Herzuma®
Trastuzumab

WARNING

Do not substitute Herzuma® for or with trastuzumab emtansine (Kadcyla). In order to prevent medication errors, check the vial labels to ensure that the medicine being prepared and administered is Herzuma® (trastuzumab) and not trastuzumab emtansine (Kadcyla).

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1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent.

ATC code: L01XC03

1.2 Type of Dosage Form

Intravenous (IV) formulation: Powder for concentrate for solution for infusion.

1.3 Route of Administration

Intravenous infusion.

1.4 Sterile / Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

Active ingredient: trastuzumab.

Dosage Preparations: 150 mg single dose vials, and 440 mg multidose vial containing powder for concentrate for solution for infusion. Reconstituted Herzuma® concentrate contains 21 mg/ml of trastuzumab.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indications

Metastatic Breast Cancer (MBC)

Herzuma® is indicated for the treatment of patients with metastatic breast cancer who have tumors that overexpress HER2:

a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease
b) in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease
c) in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab. This indication is based on data from one Phase III trial which studied the use of Herzuma® in combination with anastrozole (see 3.1.2 Clinical/ Efficacy Studies).

Experience with other aromatase inhibitors is limited.

Early Breast Cancer (EBC)
Herzuma® is indicated for the treatment of patients with HER2 positive early breast cancer.

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 3.1).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Herzuma® therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 2.4 and 3.1).
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Herzuma® should only be used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

Metastatic Gastric Cancer (MGC)
Herzuma® in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro- esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herzuma® should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, or IHC 3+, as determined by an accurate and validated assay.

2.2 Dosage and Administration

HER2 testing is mandatory prior to initiation of Herzuma® therapy.
Herzuma is a biosimilar product.
Substitution by any other biological medicinal product requires the consent of the prescribing physician. Physician to assess and monitor response upon switching of product.

Herzuma® should be administered by a qualified health care professional.

In order to prevent medication errors it is important to check the vial labels to ensure that the drug being prepared and administered is Herzuma® (trastuzumab) and not Kadcyla (trastuzumab emtansine).

Herzuma® (see section 4. Pharmaceutical Particulars):
Herzuma® is not to be used for subcutaneous administration and should be administered as intravenous infusion.

Do not administer as an intravenous push or bolus.

Metastatic breast cancer
Weekly schedule:
Loading dose: The recommended initial loading dose is 4 mg/kg body weight Herzuma® administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see 2.6 Undesirable effects). Interruption of the

infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses: The recommended weekly dose of Herzuma® is 2 mg/kg body weight. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see 2.6 Undesirable effects).

Administration in combination with an aromatase inhibitor
In the pivotal trial 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 Product Information for anastrozole or other aromatase inhibitors).

3-weekly schedule:
Alternatively the following loading and subsequent doses are recommended for monotherapy and in combination with paclitaxel or an aromatase inhibitor.

Initial Herzuma® loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

Early breast cancer
3-weekly schedule:
As a three-weekly regimen the recommended initial loading dose of Herzuma® is 8 mg/kg body weight. The recommended maintenance dose of Herzuma® at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Alternative weekly schedule:
As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

Metastatic Gastric Cancer
3-weekly schedule:
Herzuma® is administered at an initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the initial loading dose is well tolerated, the subsequent doses can be administered as a 30-minute infusion (See section 3.1 for chemotherapy combination dosing).

Duration of treatment
In clinical studies, patients with metastatic breast cancer or metastatic gastric cancer were treated with trastuzumab until progression of disease. Patients with early breast cancer should be treated for 1 year or until disease recurrence, whichever occurs first. Extending treatment in EBC beyond one year is not recommended (see section 3.1.2 Clinical / Efficacy Studies).

For instructions for use and handling refer to Section 4.2.

Dose reduction

If the patient develops an infusion-related reaction (IRR), the infusion rate of Herzuma IV may be slowed or interrupted.
No reductions in the dose of trastuzumab were made during clinical trials. Patients may continue Herzuma® therapy during periods of reversible, chemotherapy-induced myelosuppression, but they should be monitored carefully for complications of neutropenia during this time. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Missed doses
If the patient has missed a dose of Herzuma® 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 Herzuma® maintenance doses 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 Herzuma® by more than one week, a re-loading dose of Herzuma® should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; 3- weekly regimen: 8 mg/kg) as soon as possible. Subsequent Herzuma® 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.

Duration of treatment
In clinical studies, patients with metastatic breast cancer were treated with trastuzumab until progression of disease. Patients with early breast cancer should be treated for 1 year or until disease recurrence, whichever occurs first. Extending treatment in EBC beyond one year is not recommended (see section 3.1.2 Clinical / Efficacy Studies).

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2.2.1 Special Dosage Instructions

Elderly
Data suggest that the disposition of trastuzumab is not altered based on age or serum creatinine (see Pharmacokinetics in special populations). In clinical trials, elderly patients did not receive reduced doses of trastuzumab. Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. However in a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Children
The safety and efficacy of trastuzumab in pediatric patients have not been established.

