53.8% vs. 56.4%, respectively; for the sequence SC→IV (SC vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre- and post-switching as 65.4% vs. 48.7%, respectively. Pre-switching rates (Cycles 1-4) for serious adverse events, grade 3 adverse events and treatment discontinuations due to adverse events were low (<5%) and similar to post-switching rates (Cycles 5- 8). No grade 4 or grade 5 adverse events were reported.

Details of risk minimization measures that are consistent with the EU risk management plan are presented in the section warnings and precautions.

4.9 Overdose

As per the published literature, there is no experience with overdose in human clinical trials. As reported in published literature on another trastuzumab product, 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

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

Trastuzumab is a recombinant humanized IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2).

As per the published literature, in 20 %-30 % of primary breast cancers overexpression of HER2 is observed. Studies of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8 % to 34.0 % for IHC and 7.1 % to 42.6 % for FISH. Studies also indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples.

Mechanism of action

As per the published literature, trastuzumab has a tendency to bind 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 generally prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, in both *in vitro* animal assays, trastuzumab has been shown to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, it is known that trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). As per the published literature, *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.

Detection of HER2 overexpression or HER2 gene amplification

Detection of HER2 overexpression or HER2 gene amplification in breast cancer

Trastuzumab should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. HER2

overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks (see section 4.4). HER2 gene amplification should be detected using fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) of fixed tumour blocks (see section 4.4). Patients are generally eligible for trastuzumab treatment if they show strong HER2 overexpression as described by a 3+ score by IHC or a positive FISH or CISH result.

To ensure accurate and reproducible results, the testing must be performed in a specialized laboratory, which can ensure validation of the testing procedures.

The recommended scoring system to evaluate the IHC staining patterns is as stated in **Table 2**:

Table 2: Recommended Scoring System to Evaluate the IHC Staining Patterns in Breast Cancer

Score	Staining pattern	HER2 overexpression
0	No staining is observed or membrane staining is observed in < 10 % of the tumour cells	Negative
1+	A faint/barely perceptible membrane staining is detected in > 10 % of the tumour cells. The cells are only stained in part of their membrane.	Negative
2+	A weak to moderate complete membrane staining is detected in > 10 % of the tumour cells.	Equivocal
3+	Strong complete membrane staining is detected in > 10 % of the tumour cells.	Positive

As per the published literature, FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2, or if there are more than 4 copies of the HER2 gene per tumour cell if no chromosome 17 control is used.

As per the published literature, CISH is considered positive if there are more than 5 copies of the HER2 gene per nucleus in greater than 50 % of tumour cells.
For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH and CISH assays. Official recommendations on HER2 testing may also apply.

For any other method that may be used for the assessment of HER2 protein or gene expression, the analyses should only be performed by laboratories that provide adequate state-of-the-art performance of validated methods. Such methods must clearly be precise and accurate enough to demonstrate overexpression of HER2 and must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) overexpression of HER2.

Detection of HER2 over expression or HER2 gene amplification in gastric cancer

Only an accurate and validated assay should be used to detect HER2 over expression or HER2 gene amplification. IHC is generally recommended as the first testing modality and in cases where HER2 gene amplification status is also required, either a silver-enhanced *in situ* hybridization (SISH) or a FISH technique must be applied. SISH technology is however, recommended to allow for the parallel evaluation of tumor histology and morphology. HER2 testing must be performed in a laboratory staffed by trained personnel/analysts to ensure validation of testing procedures and the generation of accurate and reproducible results. Full

instructions on assay performance and results interpretation should be taken from the product information leaflet provided with the HER2 testing assays used.

As per the published literature on another trastuzumab product, HER2 positive were defined as patients whose tumours were either IHC3+ or FISH positive and thus included in the trial. Based on the clinical trial results, the beneficial effects were limited to patients with the highest level of HER2 protein overexpression, defined by a 3+ score by IHC, or a 2+ score by IHC and a positive FISH result.

As per the published literature on another trastuzumab product, in a method comparison study for the detection of HER2 gene amplification in gastric cancer patients a high degree of concordance (>95 %) was observed for SISH and FISH techniques.

HER2 over expression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumor blocks; HER2 gene amplification should be detected using *in situ* hybridization using either SISH or FISH on fixed tumor blocks.

The recommended scoring system to evaluate the IHC staining patterns is as stated in **Table 3**:

Table 3: Recommended Scoring System to Evaluate the IHC Staining Patterns (as per published literature)

Score	**Surgical specimen – staining pattern**	**Biopsy specimen – staining pattern**	**HER2 Overexpression assessment**
0	No reactivity or membranous reactivity in < 10 % of tumour cells	No reactivity or membranous reactivity in any tumour cell	Negative
1+	Faint ⁄ barely perceptible membranous reactivity in ≥ 10 % of tumour cells; cells are reactive only in part of their membrane	Tumour cell cluster with a faint ⁄ barely perceptible membranous reactivity irrespective of percentage of tumour cells stained	Negative
2+	Weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10 % of tumour cells	Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥ 10 % of tumour cells	Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained	Positive

In general, SISH or FISH is considered positive if the ratio of the HER2 gene copy number per tumour cell to the chromosome 17 copy number is greater than or equal to 2.

