

1. NAME OF THE MEDICINAL PRODUCT

Hervycta® (Trastuzumab) lyophilized powder for concentrate for solution for Intravenous Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance: Trastuzumab (r-DNA origin)

Trastuzumab is a genetically engineered humanized IgG1 monoclonal antibody, expressed and produced in mammalian (Chinese hamster ovary cells) by cell suspension culture and purified by affinity and ion exchange chromatographies, including specific viral inactivation and removal procedures.

Hervycta® (Trastuzumab) is available in multiple dose vials (150 mg/vial and 440 mg/vial). Reconstituted solution contains 21 mg/mL of trastuzumab.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilized powder for concentrate for solution for Intravenous Infusion. Sterile, white to pale yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hervycta® is indicated for the following:

Early Breast Cancer (EBC)

Hervycta® is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC).

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- as a single agent following multi-modality anthracycline based therapy
- in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.

Metastatic Breast Cancer (MBC)

Hervycta® is indicated for 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 MBC, not previously treated with trastuzumab.

Hervycta® 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 (MGC)

Hervycta® 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.

Hervycta® 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.

4.2 Posology and method of administration

HER2 testing is mandatory prior to initiation of therapy (Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Hervycta® therapy because these are the only patients studied and for whom benefit has been shown in clinical trials). Hervycta® treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy, 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. Hervycta® intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion only.

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

Recommended Doses and Schedules:

Do not administer as an intravenous push or bolus. Do not mix Hervycta® with other drugs.

Metastatic breast cancer

Weekly schedule

The recommended initial loading dose of Hervycta® is 4 mg/kg body weight as a 90-minute intravenous infusion. The recommended weekly maintenance dose of Hervycta® is 2 mg/kg body weight as, beginning one week after the loading dose or 2 mg/kg as 30-minute intravenous infusions until disease progression.

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.

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

Weekly schedule and three-weekly

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.

As a three-weekly regimen the recommended initial loading dose of Hervycta® is 8 mg/kg body weight. The recommended maintenance dose of Hervycta® at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Adjuvant treatment, Breast cancer:

Administer according to one of the following doses and schedules for a total of 52 weeks of Hervycta® therapy:

During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

- Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Hervycta®, administer Hervycta® at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:

- Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes
- Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks
- Extending adjuvant treatment beyond one year is not recommended.

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 or recommend initial dose of 8 mg/kg as a 90 minutes' intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30 to 90 minutes every 3 weeks until disease progression.

Duration of treatment

Patients with MBC or MGC should be treated with Hervycta® until progression of disease. Patients with EBC should be treated with Hervycta® for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended.

Dosage adjustments during treatment

No reductions in the dose of Hervycta® 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.

Assess left ventricular ejection fraction (LVEF) prior to initiation of Hervycta® and at regular intervals during treatment. Withhold Hervycta® dosing for at least 4 weeks for either of the following:

- $\geq 16\%$ absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and $\geq 10\%$ absolute decrease in LVEF from pretreatment values.

Hervycta® may be resumed if, within 4–8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is $\leq 15\%$.

Permanently discontinue Hervycta® for a persistent (> 8 weeks) LVEF decline or for suspension of Hervycta® dosing on more than 3 occasions for cardiomyopathy.

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 Hervycta® 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 Hervycta® 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 Hervycta® by more than one week, a re-loading

dose of Hervycta® should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) as soon as possible. Subsequent Hervycta® 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

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.

Pediatric population

There is no relevant use of trastuzumab in the pediatric population.

Method of Administration

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

4.3 Contraindications

Hervycta® is contraindicated in following conditions.

Hypersensitivity to trastuzumab, murine proteins or to any of the other excipients [L-histidine, L-histidine HCl monohydrate, α,α-trehalose dihydrate, and Polysorbate 20].

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

4.4 Special warnings and precautions for use

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 trastuzumab therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin) containing chemotherapy. These may be moderate to severe and have been associated with death. In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age.