2.3 Contraindications

Patients with known hypersensitivity to trastuzumab, murine proteins, hyaluronidase or to any other component of the product. Patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

2.4 Warnings and Precautions

2.4.1 General

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Herzuma® therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

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

Cardiac dysfunction

General considerations

Patients treated with trastuzumab are at increased risk of developing congestive heart failure (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 taxane following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. This may be moderate to severe and has been associated with death (see section 2.6 Undesirable Effects). In addition, caution should be exercised in treating patients with increased cardiac risk (e.g. hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age).

Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment (see 3.2 Pharmacokinetic Properties). Patients who receive anthracycline after stopping trastuzumab may also 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.

Candidates for treatment with trastuzumab, especially those with prior exposure to an anthracycline, should undergo baseline cardiac assessment including history and physical examination, and electrocardiogram (ECG) echocardiogram, and/or multigated acquisition scanning (MUGA) scan. In EBC, the following patients were excluded from the HERA trial, there are no data about the benefit-risk balance, and therefore treatment cannot be recommended in such patients:

- History of documented congestive heart failure
- High-risk uncontrolled arrhythmias
- Angina pectoris requiring a medicinal product
- Clinically significant valvular disease
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension

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Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. Cardiac function should be further monitored during treatment (e.g. every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction, including signs and symptoms of CHF. 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.

If LVEF percentage drops 10 points from baseline and to below 50%, trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further or if clinically significant CHF has developed, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. 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 symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with standard medications for heart failure (HF). In the pivotal trials, most patients who developed HF or asymptomatic cardiac dysfunction improved with standard HF treatment consisting of diuretics, cardiac glycosides, angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a β-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of trastuzumab treatment continued with trastuzumab without additional clinical cardiac events.

Metastatic breast cancer (MBC)
Trastuzumab and anthracyclines should not be given concurrently in the metastatic breast cancer setting.

Early breast cancer (EBC)
For patients with EBC, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. In patients who receive anthracycline containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of trastuzumab, or longer if a continuous decrease of LVEF is observed.

Patients with history of myocardial infarction (MI), angina pectoris requiring medication, history of or present CHF (NYHA Class II –IV), other cardiomyopathy, cardiac arrhythmia requiring medication, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medication eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant breast cancer clinical trials with trastuzumab.

Adjuvant treatment

Trastuzumab and anthracyclines should not be given concurrently 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. The incidence 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.

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low level of baseline and declining LVEF (< 55%), low LVEF prior to or following the initiation of paclitaxel treatment, trastuzumab treatment, and prior or concurrent use of anti- hypertensive medications. 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 high body mass index (BMI>25 kg/m^2).

Neoadjuvant-adjuvant treatment
In patients with EBC eligible for neoadjuvant-adjuvant treatment, trastuzumab concurrently with anthracyclines should be used with caution and only in chemotherapy-naive patients. The maximum cumulative doses of the low-dose anthracycline regimens should not exceed 180 mg/m2 (doxorubicin) or 360 mg/m2 (epirubicin).

If patients have been treated concurrently with low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery.

Clinical experience in the neoadjuvant-adjuvant setting is limited in patients above 65 years of age.

Administration related reactions
Administration related reactions (ARRs) are known to occur with the administration of trastuzumab. ARRs may be clinically difficult to distinguish from hypersensitivity reactions. Pre-medication may be used to reduce risk of occurrence of ARRs.

Caution should be exercised as serious ARRs, including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, supraventricular tachyarrhythmia and urticaria have been associated with the intravenous formulation. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms (see section 4.2). The majority of patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab. Patients should be observed for IRRs. Interruption of an IV infusion may help control such symptoms and the infusion may be resumed when symptoms abate. They can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions to trastuzumab have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions were 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 ARR. Therefore, these patients should not be treated with trastuzumab (see section 2.3).

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms or 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 resulted in fatal outcome and may occur as part of an infusion related reaction (IRR) or with a delayed onset. In addition, cases of lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with trastuzumab (see section 2.3). Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

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.

Benzyl alcohol
Benzyl alcohol, used as a preservative in bacteriostatic water for injection in the 440 mg multidose vial, has been associated with toxicity in neonates and children up to 3 years old. When administering trastuzumab to a patient with a known hypersensitivity to benzyl alcohol, trastuzumab should be reconstituted with water for injection, and only one dose per trastuzumab vial should be used. Any unused portion must be discarded. Sterile water for injection, used to reconstitute the 150 mg single dose vial, does not contain benzyl alcohol.

2.4.2 Ability to Drive and Use Machines
No studies on the effects on the ability to drive and to use machines have been performed. Patients experiencing administration-related symptoms should be advised not to drive or use machines until symptoms resolve completely.