Clinical efficacy and safety

Metastatic breast cancer

Trastuzumab has generally been used in clinical trials as monotherapy for patients with Metastatic Breast Cancer (MBC) who have tumours that overexpress HER2 and who have also failed one or more chemotherapy regimens for their metastatic disease (trastuzumab alone).

As per the published literature on another trastuzumab product, trastuzumab has also been used in combination with paclitaxel or docetaxel for the treatment of patients who have not received

chemotherapy for their metastatic disease. Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m^2 infused over 3 hours) with or without trastuzumab. In the pivotal trial of docetaxel (100 mg/m^2 infused over 1 hour) with or without trastuzumab, 60 % of the patients had received prior anthracycline-based adjuvant chemotherapy. Patients were treated with trastuzumab until progression of disease.

As per the published literature, the efficacy of trastuzumab in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been studied. However, trastuzumab plus docetaxel was efficacious in patients whether or not they had received prior adjuvant anthracyclines.

As per the published literature, the test method for HER2 overexpression used to determine eligibility of patients in the pivotal trastuzumab monotherapy and trastuzumab plus paclitaxel clinical trials employed immunohistochemical staining for HER2 of fixed material from breast tumors using the murine monoclonal antibodies CB11 and 4D5. These tissues were fixed in formalin or Bouin's fixative. This investigative clinical trial assay performed in a central laboratory utilized a 0 to 3+ scale. Patients classified as staining 2+ or 3+ were included, while those staining 0 or 1+ were excluded. Greater than 70 % of patients enrolled exhibited 3+ overexpression. The data suggest that beneficial effects were greater among those patients with higher levels of overexpression of HER2 (3+).

As per the published literature on another trastuzumab product, the main test method used to determine HER2 positivity in the pivotal trial of docetaxel, with or without trastuzumab, was immunohistochemistry. A minority of patients was tested using fluorescence *in-situ* hybridization (FISH). In this trial, 87 % of patients entered had disease that was IHC3+, and 95 % of patients entered had disease that was IHC3+ and/or FISH-positive.

Weekly dosing in metastatic breast cancer

The efficacy results from the monotherapy and combination therapy studies as per the published literature are summarized in **Table 4**:

Table 4: Efficacy Results from the Monotherapy and Combination Therapy Studies

Parameter	**Monotherapy**	**Combination Therapy**			
	Another trastuzumab product N=172 (IHC3+ patient subset)	**Another trastuzumab product plus paclitaxel[2] N=68** (IHC3+ patient subset)	**Paclitaxel N=77**	**Another trastuzumab product plus docetaxel N=92** (Full analysis set [intent-to-treat], 24 months' results)	**Docetaxel N=94**
Response rate (95 %CI)	18 % (13 - 25)	49 % (36 - 61)	17 % (9 - 27)	61 % (50-71)	34 % (25-45)
Median duration of response (months) (95 %CI)	9.1 (5.6-10.3)	8.3 (7.3-8.8)	4.6 (3.7-7.4)	11.7 (9.3 – 15.0)	5.7 (4.6-7.6)
Median Time to Progression	3.2 (2.6-3.5)	7.1 (6.2-12.0)	3.0 (2.0-4.4)	11.7 (9.2-13.5)	6.1 (5.4-7.2)

(months) (95 %CI)					
Median Survival (months) (95 %CI)	16.4 (12.3-ne[1])	24.8 (18.6-33.7)	17.9 (11.2-23.8)	31.2 (27.3-40.8)	22.74 (19.1-30.8)
1. "ne" indicates that it could not be estimated or it was not yet reached.					

Combination treatment with Trastuzumab and anastrozole

As per the published literature on another trastuzumab product, trastuzumab has been studied in combination with anastrozole for first line treatment of MBC in HER2 overexpressing, hormone-receptor (i.e. estrogen-receptor (ER) and/or progesterone-receptor (PR)) positive postmenopausal patients. Progression free survival was doubled in the trastuzumab plus anastrozole arm compared to anastrozole (4.8 months versus 2.4 months). For the other parameters the improvements seen for the combination were for overall response (16.5 % versus 6.7 %); clinical benefit rate (42.7 % versus 27.9 %); time to progression (4.8 months versus 2.4 months). For time to response and duration of response no difference could be recorded between the arms. The median overall survival was extended by 4.6 months for patients in the combination arm. The difference was not statistically significant, however more than half of the patients in the anastrozole alone arm crossed over to a trastuzumab containing regimen after progression of disease.