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

Trastuzumab may persist in the circulation for up to 7 months after stopping treatment based on population pharmacokinetic analysis of all available data. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

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

Withhold trastuzumab for $\geq 16\%$ absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and $\geq 10\%$ absolute decrease in LVEF from pretreatment values. The safety of continuation or resumption of trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. 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.

Treatment with trastuzumab is not recommended in 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.

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 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 clinical trial 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).

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) $>25 \text{ kg/m}^2$.

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, trastuzumab should be used concurrently with anthracyclines only in chemotherapy-naïve 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.

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. Pre-medication may be used to reduce risk of occurrence of these events. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms. These symptoms can be treated with an analgesic/antipyretic such as 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.

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

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting. 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. 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. 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 based on the studies conducted by the Innovator

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 Hervycta[®] (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 Hervycta[®] had no effect on the single dose pharmacokinetics of docetaxel. Study JP19959 was a substudy 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 Hervycta[®]. The results of this substudy 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 Hervycta®. However, capecitabine itself showed higher concentrations and a longer half-life when combined with Hervycta®. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Hervycta®.

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 based on the studies conducted by the Innovator

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 (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 trastuzumab 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.

4.6 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 7 months after treatment has concluded (see section 4.4).

Pregnancy

Trastuzumab should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Animal reproduction studies revealed no evidence of impaired fertility or harm to foetus.

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.

Lactation

There is no information regarding the presence of trastuzumab in human milk, and the potential for harm to the baby is unknown. However, human IgG is secreted into human milk, hence breastfeeding should be avoided during trastuzumab therapy and for 7 months after the last dose.

Fertility

Fertility data is not available for trastuzumab.

4.7 Effects on ability to drive and use machines

Trastuzumab may have minor influence on the ability to drive or use machines. Dizziness and somnolence may occur during treatment with trastuzumab. Patients experiencing infusion-related symptoms (see special warnings and precautions for use) should be advised not to drive and use machines until symptoms subside.

4.8 Undesirable effects

Summary of the safety profile

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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.

Presented in Table 1 are 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.

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

Table 1 Undesirable Effects Reported with trastuzumab Monotherapy or in Combination with Chemotherapy in Pivotal Clinical Trials (N = 8386) and in Post-Marketing surveillance

System organ class	Adverse reaction	Frequency
Infections and infestations	Infection	Very common
	Nasopharyngitis	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Influenza	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Pharyngitis	Common
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
	Febrile neutropenia	Very common

Blood and lymphatic system disorders	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	Rare

System organ class	Adverse reaction	Frequency
	+Anaphylactic shock	Rare
Metabolism and nutrition disorders	Weight decreased/Weight loss	Very common
	Anorexia	Very common
	Hyperkalaemia	Not known
	Tumor lysis syndrome	Not known
Psychiatric disorders	Insomnia	Very common
	Anxiety	Common
	Depression	Common
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
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
	¹ Blood pressure decreased	Very common
	¹ Blood pressure increased	Very common
	¹ Heart beat irregular	Very common
	¹ Palpitation	common
	¹ Cardiac flutter	Very common
	Ejection fraction decreased*	Very common

Cardiac disorders	+Cardiac failure (congestive)	Common
	+ ¹ Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very common
	+ ¹ Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	+ ¹ Wheezing	Uncommon
	+Dyspnoea	Very common
	Cough	Very common

System organ class	Adverse reaction	Frequency
	Epistaxis	Very common
	Rhinorrhoea	Very common
	+Pneumonia	Common
	Asthma	Common
	Lung disorder	Common
	+Pleural effusion	Common
	Pneumonitis	uncommon
	+Pulmonary fibrosis	Not known
	+Respiratory distress	Not known
	+Respiratory failure	Not known
	+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
	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common

Gastrointestinal disorders	¹ Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular injury	Common
	Hepatitis	Common
	Liver tenderness	Common
	Jaundice	Rare
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 erythrodysesthesia syndrome	Very common

System organ class	Adverse reaction	Frequency
	Acne	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasia	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
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck Pain	Common
	Pain in extremity	Common
	Renal disorder	Common
	Glomerulonephritis	Not known

Renal and urinary disorders	membranous	
	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

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. 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.