2.4.3 Interactions with other Medicinal Products and other Forms of Interaction
There have been no formal drug interaction studies performed with trastuzumab in humans. Clinically significant interactions between trastuzumab and the concomitant medications used in clinical trials have not been observed.

In studies where trastuzumab was administered in combination with docetaxel, carboplatin, or anastrozole, the pharmacokinetics of these medications was not altered nor was the pharmacokinetics of trastuzumab altered.

Concentrations of paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) were not altered in the presence of trastuzumab.

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 is unclear. No changes were observed in trastuzumab concentrations in the presence of paclitaxel and doxorubicin.

The results of a drug interaction substudy evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab

2.5 Use in Special Populations

2.5.1 Pregnancy

Herzuma® should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus. In the postmarketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herzuma®. Women of childbearing potential should be advised to use effective contraception during treatment with Herzuma® and for at least 7 months after treatment has concluded (see 3.2 Pharmacokinetic Properties). Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herzuma®, or if a patient becomes pregnant while receiving Herzuma® or within 7 months following last dose of Herzuma®, close monitoring by a multidisciplinary team is desirable. It is not known whether Herzuma® can affect reproductive capacity. Animal reproduction studies revealed no evidence of impaired fertility or harm to the fetus (see section 3.3.1 Teratogenicity).

2.5.2 Nursing Mothers

It is not known whether trastuzumab is secreted in human milk. As human IgG is secreted into human milk, and the potential for harm to the infant is unknown, breast-feeding should be avoided during Herzuma® therapy (see section 3.3.3 Other, *Lactation*).

2.5.3 Renal Impairment

In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition

2.6 Undesirable Effects

2.6.1 Clinical Trials

Amongst the most serious and/or common adverse reactions reported in trastuzumab usage to date are cardiac dysfunction, administration- 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 should be presented in order of decreasing seriousness.

List of adverse reactions
Presented in the following table 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.

As trastuzumab is commonly used with other chemotherapeutic agents and radiotherapy it is often difficult to ascertain the causal relationship of an adverse event to a particular drug/radiotherapy.

Table 1

System organ class	**Adverse reaction**	**Frequency**
Infections and infestations	Infection	Very common
	Nasopharyngitis	Very common
	+Pneumonia	Common (<1 %)
	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
	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
	Thrombocytopenia	Very common
	Neutropenia	Common
	White blood cell count decreased/leukopenia	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 Increased	Very common
	Weight Decreased/Weight Loss	Common
	Anorexia	Common
	Hyperkalaemia	Not known
Psychiatric disorders	Insomnia	Very common
	Anxiety	Common
	Depression	Common

	Thinking abnormal	Common
Nervous system disorders	[1]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Peripheral neuropathy	Common
	Paraesthesia	Common
	Hypertonia	Common
	Somnolence	Common
	Dysgeusia	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and Labyrinth Disorders	Deafness	Uncommon
Cardiac disorders	1 Blood pressure decreased	Very common
	1 Blood pressure increased	Very common
	1 Heart beat irregular	Very common
	1Palpitation	Very common
	1Cardiac flutter	Very common
	+1Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Ejection fraction decreased*	Very Common
	+Cardiac failure (congestive)	Common (2 %)
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis	Not known
	Bradycardia	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very common
	Lympohedema	Very common
	+1 Hypotension	Common
	Hypertension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	+1Wheezing	Very common
	+Dyspnoea	Very common (14 %)
	Cough	Very Common
	Epistaxis	Very Common
	Oropharyngeal pain	Very Common
	Rhinorrhoea	Very Common
	Asthma	Common
	Lung disorder	Common
	Pharyngitis	Common
	Pneumonia	Common
	+Pleural effusion	Uncommon
	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
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Pancreatitis	Common
	Haemorrhoids	Common
	Constipation	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular Injury	Common
	Hepatitis	Common
	Liver Tenderness	Common
	Jaundice	Rare
	Hepatic Failure	Not known
Skin and subcutaneous disorders	Erythema	Very common
	Rash	Very common
	[1] Swelling face	Very common
	Nail disorder	Very common
	Acne	Common
	Alopecia	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	[1]Muscle tightness	Very common
	Myalgia	Very common

	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Pain in extremity	Common
	Neck pain	Common
Renal and urinary conditions	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal disorders	Oligohydramnios	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
	Peripheral oedema	Very common
	Mucosal inflammation	Very common
	Malaise	Common
	Oedema	Common
	Injection site pain**	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common
	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

** ADRs were added to the appropriate system organ class (SOC) category and are presented in a single table according to the highest incidence seen in any of the major clinical trials.

Note: Specific percentage frequencies have been provided in brackets for terms that have been reported in association with a fatal outcome with the frequency designation 'common' or 'very common'. The specific percentage frequencies relate to total number of these events, both fatal and non-fatal.