Three -weekly dosing in metastatic breast cancer

The efficacy results from the non-comparative monotherapy and combination therapy studies as per the published literature are summarized in **Table 5**:

Table 5: Efficacy Results from the Non-Comparative Monotherapy and Combination Therapy Studies

Parameter	**Monotherapy**		**Combination Therapy**	
	Another trastuzumab product N=105 (loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule)	**Another trastuzumab product N=72** (loading dose 6 mg/kg weekly x 3; followed by 6 mg/kg 3-weekly schedule)	**Another trastuzumab product plus paclitaxel N=32**	**Another trastuzumab product plus docetaxel N=110**
Response rate (95 %CI)	24 % (15 - 35)	27 % (14 - 43)	59 % (41-76)	73 % (63-81)
Median duration of response (months) (range)	10.1 (2.8-35.6)	7.9 (2.1-18.8)	10.5 (1.8-21)	13.4 (2.1-55.1)
Median Time to progression (months) (95 %CI)	3.4 (2.8-4.1)	7.7 (4.2-8.3)	12.2 (6.2-ne)	13.6 (11-16)
Median Survival (months) (95 %CI)	ne[1]	ne	ne	47.3 (32-ne)
1. "ne" indicates that it could not be estimated or it was not yet reached.				

Sites of progression

As per the published literature on another trastuzumab product, the frequency of progression in the liver was significantly reduced in patients treated with the combination of trastuzumab and paclitaxel, compared to paclitaxel alone (21.8 % versus 45.7 %; p=0.004). More patients treated with trastuzumab and paclitaxel progressed in the central nervous system than those treated with paclitaxel alone (12.6 % versus 6.5 %; p=0.377).

Early breast cancer (adjuvant setting)

Early breast cancer is defined as non-metastatic primary invasive carcinoma of the breast. In the adjuvant setting, trastuzumab was investigated in 4 large multicenter, randomized, trials.

- As per the published literature on another trastuzumab product, study was designed to compare one and two years of three-weekly trastuzumab treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). Comparison of two years versus one year trastuzumab treatment was performed additionally. Patients assigned to receive trastuzumab were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years.

- As per the published literature on another trastuzumab product, that comprised of joint analysis to investigate the clinical utility of combining trastuzumab treatment with paclitaxel following AC chemotherapy, along with adding trastuzumab sequentially to AC→P chemotherapy in patients with HER2 positive EBC following surgery.

- As per the published literature on another trastuzumab product, a study was designed to investigate combining trastuzumab treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2 positive EBC following surgery.

As per the published literature on another trastuzumab product, Early breast cancer in one of the trial was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative if tumors at least 1 cm in diameter.

As per the published literature on another trastuzumab product, EBC was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node positive or HER2 positive and lymph node negative with high risk features (tumor size > 1 cm and ER negative or tumor size > 2 cm, regardless of hormonal status).

As per the published literature on another trastuzumab product, EBC was defined as either lymph node positive or high risk node negative patients with no (pN0) lymph node involvement, and at least 1 of the following factors:

- tumor size greater than 2 cm,
- estrogen receptor and
- progesterone receptor negative,
- histological and/or nuclear grade 2-3, or age < 35 years).

As per the published literature on another trastuzumab product, the efficacy results following 12 months* and 8 years** median follow-up are summarized in **Table 6**:

Table 6: Efficacy Results

Parameter	Median follow-up 12 months*		Median follow-up 8 years**	
	Observation N=1693	Another trastuzumab product 1 Year N = 1693	Observation N= 1697***	Another trastuzumab product 1 Year N = 1702***
Disease-free survival				
- No. patients with event	219 (12.9 %)	127 (7.5 %)	570 (33.6 %)	471 (27.7 %)
- No. patients without event	1474 (87.1 %)	1566 (92.5 %)	1127 (66.4 %)	1231 (72.3 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.54		0.76	
Recurrence-free survival				
- No. patients with event	208 (12.3 %)	113 (6.7 %)	506 (29.8 %)	399 (23.4 %)
- No. patients without event	1485 (87.7 %)	1580 (93.3 %)	1191 (70.2 %)	1303 (76.6 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease-free survival				
- No. patients with event	184 (10.9 %)	99 (5.8 %)	488 (28.8 %)	399 (23.4 %)
- No. patients without event	1508 (89.1 %)	1594 (94.6 %)	1209 (71.2 %)	1303 (76.6 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death)				
- No. patients with event	40 (2.4 %)	31 (1.8 %)	350 (20.6 %)	278 (16.3 %)
- No. patients without event	1653 (97.6 %)	1662 (98.2 %)	1347 (79.4 %)	1424 (83.7 %)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

*Co-primary endpoint of DFS of 1 year versus observation met the pre-defined statistical boundary
**Final analysis (including crossover of 52 % of patients from the observation arm to another trastuzumab product)
*** There is a discrepancy in the overall sample size due to a small number of patients who were randomized after the cut-off date for the 12-month median follow-up analysis

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary for the comparison of 1-year of trastuzumab versus observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (95 % CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8 % versus 78.2 %) in favor of the trastuzumab arm.