In the 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 after 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.

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. In study BO16348, after a median follow-up of 8 years the incidence of severe CHF (NYHA Class III & IV) in the trastuzumab 1-year treatment arm 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 patients. Approximately 17 % of cardiac dysfunction related events occurred after completion of trastuzumab.

In the 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 %), and was 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

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. 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 and have been associated with a fatal outcome.

Anaphylactoid reactions have been observed in isolated

cases. Haematotoxicity

Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. 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

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.

Renal Toxicity:

In Study 7 (metastatic gastric cancer) on the Hervycta®-containing arm as compared to the chemotherapy alone arm the incidence of renal impairment was 18% compared to 14.5%. Severe (Grade 3/4) renal failure was 2.7% on the Hervycta®-containing arm compared to 1.7% on the chemotherapy only arm. Treatment discontinuation for renal insufficiency/failure was 2% on the Hervycta®-containing arm and 0.3% on the chemotherapy only arm.

In the post-marketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of Hervycta® therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

Immunogenicity

In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, , 10.1 % (30/296) of patients treated with trastuzumab intravenous developed antibodies against trastuzumab . Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 trastuzumab 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.

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>

4.9 Overdose

There is no experience with overdosage in human clinical trials. single doses of trastuzumab alone greater than 10 mg/kg have not been administered in the clinical trials; a maintenance dose of 10 mg/kg q3w following a loading dose of 8 mg/kg has been studied in a clinical trial with metastatic gastric cancer patients. Doses up to this level were well tolerated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is observed in 20 %-30 % of primary breast cancers. 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 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:

Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result,

trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Detection of HER2 overexpression or HER2 gene amplification

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. HER2 gene amplification should be detected using fluorescence in situ hybridisation (FISH) or chromogenic in situ hybridisation (CISH) of fixed tumour blocks. Patients are 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 specialised 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 assessment
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

In general, 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.

In general, 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 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 tumour histology and morphology. To ensure validation of testing procedures and the generation of accurate and reproducible results, HER2 testing must be performed in a laboratory staffed by trained personnel. Full instructions on assay performance and results interpretation should be taken from the product information leaflet provided with the HER2 testing assays used.

In the clinical trials, patients whose tumours were either IHC3+ or FISH positive were defined as HER2 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.

In a method comparison study a high degree of concordance (>95 %) was observed for SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

HER2 over expression should be detected using an immunohistochemistry (IHC)-based assessment of fixed

tumour blocks; HER2 gene amplification should be detected using in situ hybridisation using either SISH or FISH on fixed tumour 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 in Gastric Cancer

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

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/m² infused over 3 hours) with or without Trastuzumab. In the pivotal trial of docetaxel (100 mg/m² 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.

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.

Weekly dosing in metastatic breast cancer

The efficacy results from the monotherapy and combination therapy studies are summarised in Table 4:

Table 4 Efficacy Results from the Monotherapy and Combination Therapy Studies

Parameter	Monothe rapy	Combination Therapy			
	Trastuzum ab N=172	Trastuzum ab plus paclitaxel N=68	Paclitax el N=77	Trastuz umab plus docetax el N=92	Docetax el 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 TTP (months) (95 %CI)	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)
Median Survival (months) (95 %CI)	16.4 (12.3 -ne)	24.8 (18.6-33.7)	17.9 (11.2- 23.8)	31.2 (27.3- 40.8)	22.74 (19.1- 30.8)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

Combination treatment with Trastuzumab and anastrozole

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 are summarised in Table 5:

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

Parameter	Monotherapy		Combination Therapy	
	Trastuzumab N=105	Trastuzumab N=72	Trastuzumab plus paclitaxel N=32	Trastuzumab 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 TTP (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	ne	ne	47.3 (32-ne)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

Sites of progression

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 treatment setting, Trastuzumab was investigated in 4 large multicentre, randomised, trials.