The following adverse reactions were reported in pivotal clinical trials with a frequency of ≥ 1/10 in either treatment arm (in HERA, BO16348 ≥1% at 1 year) and with no significant difference between the trastuzumab-containing arm and the comparator arm: lethargy, hypoaesthesia, pain in extremity, oropharyngeal pain, conjunctivitis, lymphoedema, weight increased, nail toxicity, musculoskeletal pain, pharyngitis, bronchitis, chest discomfort, abdominal pain upper, gastritis, stomatitis, vertigo, hot flush, hypertension, hiccups, palmar-

plantar erythrodysaesthesia syndrome, breast pain, onychorrhexis, dyspnoea exertional and dysuria.

Immunogenicity

Infusion/Administration-related reactions (IRRs) and Hypersensitivity
IRRs/ARRs such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress were seen in all trastuzumab clinical trials (see section 2.4 Warnings and Precautions).

IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions.

The rate of IRRs/ARRs of all grades varied between studies depending on the indication, whether trastuzumab was given concurrently with chemotherapy or as monotherapy and data collection methodology.

In MBC, the rate of IRRs ranged from 49% to 54% in the trastuzumab containing arm compared to 36% to 58% in the comparator arm (which may have contained other chemotherapy). Severe (grade 3 and above) ranged from 5% to 7% in the trastuzumab containing arm compared to 5 to 6% in the comparator arm.

In EBC, the rate of IRRs ranged from 18% to 54% in the trastuzumab containing arm compared to 6% to 50% in the comparator arm (which may have contained other chemotherapy). Severe (grade 3 and above) ranged from 0.5% to 6% in the trastuzumab containing arm compared to 0.3 to 5% in the comparator arm.

Anaphylactoid reactions were observed in isolated cases.

Serious Pulmonary Events
Single cases of pulmonary infiltrates, pneumonia, pulmonary fibrosis, pleural effusion, respiratory distress, acute pulmonary oedema, acute respiratory distress syndrome (ARDS) and respiratory insufficiency have been reported rarely. These events have been reported rarely with fatal outcome (see Section 2.4).

Cardiac Dysfunction
Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to trastuzumab. It has been associated with 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 (see section 2.4 Warnings and Precautions).

Metastatic Breast Cancer
Depending on the criteria used to define cardiac dysfunction, the incidence in the pivotal metastatic trials varied between 9% and 12% in the trastuzumab + paclitaxel group, compared with 1% – 4% in the paclitaxel alone group. For trastuzumab monotherapy, the rate was 6% – 9%. The highest rate of cardiac dysfunction was seen in patients receiving concurrent trastuzumab + anthracycline/cyclophosphamide (27%), and was significantly higher than in the anthracycline/ cyclophosphamide alone group (7% – 10%). In a subsequent trial with prospective monitoring of cardiac function, the incidence of

symptomatic heart failure 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.

Early Breast Cancer (adjuvant setting)
In three pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone 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%). At 3 years, the cardiac event rate in patients receiving AC→P (doxorubicin plus cyclophosphamide followed by paclitaxel) + H (trastuzumab) was estimated at 3.2%, compared with 0.8% in AC→P treated patients. No increase in the cumulative incidence of cardiac events was seen with further follow-up at 5 years.

At 5.5 years, the rates of symptomatic cardiac or LVEF events were 1.0%, 2.3%, and 1.1% in the AC→D (doxorubicin plus cyclophosphamide, followed by docetaxel), AC→DH (doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab), and DCarbH (docetaxel, carboplatin and trastuzumab) treatment arms, respectively. For symptomatic CHF (NCI-CTC Grade 3 - 4), the 5-year rates were 0.6%, 1.9%, and 0.4% in the AC→D, AC→DH, and DCarbH treatment arms, respectively. The overall risk of developing symptomatic cardiac events was low and similar for patients in the AC→D and DCarbH arms; relative to both the AC→D and DCarbH arms there was an increased risk of developing a symptomatic cardiac event for patients in the AC→DH arm, being discernable by a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events up to 2.3% compared to approximately 1% in the two comparator arms (AC→D and DCarbH).

When trastuzumab was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6% of patients in the one-year arm after a median follow-up of 12 months. After a median follow-up of 3.6 years the incidence of severe CHF and left ventricular dysfunction after 1 year trastuzumab therapy remained low at 0.8% and 9.8%, respectively.

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 $\geq$ 50% after the event) was evident for 71.4% of trastuzumab-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of trastuzumab-treated patients. Approximately 17% of cardiac dysfunction related events occurred after completion of trastuzumab.

In the joint analysis of studies NSABP B-31 and NCCTG N9831, with a median follow-up of 8.1 years for the AC→PH group (doxorubicin plus cyclophosphamide, followed by paclitaxel plus trastuzumab), the per patient incidence of new onset cardiac dysfunction, as determined by LVEF, remained unchanged compared to the analysis performed at a median follow up of 2.0 years in the AC→PH group: 18.5% of AC→PH patients with an LVEF

decrease of ≥10% to below 50%. Reversibility of left ventricular dysfunction was reported in 64.5% of patients who experienced a symptomatic CHF in the AC→PH group being asymptomatic at latest follow up, and 90.3% having full or partial LVEF recovery.