A final analysis was performed after a median follow-up of 8 years, which showed that 1 year trastuzumab treatment is associated with a 24 % risk reduction compared to observation only (HR=0.76, 95 % CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8-year disease free survival rate of 6.4 percentage points in favor of 1 year trastuzumab treatment.

In this final analysis, extending trastuzumab treatment for a duration of two years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years versus 1 year=0.99 (95 % CI: 0.87, 1.13), p-value=0.90 and OS HR=0.98 (0.83, 1.15); p-value= 0.78]. The rate of asymptomatic cardiac dysfunction was increased in the 2-year treatment arm (8.1 % versus 4.6 % in the 1-year treatment arm). More patients experienced at least one grade 3 or 4 adverse event in the 2-year treatment arm (20.4 %) compared with the 1-year treatment arm (16.3 %).
As per the published literature on another trastuzumab product, trastuzumab was administered in combination with paclitaxel, following AC chemotherapy.

As per the published literature on another trastuzumab product, Doxorubicin and cyclophosphamide were administered concurrently as follows:

- Intravenous push doxorubicin, at 60 mg/ m^2, given every 3 weeks for 4 cycles.
- Intravenous cyclophosphamide, at 600 mg/ m^2 over 30 minutes, given every 3 weeks for 4 cycles.

As per the published literature, Paclitaxel, in combination with another trastuzumab product, was administered as follows:

- Intravenous paclitaxel - 80 mg/m^2 as a continuous intravenous infusion, given every week for 12 weeks, or
- Intravenous paclitaxel - 175 mg/m^2 as a continuous intravenous infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

As per the published literature on another trastuzumab product, the efficacy results are summarized in **Table 7**. The median duration of follow up was 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm.

Table 7: Efficacy Results

Parameter	**AC→P (n=1679)**	**AC→PH (n=1672)**	**Hazard Ratio vs AC→P (95% CI) p-value**
Disease-free survival No. patients with event (%)	261 (15.5)	133 (8.0)	0.48 (0.39, 0.59) p<0.0001
Distant Recurrence No. patients with event	193 (11.5)	96 (5.7)	0.47 (0.37, 0.60) p<0.0001
Death (OS event): No. patients with event	92 (5.5)	62 (3.7)	0.67 (0.48, 0.92) p=0.014
A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: another trastuzumab product			

For the primary endpoint, DFS, the addition of trastuzumab to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 11.8 percentage points (87.2 % versus 75.4 %) in favor of the AC→PH (another trastuzumab product) arm.

At the time of a safety update after a median of 3.5-3.8 years follow up, an analysis of DFS reconfirms the magnitude of the benefit shown in the definitive analysis of DFS. Despite the cross-over to trastuzumab in the control arm, the addition of trastuzumab to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The addition of trastuzumab to paclitaxel chemotherapy also resulted in a 37 % decrease in the risk of death.

As per the published literature on another trastuzumab product, the pre-planned final analysis of OS was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→P H group). Treatment with AC→PH resulted in a statistically significant improvement in OS compared with AC→P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p-value < 0.0001). At 8 years, the survival rate was estimated to be 86.9% in the AC→PH arm and 79.4% in the AC→P arm, an absolute benefit of 7.4% (95% CI 4.9%, 10.0%).

The final OS results on another trastuzumab product from the joint analysis are summarized in Table 8 below:

Table 8 Final Overall Survival Analysis

Parameter	AC→P (N=2032)	AC→PH (N=2031)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	< 0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: another trastuzumab product

As per the published literature on another trastuzumab product, DFS analysis was also performed at the final analysis of OS. The updated DFS analysis results (stratified HR = 0.61; 95% CI [0.54, 0.69]) showed a similar DFS benefit compared to the definitive primary DFS analysis, despite 24.8% patients in the AC→P arm who crossed over to receive trastuzumab. At 8 years, the disease-free survival rate was estimated to be 77.2% (95% CI: 75.4, 79.1) in the AC→PH arm, an absolute benefit of 11.8% compared with the AC→P arm.

As per the published literature on another trastuzumab product, trastuzumab was administered either in combination with docetaxel, following AC chemotherapy (AC→DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenous docetaxel - 100 mg/m^2 as an intravenous infusion over 1 hour, given every 3 weeks for 4 cycles (day 2 of first docetaxel cycle, then day 1 of each subsequent cycle), or

- intravenous docetaxel - 75 mg/m^2 as an intravenous infusion over 1 hour, given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each subsequent cycle) which was followed by:
- carboplatin – at target AUC = 6 mg/mL/min administered by intravenous infusion over 30-60 minutes repeated every 3 weeks for a total of six cycles

Trastuzumab was administered weekly with chemotherapy and 3 weekly thereafter for a total of 52 weeks.

As per the published literature on another trastuzumab product, the efficacy results are summarized in **Tables 9 and 10**. The median duration of follow up was 2.9 years in the AC→D arm and 3.0 years in each of the AC→DH and DCarbH arms.