The efficacy results from the clinical trial following 12 months* and 8 years**

median follow-up are summarized in Table 6:

Table 6 Efficacy Results:

	Median follow-up 12 months*		Median follow-up 8 years**	
Parameter	Observation N=1693	Trastuzumab 1 Year N = 1693	Observation N= 1697***	Trastuzumab 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	

	Median follow-up 12 months*		Median follow-up 8 years**	
Parameter	Observation N=1693	Trastuzumab 1 Year N = 1693	Observation N= 1697***	Trastuzumab 1 Year N = 1702***
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 Trastuzumab)

*** 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 favour 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 favour 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 %).

In the clinical studies Trastuzumab was administered in combination with paclitaxel, following AC chemotherapy.

Doxorubicin and cyclophosphamide were administered concurrently as follows:

- intravenous push doxorubicin, at 60 mg/ m², given every 3 weeks for 4 cycles.
- intravenous cyclophosphamide, at 600 mg/ m² over 30 minutes, given every 3 weeks for 4 cycles.

Paclitaxel, in combination with Trastuzumab, was administered as follows:

- intravenous paclitaxel - 80 mg/m² as a continuous intravenous infusion, given every week for 12 weeks. or
- intravenous paclitaxel - 175 mg/m² as a continuous intravenous infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

The efficacy results from the joint analysis of the NSABP B-31 and NCCTG 9831 trials at the time of the definitive analysis of DFS* 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 Summary of Efficacy results from the joint analysis of the clinical trials at the time of the definitive DFS analysis*

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: trastuzumab

* At median duration of follow up of 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm

** p value for OS did not cross the pre-specified statistical boundary for comparison of AC→PH vs. AC→P

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 favour of the AC→PH (Trastuzumab) 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.

The pre-planned final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831 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 from the joint analysis of clinical studies are summarized in Table 8 below:

Table 8 Final Overall Survival Analysis from the joint analysis of clinical trials

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: trastuzumab

DFS analysis was also performed at the final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831. 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.

In the clinical study 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/m² 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/m² 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.

The efficacy results from the clinical study are summarized in Tables 9 and Table 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 BCIRG 006 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 trastuzumab; 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)
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 trastuzumab; CI = confidence interval

In the clinical study 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 favour of the AC→DH (Trastuzumab) arm and 4.6 percentage points (85.5 % versus 80.9 %) in favour of the DCarbH (Trastuzumab) arm compared to AC→D.

In the clinical study, 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).

In addition, a post-hoc exploratory analysis was performed on the data sets from the joint analysis (JA) clinical studies combining DFS events and symptomatic cardiac events and summarised in Table 11.

Table 11 Post-Hoc Exploratory Analysis Results from the Joint Analysis Clinical Studies *Combining DFS Events and Symptomatic Cardiac Events

	AC→PH (vs. AC→P) (NSABP B-31 and NCCTG N9831)*	AC→DH (vs. AC→D) (BCIRG 006)	DCarb H (vs. AC→D) (BCIRG 006)
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	0.67	0.77	0.77
DFS and symptomatic cardiac events Long term follow-up** Hazard ratios (95 % CI)	(0.60, 0.75)	(0.66, 0.90)	(0.66, 0.90)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel; Carb: carboplatin; H: trastuzumab 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 clinical 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.

In the neoadjuvant-adjuvant treatment setting, a clinical study, a multicentre randomised 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+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant Trastuzumab, or neoadjuvant chemotherapy alone.

In this study, 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/m² and paclitaxel 150 mg/m², administered 3-weekly for 3 cycles, which was followed by
- Paclitaxel 175 mg/m² 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 after surgery by
- additional cycles of adjuvant Trastuzumab (to complete 1 year of treatment)

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

Table 12 Efficacy Results:

Parameter	Chemo + Trastuzumab (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 favour of the Trastuzumab arm was estimated in terms of 3-year event-free survival rate (65 % versus 52 %).

Metastatic gastric cancer

Trastuzumab has been investigated in one randomised, open-label phase III trial in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine - 1000 mg/m² 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/m²/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/m² every 3 weeks for 6 cycles on day

1 of each cycle. The efficacy results from study 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 +

Trastuzumab FP:

Fluoropyrimidine/cisplatin

a: 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-oesophageal 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 tumours 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.