Early Breast Cancer (neoadjuvant-adjuvant setting)
In the pivotal trial MO16432, trastuzumab was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2). The incidence of symptomatic cardiac dysfunction was 1.7 % in the trastuzumab arm.

Metastatic Gastric Cancer
In BO18255 study, at screening, the median LVEF value was 64% (range 48 %-90 %) in the Fluoropyrimidine/Cisplatin arm (FP) and 65 % (range 50 %-86 %) in the trastuzumab plus Fluoropyrimidine/Cisplatin arm (FP+H).

The majority of the LVEF decreases noted in BO18255 study were asymptomatic, with the exception of one patient in the trastuzumab-containing arm whose LVEF decrease coincided with cardiac failure.

Table 2: Summary of LVEF Change from baseline (BO18255 study)

LVEF Decrease : Lowest Post-screening Value	Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)
*LVEF decrease of ≥ 10% to a value of < 50%	4.6%	1.1%
Absolute Value < 50%	5.9%	1.1%
*LVEF decrease of ≥ 10% to a value of ≥ 50%	16.5%	11.8%

*Only includes patients whose method of assessment at that visit is the same as at their initial assessments (FP, n = 187 and FP+H, n = 37)

Table 3: Cardiac Adverse Events (BO18255 study)

	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)	**Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)**
Total Cardiac Events	6%	6%
≥Grade 3 NCI CTCAE v3.0	*3%	**1%

* 9 patients experienced 9 Events
** 4 patients experienced 5 Events

Overall, there were no significant differences in cardiac dysfunction between the treatment arm and the comparator arm.

Haematological toxicity

Breast Cancer
Haematological toxicity was infrequent following the administration of trastuzumab as a single agent in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in < 1 % of patients. No WHO Grade 4 toxicities were observed.

There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of trastuzumab and paclitaxel compared with patients receiving paclitaxel alone (34 % versus 21 %). Haematological toxicity was also increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32 % grade 3/4 neutropenia versus 22 %, using NCI- CTC criteria). Note that this is likely to be an underestimate since docetaxel alone at a dose of 100mg/m^2 is known to result in neutropenia in 97 % of patients, 76% grade 4, based on nadir blood counts. The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with trastuzumab plus docetaxel (23 % versus 17 % for patients treated with docetaxel alone).

Using NCI-CTC criteria, in the BO16348 study trial, 0.4% of trastuzumab-treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

Advanced Gastric Cancer
The most frequently reported AEs, of Grade ≥ 3 occurring with an incidence rate of at least 1% by trial treatment, that were categorised under the Blood and Lymphatic System Disorders SOC are shown below:

Table 4: Frequently reported AEs grade ≥ 3 in blood and lymphatic system disorders SOC

	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)	**Trastuzumab/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)**
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile neutropenia	3%	5%
Thrombocytopenia	3%	5%

The total percentage of patients who experienced an AE of ≥ grade 3 NCI-CTCAE v3.0 that has been categorised under this SOC were 38% in the FP arm and 40% in the FP + H arm.

Overall, there were no significant differences in haematotoxicity between the treatment arm and the comparator arm.

Hepatic and renal toxicity
Breast Cancer
WHO Grade 3 or 4 hepatic toxicity was observed in 12 % of patients following administration of trastuzumab as single agent, in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60 % of these patients. WHO Grade 3 or 4 hepatic toxicity was less frequently observed among patients receiving trastuzumab and paclitaxel than among

patients receiving paclitaxel (7 % compared with 15 %). No WHO Grade 3 or 4 renal toxicity was observed.

Metastatic Gastric Cancer
In BO18255 study no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

NCI-CTCAE (version 3.0) grade ≥3 renal toxicity was not significantly higher in patients receiving trastuzumab + FP than those in the FP arm (3% and 2% respectively).

NCI-CTCAE (version 3.0) grade ≥3 adverse event in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported AE and was not significantly higher in patients receiving trastuzumab + FP than those in the FP arm (1% and < 1% respectively).

Diarrhoea
Breast Cancer
Of patients treated with trastuzumab as a single agent in the metastatic setting, 27 % experienced diarrhoea. An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has also been observed in patients receiving trastuzumab in combination with paclitaxel compared with patients receiving paclitaxel alone.

In the BO16348 study trial, 8 % of trastuzumab-treated patients experienced diarrhea during the first year of treatment.

Metastatic Gastric Cancer
In BO18255 study, 109 patients (37 %) participating in the trastuzumab-containing treatment arm versus 80 patients (28 %) in the comparator arm experienced any grade diarrhoea. Using NCI CTCAE severity criteria, the percentage of patients experiencing grade ≥3 diarrhoea was 4 % in the FP arm vs 9 % in the FP+H arm.