Table 9: Overview of Efficacy Analyses AC→D versus AC→DH

Parameter	**AC→D (n=1073)**	**AC→DH (n=1074)**	**Hazard Ratio vs AC→D (95% CI) p-value**
Disease-free survival No. patients with event	195	134	0.61 (0.49, 0.77) p<0.0001
Distant Recurrence No. patients with event	144	95	0.59 (0.46, 0.77) p<0.0001
Death (OS event): No. patients with event	80	49	0.58 (0.40, 0.83) p=0.0024
AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; AC→DH = doxorubicin plus cyclophosphamide, followed by docetaxel plus another trastuzumab product; CI = confidence interval			

Table 10: Overview of Efficacy Analyses AC→D versus DCarbH

Parameter	**AC→D (n=1073)**	**DCarbH (n=1074)**	**Hazard Ratio vs AC→D (95% CI) p-value**
Disease-free survival No. patients with event	195	145	0.67 (0.54, 0.83) p=0.0003
Distant Recurrence No. patients with event	144	103	0.65 (0.50, 0.84) p=0.0008
Death (OS event): No. patients with event	80	56	0.66 (0.47, 0.93) p=0.0182
AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; DCarbH = docetaxel, carboplatin and another trastuzumab product; CI = confidence interval			

As per the published literature on another trastuzumab product, for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 5.8 percentage points (86.7 % versus 80.9 %) in favor of the AC→DH (trastuzumab) arm and 4.6 percentage points (85.5 % versus 80.9 %) in favor of the DCarbH (trastuzumab) arm compared to AC→D.

As per the published literature on another trastuzumab product, 213/1075 patients in the DCarbH (TCH) arm, 221/1074 patients in the AC→DH (AC→TH) arm, and 217/1073 in the AC→D (AC→T) arm had a Karnofsky performance status ≤90 (either 80 or 90). No disease-free survival (DFS) benefit was noticed in this subgroup of patients (hazard ratio = 1.16, 95 % CI [0.73, 1.83] for DCarbH (TCH) versus AC→D (AC→T); hazard ratio 0.97, 95 % CI [0.60, 1.55] for AC→DH (AC→TH) versus AC→D).

As per the published literature on another trastuzumab product, a post-hoc exploratory analysis was performed on the data sets from the joint analysis combining DFS events and symptomatic cardiac events and summarized in **Table 11:**

Table 11: Post-Hoc Exploratory Analysis Results from Combining DFS Events and Symptomatic Cardiac Events

	AC→PH (vs. AC→P)	**AC→DH (vs. AC→D)**	**DCarbH (vs. AC→D)**
Primary efficacy analysis DFS Hazard ratios (95 % CI) p-value	 0.48 (0.39, 0.59) p<0.0001	 0.61 (0.49, 0.77) p< 0.0001	 0.67 (0.54, 0.83) p=0.0003
Long term follow-up efficacy analysis** DFS Hazard ratios (95% CI) p-value	 0.61 (0.54, 0.69) p<0.0001	 0.72 (0.61, 0.85) p<0.0001	 0.77 (0.65, 0.90) p=0.0011
Post-hoc exploratory analysis with DFS and symptomatic cardiac events Hazard ratios (95 % CI)	 0.64 (0.53, 0.77)	 0.70 (0.57, 0.87)	 0.71 (0.57, 0.87)
A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel; Carb: carboplatin; H: another trastuzumab product; CI = confidence interval. * At the time of the definitive analysis of DFS. Median duration of follow up was 1.8 years in the AC→P arm			

and 2.0 years in the AC→PH arm
** Median duration of long term follow-up for the Joint Analysis clinical studies was 8.3 years (range: 0.1 to 12.1) for the AC→PH arm and 7.9 years (range: 0.0 to 12.2) for the AC→P arm; Median duration of long term follow-up for the BCIRG 006 study was 10.3 years in both the AC→D arm (range: 0.0 to 12.6) arm and the DCarbH arm (range: 0.0 to 13.1), and was 10.4 years (range: 0.0 to 12.7) in the AC→DH arm

Early breast cancer (neoadjuvant-adjuvant setting)

So far, no results are available which compare the efficacy of trastuzumab administered with chemotherapy in the adjuvant setting with that obtained in the neo-adjuvant/adjuvant setting.

As per the published literature on another trastuzumab product, in the neoadjuvant-adjuvant setting, a multicenter randomized trial, was designed to investigate the clinical efficacy of concurrent administration of trastuzumab with neoadjuvant chemotherapy including both an anthracycline and a taxane, followed by adjuvant trastuzumab, up to a total treatment duration of 1 year. The study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory EBC. Patients with HER2+ tumors were randomized to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone.

