For the use of a Registered Medical Practitioner or Hospital/Laboratory only

Hervycta®

(Trastuzumab)

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

Sterile lyophilized powder for concentrate for solution for Intravenous Infusion.

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.
- 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.

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).

Metastatic breast cancer

Weekly schedule

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

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.

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.

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.

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.
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.
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 the clinical trials 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 kg/m^2.
Neoadjuvant-adjuvant treatment
In patients with EBC eligible for neoadjuvant-adjuvant treatment, trastuzumab should be used concurrently with anthracyclines only in chemotherapy-naive patients and only with low-dose anthracycline regimens i.e. maximum cumulative doses of doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2.
If patients have been treated concurrently with a full course of low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.
Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited.
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 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.
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.

4.6 Fertility, Pregnancy and lactation
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 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 has no or negligible influence on the ability to drive or use machines. However, patients experiencing infusion-related symptoms (see special warnings and preacutions 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 (≥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.
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

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
Nervous system disorders	†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
	[1]Palpitation	Very common
	[1]Cardiac flutter	Very common
	Ejection fraction decreased*	Very common
	*Cardiac failure (congestive)	Common
	*[1]Supraventricular 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
	*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
	1Muscle 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 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

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.
Immunogenicity
In the neoadjuvant-adjuvant EBC treatment setting, 8.1 % (24/296) of patients treated with trastuzumab 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 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.

4.9 Overdose

There is no experience with overdosage in human clinical trials. Single doses of up to 960 mg of trastuzumab subcutaneous formulation have been administered with no reported untoward effects.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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
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. 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.

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 mantainence 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 teriminal 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 anastrazole 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.

5.3 Preclinical safety data
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
Do not dilute with glucose solutions since these cause aggregation of the protein.

6.3 Shelf life
3 years
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 Chloro 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 Chloro 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
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.
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.
Use of other reconstitution solvents should be avoided.
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:
3. 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.
4. 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:

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

- 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:

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

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
Dr. Reddy's Laboratories Ltd.
Survey No. 47, Bachupally Village,
Bachupally Mandal, Medchal
Malkajgiri District, Telangana,
INDIA – 500090.

8. MARKETING AUTHORISATION NUMBER(S)
MF-69/2018

March 2018

Patient Information

1.What Hervycta® is and what it is used for

Hervycta® contains the active substance trastuzumab, which is a monoclonal antibody. Monoclonal antibodies attach to specific proteins or antigens. Trastuzumab is designed to bind selectively to an antigen called human epidermal growth factor receptor 2 (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When trastuzumab binds to HER2 it stops the growth of such cells and causes them to die.
Your doctor may prescribe Hervycta® for the treatment of breast and gastric cancer when:

- You have early breast cancer, with high levels of a protein called HER2.
- You have metastatic breast cancer (breast cancer that has spread beyond the original tumour) with high levels of HER2. Hervycta® may be prescribed in combination with the chemotherapy medicine paclitaxel or docetaxel as first treatment for metastatic breast cancer or it may be prescribed alone if other treatments have proved unsuccessful. It is also used in combination with medicines called aromatase inhibitors with patients with high levels of HER2 and hormone receptor-positive metastatic breast cancer (cancer that is sensitive to the presence of female sex hormones).
- You have metastatic gastric cancer with high levels of HER2, when it is in combination with the other cancer medicines capecitabine or 5-flououracil and cisplatin.

2. Before you use Hervycta®

Do not use Hervycta® if:

- you are allergic to trastuzumab, to murine (mouse) proteins, or to any of the other ingredients of this medicine.
- you have severe breathing problems at rest due to your cancer or if you need oxygen treatment.

Warnings and precautions

Your doctor will closely supervise your therapy.