Infection
An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections has been observed in patients treated with trastuzumab.

2.6.1.1 Laboratory Abnormalities
Febrile neutropenia occurs very commonly. Commonly occurring adverse reactions include anaemia, leukopenia, thrombocytopenia and neutropenia. The frequency of occurrence of hypoprothrombinemia is not known.

2.7 Overdose
Trastuzumab
There is no experience with overdose in human clinical trials. Single doses higher than 10 mg/kg have not been tested.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 Pharmacodynamic Properties
3.1.1 Mechanism of Action

Trastuzumab is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG1 that contains human framework regions with the complementarity- determining regions of a murine anti-p185 HER2 antibody that binds to HER2.

The HER2 proto-oncogene or c-erbB2 encodes for a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 15%-20% of primary breast cancer. The overall rate of HER2 positivity in advanced gastric cancers as observed during screening for study BO18255 is 15% for IHC3+ and IHC2+/FISH+ or 22.1% when applying the broader definition of IHC3+ or FISH+ A consequence of HER2 gene amplification is an increase in HER2 protein expression on the surface of these tumour cells, which results in a constitutively activated HER2 receptor.

Studies indicate that patients whose tumors have amplification or overexpression of HER2 have a shortened disease-free survival compared to patients whose tumors do not have amplification or overexpression of HER2.

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

3.1.2 Clinical / Efficacy Studies

Efficacy

MBC

Trastuzumab monotherapy has been used in clinical trials for patients with metastatic breast cancer who have tumors that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease.

Trastuzumab has also been used in clinical trials in combination with paclitaxel or an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC) as first line therapy for patients with metastatic breast cancer who have tumors that overexpress HER2.

Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m^2 infused over 3 hours) with or without trastuzumab. Patients could be treated with trastuzumab until progression of disease.

Trastuzumab monotherapy, when used as second- or third-line treatment of women with metastatic breast cancer which overexpresses HER-2, results in an overall tumor response rate of 15% and a median survival of 13 months.

The use of trastuzumab in combination with paclitaxel as first-line treatment of women with metastatic breast cancer that overexpresses HER-2 significantly prolongs the median time to disease progression, compared with patients treated with paclitaxel alone. The increase in median time to disease progression for patients treated with trastuzumab and paclitaxel is 3.9 months (6.9 months vs. 3.0 months). Tumor response and one year survival rate are also

increased for trastuzumab in combination with paclitaxel versus paclitaxel alone.

Combination treatment with trastuzumab and anastrozole
Trastuzumab has been studied in combination with anastrozole for first line treatment of metastatic breast cancer 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.

3-weekly dosing in MBC
The efficacy results from the non-comparative monotherapy and combination therapy studies are summarised in the following table:

Table 5

Parameter	Monotherapy		Combination Therapy
	Trastuzumab[1] N=105	**Trastuzumab[2] N=72**	**Trastuzumab plus paclitaxel[3] N=32**
Response rate (95%CI)	24% (15 - 35)	27% (14 - 43)	59% (41-76)
Median duration of response (months) (range)	10.1 (2.8-35.6)	7.9 (2.1-18.8)	10.5 (1.8-21)
Median TTP (months) (95%CI)	3.4 (2.8-4.1)	7.7 (4.2-8.3)	12.2 (6.2-ne)
Median Survival (months) (95%CI)	ne	ne	ne

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.
1. Study WO16229: loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule
2. Study MO16982: loading dose 6mg/kg weekly x 3; followed by 6mg/kg 3-weekly schedule
3. BO15935

EBC
In the adjuvant treatment setting, trastuzumab was investigated in 4 large multicentre, randomised, phase 3 trials:

- Study BO16348 study was designed to compare one year and two years of three-weekly

trastuzumab treatment versus observation in patients with HER2 positive early breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of two years of trastuzumab treatment versus one year of trastuzumab treatment was performed. Patients assigned to receive trastuzumab were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years.

- Studies NSABP B-31 and NCCTG N9831 that comprise the joint analysis were designed to investigate the clinical utility of combining trastuzumab treatment with paclitaxel following AC chemotherapy; additionally the NCCTG N9831 study investigated adding trastuzumab sequentially to AC-paclitaxel chemotherapy in patients with HER2 positive early breast cancer following surgery.
- Study BCIRG 006 study was designed to investigate combining trastuzumab treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2 positive early breast cancer following surgery.

Early breast cancer in the Study BO16348 was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative tumours of at least 1 cm in diameter.