As per the published literature on another trastuzumab product, trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg maintenance every 3 weeks) was administered concurrently with 10 cycles of neoadjuvant chemotherapy as follows:

- Doxorubicin 60mg/m^2 and paclitaxel 150 mg/m^2, administered 3-weekly for 3 cycles, which was followed by
- Paclitaxel 175 mg/m^2 administered 3-weekly for 4 cycles, which was followed by
- CMF on day 1 and 8 every 4 weeks for 3 cycles, which was followed surgery by
- additional cycles of adjuvant trastuzumab (to complete 1 year of treatment)

The efficacy results are summarized in **Table 12**. The median duration of follow-up in the another trastuzumab arm was 3.8 years.

Table 12: Efficacy Results

Parameter	**Chemo + Another Trastuzumab product (n=115)**	**Chemo only(n=116)**	
Event-free survival No. patients with event	46	59	Hazard Ratio (95% CI) 0.65 (0.44, 0.96) p=0.0275
Total pathological complete response* (95 % CI)	40 % (31.0, 49.6)	20.7 % (13.7, 29.2)	P=0.0014
Overall survival No. patients with event	22	33	Hazard Ratio (95 % CI) 0.59 (0.35, 1.02) p=0.0555
* defined as absence of any invasive cancer both in the breast and axillary nodes			

An absolute benefit of 13 percentage points in favor of the trastuzumab arm was estimated in terms of 3-year event-free survival rate (65 % versus 52 %).

Metastatic gastric cancer

As per the published literature on another trastuzumab product, trastuzumab has been investigated in one randomized, open-label phase III trial in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine - 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle), or
- intravenous 5-fluorouracil - 800 mg/m^2/day as a continuous intravenous infusion over 5 days, given every 3 weeks for 6 cycles (days 1 to 5 of each cycle)

Either of which was administered with:

- cisplatin - 80 mg/m^2 every 3 weeks for 6 cycles on day 1 of each cycle.

As per the published literature on another trastuzumab product, the efficacy results from are summarized in **Table 13**:

Table 13: Efficacy Results

Parameter	**FP N = 290**	**FP +H N = 294**	**HR (95 % CI)**	**p-value**
Overall Survival, Median months	11.1	13.8	0.74 (0.60-0.91)	0.0046
Progression-Free Survival, Median months	5.5	6.7	0.71 (0.59-0.85)	0.0002
Time to Disease Progression, Median months	5.6	7.1	0.70 (0.58-0.85)	0.0003
Overall Response Rate, %	34.5 %	47.3 %	1.70a (1.22, 2.38)	0.0017
Duration of Response, Median months	4.8	6.9	0.54 (0.40-0.73)	< 0.0001
FP + H: Fluoropyrimidine/cisplatin + Another Trastuzumab product; FP: Fluoropyrimidine/cisplatin; an Odds ratio				

Patients were recruited to the trial who were previously untreated for HER2-positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-esophageal junction not amenable to curative therapy. The primary endpoint was overall survival which was defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis a total of 349 randomized patients had died: 182 patients (62.8 %) in the control arm and 167 patients (56.8 %) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

Post-hoc subgroup analyses indicate that positive treatment effects are limited to targeting tumors with higher levels of HER2 protein (IHC 2+/FISH+ or IHC 3+). The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR 0.65 (95 % CI 0.51-0.83) and the median progression free survival was 5.5 months versus 7.6 months, HR 0.64 (95 % CI 0.51-0.79) for FP versus FP + H, respectively. For overall survival, the HR was 0.75 (95 % CI 0.51-1.11) in the IHC 2+/FISH+ group and the HR was 0.58 (95 % CI 0.41-0.81) in the IHC 3+/FISH+ group.

As per the published literature on another trastuzumab product, in an exploratory subgroup analysis there was no apparent benefit on overall survival with the addition of trastuzumab in patients with ECOG PS 2 at baseline [HR 0.96 (95 % CI 0.51-1.79)], non-measurable [HR 1.78 (95 % CI 0.87-3.66)] and locally advanced disease [HR 1.20 (95 % CI 0.29-4.97)].

5.2 Pharmacokinetic properties

The pharmacokinetics of another trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects, including patients with HER2 positive MBC, EBC, AGC or other tumor types, and healthy volunteers, in 18 Phase I, II and III trials receiving trastuzumab IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment

described the trastuzumab concentration-time profile. Due to non-linear elimination, total clearance increased with decreasing concentration. Therefore, no constant value for half-life of trastuzumab can be deduced. The $t_{1/2}$ decreases with decreasing concentrations within a dosing interval (see Table 16). MBC and EBC patients had similar PK parameters (e.g. clearance (CL), the central compartment (V_c)) and population-predicted steady-state exposures (C_{min}, C_{max} and AUC). Linear clearance was 0.136 L/day for MBC, 0.112 L/day for EBC and 0.176 L/day for AGC. The non-linear elimination parameter values were 8.81 mg/day for the maximum elimination rate (V_{max}) and 8.92 μg/mL for the Michaelis-Menten constant (K_m) for the MBC, EBC, and AGC patients. The central compartment volume was 2.62 L for patients with MBC and EBC and 3.63 L for patients with AGC. In the final population PK model, in addition to primary tumor type, body-weight, serum aspartate aminotransferase and albumin were identified as a statistically significant covariates affecting the exposure of trastuzumab. However, the magnitude of effect of these covariates on Trastuzumab exposure suggests that these covariates are unlikely to have a clinically meaningful effect on trastuzumab concentrations.