Heart checks

Treatment with Hervycta® alone or with a taxane may affect the heart, especially if you have ever used an anthracycline (taxanes and anthracyclines are two other kinds of medicine used to treat cancer). The effects may be moderate to severe and could cause death. Therefore, your heart function will be checked before, during (every three months) and after (up to two to five years) treatment with Hervycta®. If you develop any signs of heart failure (inadequate pumping of blood by the heart), your heart function may be checked more frequently (every six to eight weeks), you may receive treatment for heart failure or you may have to stop Hervycta® treatment.
Talk to your doctor, pharmacist or nurse before you are given Hervycta® if:

- you have had heart failure, coronary artery disease, heart valve disease (heart murmurs), high blood pressure, taken any high blood pressure medicine or are currently taking any high blood pressure medicine.
- you have ever had or are currently using a medicine called doxorubicin or epirubicin (medicines used to treat cancer). These medicines (or any other anthracyclines) can damage heart muscle and increase the risk of heart problems with trastuzumab.
- you suffer from breathlessness, especially if you are currently using a taxane. Trastuzumab can cause breathing difficulties, especially when it is first given. This could be more serious if you are already breathless. Very rarely, patients with severe breathing difficulties before treatment have died when they were given trastuzumab.
- you have ever had any other treatment for cancer.

If you receive Hervycta® with any other medicine to treat cancer, such as paclitaxel, docetaxel, an aromatase inhibitor, capecitabine, 5-fluorouracil, or cisplatin you should also read the patient information leaflets for these products.

Children and adolescents

Hervycta® is not recommended for anyone under the age of 18 years.

Other medicines and Hervycta®

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or may take any other medicines.
It may take up to 7 months for trastuzumab to be removed from the body. Therefore you should tell your doctor, pharmacist or nurse that you have had trastuzumab if you start any new medicine in the 7 months after stopping treatment.

Pregnancy

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine.
- You should use effective contraception during treatment withHervycta® and for at least 7 months after treatment has ended.
  Your doctor will advise you of the risks and benefits of taking trastuzumab during pregnancy. In rare cases, a reduction in the amount of (amniotic) fluid that surrounds the developing baby within the womb has been observed in pregnant women receiving trastuzumab. This condition may be harmful to your baby in the womb and has been associated with the lungs not developing fully resulting in foetal death.

Breast-feeding

Do not breast-feed your baby during Hervycta® therapy and for 7 months after the last dose of Hervycta® as trastuzumab may pass to your baby through your breast milk.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

It is not known whether Hervycta® can affect your ability to drive a car or operate machines. However, if during treatment, you experience symptoms, such as chills or fever, you should not drive or use machines until these symptoms disappear.

3. How to use Hervycta®

Before starting the treatment your doctor will determine the amount of HER2 in your tumour. Only patients with a large amount of HER2 will be treated with Hervycta®. Hervycta® should only be given by a doctor or nurse.
Hervycta® intravenous formulation is given as an intravenous infusion (“drip”) directly into your veins. The first dose of your treatment is given over 90 minutes and you will be observed by a health professional while it is being given in case you have any side effects. If the first dose is well tolerated the next doses may be given over 30 minutes (see section 2 under “Warnings and precautions”). The number of infusions you receive will depend on how you respond to the treatment. Your doctor will discuss this with you.
For early breast cancer, metastatic breast cancer and metastatic gastric cancer, Hervycta® is given every 3 weeks. Hervycta® may also be given once a week for metastatic breast cancer.

If you stop using Hervycta®

Do not stop using this medicine without talking to your doctor first. All doses should be taken at the right time every week. This helps your medicine work as well as it can.
It may take up to 7 months for trastuzumab to be removed from your body. Therefore your doctor may decide to continue to check your heart functions, even