The efficacy results from the BO16348 study are summarized in the following table:

Table 6: Efficacy Results BO16348 study: Results at 12months* and 8 years of median follow-up**

Parameter	Median follow-up 12 months		Median follow-up 8 years	
	Observation N=1693	Trastuzumab 1 Year N = 1693	Observation N= 1697***	Trastuzumab 1 Year N = 1702***
Disease-free survival - No. patients with event - No. patients without event	219 (12.9%) 1474 (87.1%)	127 (7.5%) 1566(92.5%)	570 (33.6%) 1127 (66.4%)	471 (27.7%) 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 - No. patients without event	208 (12.3%) 1485 (87.7%)	113 (6.7%) 1580 (93.3%)	506 (29.8%) 1191 (70.2%)	399 (23.4%) 1303 (76.6%)
P-value versus Observation	<0.0001		<0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease-free survival - No. patients with event - No. patients without event	184 (10.9%) 1508 (89.1%)	99 (5.8%) 1594 (94.6%)	488 (28.8%) 1209 (71.2%)	399 (23.4%) 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 vs 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 vs. observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 1.54 (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 vs 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 joint analysis of the NSABP B-31 and NCCTG N9831 studies, early breast cancer was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node positive or HER2 positive and lymph node negative with high risk features (tumour size > 1 cm and ER negative or tumour size > 2 cm, regardless of hormonal status). Trastuzumab was administered in combination with paclitaxel, following AC chemotherapy. Paclitaxel was administered as follows:

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

Table 7: Summary of Efficacy results from the joint analysis studies NSABP B-31 and NCCTG N9831 at the time of the definitive DFS analysis*

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

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

Source: Table 15 Clinical Study Report: Joint Analysis of B-31 and N9831, 04 February 2006, Genentech, Inc.

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 a 3-year disease-free survival rate, of 11.8 percentage points (87.2% versus 75.4%) in favour of the AC→PH (trastuzumab) arm.

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→P H 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→ P H 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 studies NSABP B-31 and NCCTG N9831 are summarized in the following table:

Table 8: Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831:

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

In the BCIRG 006 study, HER-2 positive, early breast cancer was limited to either lymph node positive or high risk node negative patients, defined as negative (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, estrogen receptor and progesterone receptor negative, histologic and/or nuclear grade 2-3, or age < 35 years. 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:

- intravenously (100 mg/m^2 as an IV 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
- intravenously (75 mg/m^2 as an IV infusion over 1 hour) given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each cycle).
-

Docetaxel therapy was followed by carboplatin (at target AUC = 6 mg/mL/min) administered by IV infusion over 30-60 minutes repeated every 3 weeks for a total of 6 cycles.

The efficacy results from the BCIRG 006 study are summarized in the following tables:

Table 9: Overview of Efficacy Analyses AC→D versus AC→DH (BCIRG 006 study)

Parameter	AC→D (N=1073)	AC→DH (N=1074)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival				
No. patients with event Distant recurrence	195	134	< 0.0001	0.61 (0.49, 0.77)
No. patients with event Overall Survival	144	95	< 0.0001	0.59 (0.46, 0.77)
(Death) No. patients with event	80	49	0.0024	0.58 (0.40, 0.83)

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 (BCIRG 006 study)

Parameter	AC→D (N=1073)	DCarbH (N=1075)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
Distant recurrence No. patients with event	144	103	0.0008	0.65 (0.50, 0.84)
Death (OS event) No. patients with event	80	56	0.0182	0.66 (0.47, 0.93)

AC→D = doxorubicin plus cyclophosphamide, followed by docetaxel; DCarbH = docetaxel, carboplatin and trastuzumab; CI = confidence interval

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of a 3-year disease-free survival rate, 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.

For the secondary endpoint overall survival, treatment with AC→DH reduced the risk of death by 42% when compared to AC→D (hazard ratio 0.58 [95% CI: 0.40, 0.83] p = 0.0024, log-rank test) and the risk of death was reduced by 34% for patients treated with DCarbH compared to patients treated with AC→D (hazard ratio 0.66 [95% CI: 0.47, 0.93], p = 0.0182). In the BCIRG 006 study at the second interim analysis, 185 randomized patients

had died: 80 patients (7.5%) in the AC→D arm, 49 patients (4.6%) in the AC→DH arm, and 56 patients (5.2%) in the DCarbH arm. The median duration of follow-up was 2.9 years in the AC→D arm and 3.0 years in both the AC→DH and DCarbH arms.

In the neoadjuvant-adjuvant treatment setting, trastuzumab was evaluated in two phase 3 trials.

Study MO16432, a multicenter randomised trial, was designed to investigated a total of 10 cycles of neoadjuvant chemotherapy [an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H] concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone, followed by adjuvant trastuzumab for up to a total treatment duration of 1 year) in newly diagnosed locally advanced (Stage III) or inflammatory HER2 positive breast cancer patients. The clinical utility of concurrent administration of trastuzumab with neoadjuvant chemotherapy including both an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H, followed by adjuvant trastuzumab, up to a total treatment duration of 1 year) as follow:

- 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 study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory breast cancer. Patients with HER2+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone.