In an exploratory subgroup analysis performed in the clinical trial 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 trastuzumab has been studied in patients with metastatic breast cancer and early breast cancer. Mean half-life increased and clearance decreased with increased dose level.

Breast Cancer

Steady State Pharmacokinetics in Breast Cancer

A population pharmacokinetic method was used to estimate the steady state pharmacokinetics in patients with metastatic breast cancer administered trastuzumab at a loading dose of 4 mg/kg followed by weekly maintenance dose of 2 mg/kg. In this assessment, the typical clearance of trastuzumab was 0.225 L/day and the typical volume of distribution was 2.95 L, with a corresponding terminal half-life of 28.5 days (95% confidence interval, 25.5 – 32.8 days). Steady state weekly AUC of 578 mg·day/L, peak concentrations of 110 mg/L and trough concentrations of 66 mg/L should be reached by 143 days, or approximately 20 weeks. The same time interval would be predicted for trastuzumab elimination after discontinuation of therapy.

An assessment in early breast cancer patients administered trastuzumab at an initial loading dose of 8 mg/kg followed by a three weekly maintenance dose of 6 mg/kg achieved steady state trough concentrations 63 mg/L, by cycle 13. The concentrations were comparable to those reported previously in patients with metastatic breast cancer.

The administration of concomitant chemotherapy (either anthracycline/cyclophosphamide or paclitaxel) did not appear to influence the pharmacokinetics of trastuzumab. The administration of concomitant anastrozole did not appear to influence pharmacokinetics of trastuzumab.

Gastric Cancer

Steady State Pharmacokinetics in Advanced Gastric Cancer

A population pharmacokinetic method was used to estimate the steady state pharmacokinetics in patients with advanced gastric cancer administered trastuzumab 3-weekly at a loading dose of 8 mg/kg followed by a 3-weekly maintenance 6 mg/kg. In this assessment, the typical clearance of trastuzumab was 0.378 L/day and the typical volume of distribution was 3.91 L, with a corresponding equilibrium half-life of 12.2 days. The median predicted steady-state AUC values (over a period of 3 weeks at steady state) is equal to 128 mg/L and the median steady-state C_{min} value is equal to 23 mg/L. Steady state concentrations should be reached by 49 days, (four equilibrium half-lives) or approximately 7 weeks.

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.

Specific Populations

Based on a population pharmacokinetic analysis, no clinically significant differences were observed in the pharmacokinetics of trastuzumab based on age (< 65 (n = 1294); ≥ 65 (n = 288)), race (Asian (n = 264); non-Asian (n = 1324)) and renal impairment (mild (creatinine clearance [CL_{Cr}] 60 to 90 mL/min) (n = 636) or moderate (CL_{Cr} 30 to 60 mL/min) (n = 133)). The pharmacokinetics of trastuzumab in patients with severe renal impairment, end-stage renal disease with or without hemodialysis, or hepatic impairment is unknown.

Drug Interaction Studies

There have been no formal drug interaction studies performed with Hervycta® in humans. Clinically significant interactions between Hervycta® and concomitant medications used in clinical trials have not been observed.

Paclitaxel and doxorubicin: Concentrations of paclitaxel and doxorubicin and their majormetabolites (i.e., 6-α hydroxyl-paclitaxel [POH], and doxorubicinol [DOL], respectively) were not altered in the presence of trastuzumab when used as combination therapy in clinical trials.

Trastuzumab concentrations were not altered as part of this combination therapy.

Docetaxel and carboplatin: When Hervycta® was administered in combination with docetaxel or carboplatin, neither the plasma concentrations of docetaxel or carboplatin nor the plasma concentrations of trastuzumab were altered.

Cisplatin and capecitabine: In a drug interaction substudy conducted in patients in Study 7, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with Hervycta®.