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these side effects may be serious and may lead to hospitalisation.
During treatment with trastuzumab, chills, fever and other flu like symptoms may occur. These are very common (may affect more than 1 in 10 people). Other symptoms are: feeling sick (nausea), vomiting, pain, increased muscle tension and shaking, headache, dizziness, breathing difficulties, wheezing, high or low blood pressure, heart rhythm disturbances (palpitations, heart fluttering or irregular heart beat), swelling of the face and lips, rash and feeling tired. Some of these symptoms can be serious and some patients have died (see the section "Warnings and precautions").
You will be observed by a healthcare professional during the administration and for six hours after the start of the first administration and for two hours after the start of other administrations.
Heart problems can sometimes occur during treatment and occasionally after treatment has stopped and can be serious. They include weakening of the heart muscle possibly leading to heart failure, inflammation (swollen, red, hot, and in pain) of the lining around the heart and heart rhythm disturbances. This can lead to symptoms such as:

- breathlessness (including breathlessness at night)
- cough
- fluid retention (swelling) in the legs or arms
- palpitations (heart fluttering or irregular heart beat).

Your doctor will monitor your heart regularly during and after treatment but you should tell your doctor immediately if you notice any of the above symptoms.
If you experience any of the above symptoms when your treatment with trastuzumab has finished, you should see your doctor and tell them that you have previously been treated with trastuzumab.

Very common side effects of trastuzumab: may affect more than 1 in 10 people

- infections
- diarrhoea
- constipation
- heartburn (dyspepsia)
- weakness
- skin rashes
- chest pain
- abdominal pain
- joint pain
- low counts of red blood cells and white blood cells (which help fight infection) sometimes with fever
- muscle pain
- conjunctivitis
- watery eyes
- nose bleeds
- runny nose
- hair loss
- tremor
- hot flush
- dizziness
- nail disorders
- weight loss
- loss of appetite
- inability to sleep (insomnia)
- altered taste
- low platelet count
- bruising
- numbness or tingling of the fingers and toes
- redness, swelling or sores in your mouth and/or throat
- pain, swelling, redness or tingling of hands and/or feet
- breathlessness
- headache
- cough
- vomiting
- nausea

Common side effects of trastuzumab: may affect up to 1 in 10 people

- allergic reactions
- dry mouth and skin
- throat infections
- dry eyes
- bladder and skin infections
- sweating
- shingles
- feeling weak and unwell
- inflammation of the breast
- anxiety
- inflammation of the pancreas or liver

- depression
- kidney disorders
- abnormal thinking
- increased muscle tone or tension (hypertonia)
- asthma
- infection of lungs
- pain in the arms and/or legs
- lung disorders
- itchy rash
- back pain
- sleepiness (somnolence)
- neck pain
- haemorrhoids
- bone pain
- itchiness
- acne
- leg cramps

Uncommon side effects of trastuzumab: may affect up to 1 in 100 people
- deafness
- bumpy rash
- blood infection

Rare side effects of trastuzumab: may affect up to 1 in 1,000 people
- weakness
- jaundice
- inflammation or scarring of the lungs

Other side effects that have been reported with trastuzumab use: frequency cannot be estimated from the available data
- abnormal or impaired blood clotting
- anaphylactic reactions
- high potassium levels
- swelling of the brain
- swelling or bleeding at the back of the eyes
- shock
- swelling of the lining of the heart
- slow heart rate
- abnormal heart rhythm
- respiratory distress
- respiratory failure
- acute accumulation of fluid in the lungs
- acute narrowing of the airways
- abnormally low oxygen levels in the blood
- difficulty in breathing when lying flat
- liver damage/failure
- swelling of the face, lips and throat
- kidney failure
- abnormally low levels of fluid around baby in womb
- failure of lungs to develop in the womb
- abnormal kidney development in the womb

Some of the side effects you experience may be due to your underlying breast cancer. If you receive trastuzumab in combination with chemotherapy, some of them may also be due to the chemotherapy.

If you get any side effects, talk to your doctor, pharmacist or nurse.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hervycta®

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Keep the vial in the outer carton to protect from light.

Do not freeze.

Do not use this medicine if you notice any particulate matter or discoloration prior to administration.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Further Information

For further information please write to safetybiologicals@drreddys.com

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