The population predicted PK exposure values (median with 5th - 95th Percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for MBC, EBC and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 14 (Cycle 1), Table 15 (steady state), and Table 16 (PK parameters).

Table 14: Population Predicted Cycle 1 PK Exposure Values (median with 5th - 95th Percentiles) for trastuzumab IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumor	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC0-21days (µg.day/mL)
8mg/kg + 6mg/kg q3w	MBC	805	28.7 (2.9 - 46.3)	182 (134 – 280)	1376 (728 - 1998)
	EBC	390	30.9 (18.7 - 45.5)	176 (127 - 227)	1390 (1039 - 1895)
	AGC	274	23.1 (6.1 - 50.3)	132 (84.2 – 225)	1109 (588 – 1938)
4mg/kg + 2mg/kg qw	MBC	805	37.4 (8.7 - 58.9)	76.5 (49.4 - 114)	1073 (597 – 1584)
	EBC	390	38.9 (25.3 - 58.8)	76.0 (54.7 - 104)	1074 (783 - 1502)

Table 15: Population Predicted Steady State PK Exposure Values (median with 5th - 95th Percentiles) for trastuzumab IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	**Primary tumor**	**N**	**Cmin (µg/mL)**	**Cmax (µg/mL)**	**AUC 0-21days (µg.day/mL)**	**Time to Steady state (week)**
8mg/kg + 6mg/kg q3w	MBC	805	44.2 (1.8 - 85.4)	179 (123 - 266)	1736 (618 - 2756)	12
	EBC	390	53.8 (28.7 - 85.8)	184 (134 - 247)	1927 (1332 -2771)	15
	AGC	274	32.9 (6.1 – 88.9)	131 (72.5 -251)	1338 (557 - 2875)	9
4mg/kg + 2mg/kg qw	MBC	805	63.1 (11.7 - 107)	107 (54.2 - 164)	1710 (581 - 2715)	12
	EBC	390	72.6 (46 - 109)	115 (82.6 - 160)	1893 (1309 -2734)	14

Table 16: Population Predicted PK Parameter Values at Steady State for trastuzumab IV Dosing Regimens in MBC, EBC and AGC Patients

Regimen	Primary tumor	N	Total CL range from Cmax,ss to Cmin,ss (L/day)	t1/2 range from Cmax,ss to Cmin,ss (day)
8mg/kg + 6mg/kg q3w	MBC	805	0.183 - 0.302	15.1 - 23.3
	EBC	390	0.158 - 0.253	17.5 – 26.6
	AGC	274	0.189 - 0.337	12.6 - 20.6
4mg/kg + 2mg/kg qw	MBC	805	0.213 - 0.259	17.2 - 20.4
	EBC	390	0.184 - 0.221	19.7 - 23.2

Trastuzumab washout

Trastuzumab washout period was assessed following q1w or q3w intravenous administration using the population PK model. The results of these simulations indicate that at least 95% of patients will reach concentrations that are <1 µg/mL (approximately 3% of the population predicted Cmin,ss, or about 97% washout) by 7 months.

Circulating shed HER2 ECD

The exploratory analyses of covariates with information in only a subset of patients suggested that patients with greater shed HER2-ECD level had faster nonlinear clearance (lower Km) (P <0.001). There was a correlation between shed antigen and SGOT/AST levels; part of the impact of shed antigen on clearance may have been explained by SGOT/AST levels.

Baseline levels of the shed HER2-ECD observed in MGC patients were comparable to those in MBC and EBC patients and no apparent impact on trastuzumab clearance was observed.

5.3 Preclinical safety data

As per the published literature on another trastuzumab product, there was no evidence of acute or multiple dose-related toxicity in studies of up to 6 months, or reproductive toxicity in teratology, female fertility or late gestational toxicity/placental transfer studies. Trastuzumab is not genotoxic.

Long-term animal studies have not been performed to establish the carcinogenic potential of trastuzumab, or to determine its effects on fertility in males.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- L-histidine
- L-histidine hydrochloride
- Trehalose dihydrate
- Polysorbate 20

6.2 Incompatibilities

Hertraz™ 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.

6.3 Shelf life

48 month when stored under recommended storage conditions i.e. 2°C to 8°C.

6.4 Special precautions for storage

Store vials at 2^0C to 8^0C prior to reconstitution.

Store away from light.

Vials should not be used beyond the expiry date stamped on the vial, the reconstituted 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 at 2^0C to 8^0C for up to 24 hours prior to use.