5.3 Preclinical safety data

There was no evidence of repeated dose toxicity following weekly intravenous (infusion) administration of Dr. Reddy's trastuzumab to Cynomolgus monkeys at 25 mg/kg/week up to 4 weeks. In the comparative tissue cross reactive studies (using selective panel of human tissues), Dr. Reddy's trastuzumab- Biotin showed

similar positive membranous staining in epithelial cells and cytoplasmic staining in peri / epineurium of peripheral nerves of many tissues compared to Hervycta®-Biotin.

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. A study of trehalose, a major formulation excipient did not reveal any toxicities.

No long-term animal studies have 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

α,α -trehalose dihydrate
L-histidine HCl
monohydrate L-
histidine
Polysorbate 20

6.2 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.

6.3 Shelf life

Trastuzumab 150 mg (r-DNA origin) Lyophilized powder for concentrate for solution for infusion	48 Months
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Trastuzumab 440 mg (r-DNA origin) Lyophilized powder for concentrate for solution for infusion	48 Months
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After reconstitution with sterile water for injection the reconstituted solution is physically and chemically stable for 48 hours at 2°C – 8°C. Any remaining reconstituted solution should be discarded.

Solutions of trastuzumab for intravenous infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0.9 %) solution for injection for 24 hours at temperatures not exceeding 30°C.

From a microbiological point of view, the reconstituted solution and trastuzumab infusion solution should be used immediately. The product is not intended to be stored after reconstitution and dilution unless this has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After reconstitution with Bacteriostatic Water for Injection (BWFI), containing 1.1% benzyl alcohol the reconstituted solution is physically and chemically stable for 28 days at 2°C – 8°C. Any remaining reconstituted solution should be discarded after 28 days.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Please also see sections 6.3 and 6.6 for reconstituted trastuzumab.

6.5 Nature and contents of container

Trastuzumab vial:

One 15 mL clear vial USP Type-I glass with butyl rubber stopper containing 150mg of trastuzumab.

Combipack of 1 vial of 150mg trastuzumab lyophilized powder and 1 vial of 10mL Bacteriostatic Water for Injection USP (diluent)

One 50 mL clear vial USP Type-I glass with butyl rubber stopper containing 440mg of trastuzumab.

Combipack of 1 vial of 440mg trastuzumab lyophilized powder and 1 vial of 20mL Bacteriostatic Water for Injection USP (diluent).

6.6 Special precautions for disposal and other handling

Appropriate aseptic technique should be used.

Multiple dose vial (Multi-use vial) 440 mg:

Each 440 mg vial of trastuzumab is reconstituted with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21 mg/mL trastuzumab. In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Expiry validity of BWFI shall be verified before reconstitution of the lyophilized powder (trastuzumab 440mg).

Store reconstituted trastuzumab at 2°C – 8°C; discard unused trastuzumab after 28 days. If trastuzumab is reconstituted with SWFI without preservative, use immediately and discard any unused portion.

Instructions for reconstitution:

1. Using a sterile syringe, slowly inject 20 mL of Bacteriostatic Water for Injection (BWFI) in the multiple use 440 mg vial containing the lyophilised trastuzumab, directing the stream into the lyophilised 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 trastuzumab results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Multiple dose vial (Multi-use vial) 150 mg:

Each 150 mg vial of trastuzumab is reconstituted with 7.2 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21 mg/mL trastuzumab. In patients with known hypersensitivity to benzyl alcohol, reconstitute with 7.2 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Expiry validity of BWFI shall be verified before reconstitution of the lyophilized powder (trastuzumab 150mg).

Use of other reconstitution solvents/diluents should be avoided (apart from BWFI or SWFI).

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

The reconstituted solution should

not be frozen. Instructions for

reconstitution:

1. Using a sterile syringe, slowly inject 7.2 mL of Bacteriostatic Water for Injection (BWFI) in the multiple use 150 mg vial containing the lyophilised trastuzumab, directing the stream into the lyophilised 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 trastuzumab results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

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:

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

- 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:

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

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-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.

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

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Dr. Reddy's Laboratories Ltd.
Biologics, Survey No. 47 & 44
(Part), Bachupally Village,
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10. DATE OF REVISION OF THE TEXT

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