Shelf-life of the reconstituted solution

440 mg/150 mg (Multi-dose use vials)

Reconstituted solutions made with bacteriostatic water for injection (BWFI) (containing 1.1% benzyl alcohol as a preservative) for 440 mg/150 mg vials of Hertraz™, as supplied, are stable for 28 days when stored refrigerated at 2^0C to 8^0 C. The reconstituted solution contains preservative and is therefore suitable for ***multiple*** uses. Any remaining reconstituted solution should be discarded after 28 days. If sterile water is used to reconstitute the 440 mg vial, the solution is stable only for 24 hours, and must be discarded thereafter. Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product

The infusion solution (0.9% sodium chloride infusion solution) containing the reconstituted product is physically and chemically stable for 24 hours (do not store above 30^0C).

From a microbiological point of view, the Hertraz™ 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 2^0C to 8^0 C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Reconstitution details

Table 17: Reconstitution Details of 150 mg Vial (multi-dose use) and 440 mg Vial (multi-dose use)

Type of Vial	Reconstitution	Trastuzumab (mg/mL)	pH
150 mg (for multi-dose use)	7.2 mL of BWFI (containing 1.1% benzyl alcohol)	~21	~6.0
440 mg (for multi-dose use)	20 mL of BWFI (containing 1.1% benzyl alcohol)	~21	~6.0
Appropriate aseptic technique should be used. Use of other reconstitution solvents should be avoided. BWFI: bacteriostatic water for injection.			

Hertraz™ should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of Hertraz™ that can be withdrawn from the vial.

Store reconstituted Hertraz™ at 2−8°C; discard unused Hertraz™ after 28 days. The reconstituted solution should not be frozen. In patients with known hypersensitivity to benzyl alcohol, reconstitute with Sterile Water for Injection (SWFI) without preservative to yield a single use solution. If Hertraz™ is reconstituted with SWFI without preservative, use immediately and discard any unused portion.

Instructions for reconstitution-150 mg vial (multi-dose vial):

1) Using a sterile syringe, slowly inject 7.2 mL of bacteriostatic water for injection into the vial containing the lyophilized Hertraz™, directing the stream into the lyophilized cake.
2) Swirl the vial gently to aid reconstitution. DO NOT SHAKE.

Instructions for reconstitution-440 mg vial (multi-dose vial):

1) Using a sterile syringe, slowly inject 20 mL of bacteriostatic water for injection into the vial containing the lyophilized Hertraz™, directing the stream into the lyophilized cake.
2) Swirl the vial gently to aid reconstitution. DO NOT SHAKE.

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Hertraz™ results in a colorless to pale yellow transparent solution and should be essentially free of visible particles.

Instructions for dilution:

Determine the volume of the solution required:

- based on a loading dose of 4 mg trastuzumab/kg body weight, or a subsequent weekly dose of 2 mg trastuzumab/kg body weight:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{4}\ \text{mg/kg for loading or}\ \textbf{2}\ \text{mg/kg for maintenance})}{\textbf{21}\ (\text{mg/mL, concentration of reconstituted solution})}$$

- based on a loading dose of 8 mg trastuzumab/kg body weight, or a subsequent 3-weekly dose of 6 mg trastuzumab/kg body weight:

$$\textbf{Volume}\ (\text{mL}) = \frac{\textbf{Body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{8}\ \text{mg/kg for loading or}\ \textbf{6}\ \text{mg/kg for maintenance})}{\textbf{21}\ (\text{mg/mL, concentration of reconstituted solution})}$$

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with glucose/dextrose containing solutions. The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for 24 hours (do not store above 30°C).

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

No incompatibilities between trastuzumab and polyvinylchloride, polyethylene or polypropylene bags have been observed.

6.5 Nature and contents of container

Hertraz™ 150 mg is filled in 15 mL USP type 1 glass vial, closed with a halo butyl rubber stopper and sealed with 20 MM blue coloured flip-off seal. The 150 mg vials (multi-dose) are supplied with 1 vial of 10 mL bacteriostatic water for injection (containing 1.1% benzyl alcohol as preservative), for reconstitution.

Hertraz™ 440 mg is filled in 50 mL USP type 1 glass vial closed with a halo butyl rubber stopper and sealed with 20 MM blue coloured flip-off seal. The 440 mg vials are supplied with 2 vials each of 10 mL bacteriostatic water for injection (containing 1.1% benzyl alcohol as preservative), for reconstitution.

6.6 Special precautions for disposal and other handling

Any unused medicinal product should be disposed of in accordance with the local requirements.

7. MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Private Limited,
Plot No. 1-A/2, MIDC Industrial Area,
Taloja, Panvel, Raigad (Dist)
Maharashtra – 410208. India

Manufactured for Mylan Pharmaceuticals Private Limited, India by**:**

M/s. Biocon Limited
Special Economic Zone
Plot No. 2, 3, 4 & 5Phase-IV
Bommasandra – Jigani Link Road,
Bommasandra Post,
Bangalore – 560099.INDIA.

8. MARKETING AUTHORISATION NUMBER(S)

05594/07076/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

Not Applicable.