Table 11: Overview of Efficacy Analyses MO16432 study

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

*

For the primary endpoint, EFS, the addition of trastuzumab to the neoadjuvant chemotherapy followed by adjuvant trastuzumab for a total duration of 52 weeks resulted in a 35% reduction in the risk of disease recurrence/progression. The hazard ratio translates into an absolute benefit, in terms of 3- year event-free survival rate estimates of 13 percentage points (65 % vs 52 %) in favour of the trastuzumab arm.

For non-inferiority of the PK co-primary endpoint, steady-state trastuzumab C_{trough} value at the end of treatment Cycle 7, refer to section 3.2. Pharmacokinetic Properties.

Metastatic Gastric Cancer
Trastuzumab has been investigated in one randomised, open-label phase III trial BO18255 in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine - 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle)

or

- intravenous 5-fluorouracil - 800 mg/m^2/day as a continuous i.v. infusion over 5 days, given every 3 weeks for 6 cycles (days 1 to 5 of each cycle)

Either of which was administered with:

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

The efficacy results from study BO18225 are summarized in the following table:

Table 13 Summary of Efficacy (from study BO18255 study)

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 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.

In an exploratory subgroup analysis performed in the BO18255 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)].

3.2 Pharmacokinetic Properties

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects from 18 Phase I, II and III trials receiving trastuzumab. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to the non-linear elimination, total clearance increased with decreasing concentrations. Linear clearance was 0.127 L/day for breast cancer (MBC/EBC) and 0.176 L/day for AGC. The nonlinear elimination parameters were 8.81 mg/day for the maximum elimination rate (Vmax) and 8.92 mg/L for the Michaelis-Menten constant (Km). The central compartment volume was 2.62 L for patients with breast cancer and 3.63 L for patients with AGC.

The population predicted PK exposures (with 5^{th} - 95^{th} Percentiles) and PK parameter values at clinically relevant concentrations (Cmax and Cmin) for breast cancer and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 14 (Cycle 1) and Table 15 (steady- state) below.

Table 14: Population Predicted Cycle 1 PK Exposure Values (with 5^{th} - 95^{th} Percentiles) for IV Regimens in Breast Cancer and AGC Patients

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

Table 15: Population Predicted Steady State PK Exposure Values (with 5^{th} - 95^{th} Percentiles) for trastuzumab Dosing Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumor type	N	Cmin,ss (µg/mL)	Cmax,ss (µg/mL)	AUCss (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-

8mg/kg + 6mg/kg q3w	MBC/EBC	1195	47.4 (5 -115)	179 (107 -309)	1794 (673 - 3618)	12	0.173 - 0.283
	AGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9	0.189 - 0.337
4mg/kg + 2mg/kg qw	MBC/EBC	1195	66.1 (14.9 -142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 - 0.244

Trastuzumab washout

Trastuzumab washout time period was assessed following trastuzumab administration using the respective population PK models. The result of this simulation indicates that at least 95% of patients will reach serum trastuzumab concentrations that are <1 μg/mL (approximately 3% of the population predicted $C_{min, ss}$, or about 97% washout) by 7 months after the last dose.

3.2.1 Pharmacokinetics in Special Populations

Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out.

Renal Impairment

Detailed pharmacokinetic studies in patients with renal impairment have not been carried out. In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition.

Elderly

Age has been shown to have no effect on the disposition of trastuzumab (see 2.2 Dosage and administration).

3.3 Preclinical Safety

Trastuzumab was well tolerated in mice (non-binding species) and cynomolgus monkeys (binding species) in single- and repeat-dose toxicity studies of up to 6 months duration, respectively. There was no evidence of acute or chronic toxicity identified.

3.3.1 Impairment of Fertility

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab and have revealed no evidence of impaired fertility.

3.3.2 Teratogenicity

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab and have revealed no evidence of harm to the fetus. However, when assessing the risk of reproductive toxicity to humans, it is also important to consider the significance of the rodent form of the HER2 receptor in normal embryonic development and the embryonic death in mutant mice lacking this receptor. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and

late (days 120-150 of gestation) fetal development period was observed.

3.3.3 Other

Lactation

A study conducted in lactating cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast- feed during trastuzumab therapy and for 6 months after the last dose of trastuzumab.

4. COMPARATIVE CLINICAL TRIALS

4.1 Comparative Trial Design and Study Demographics

Clinical studies conducted to support similarity between Herzuma® and the reference biologic drug, Herceptin®, included:

- Study CT-P6 1.5, a randomized, double-blind, parallel-group, single-dose study to compare the PK, safety and immunogenicity of Herzuma® and Herceptin® in healthy volunteers
- Study CT-P6 3.2, a randomized, double-blind, parallel-group, active-controlled study to compare the efficacy and safety of Herzuma® and Herceptin® as neoadjuvant and adjuvant treatment in patients with HER2-positive early breast cancer.

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study are presented in Table 16.

Table 16 Summary of trial design and patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range) (years)	Sex (n)
CT-P6 1.5	Randomized, controlled, 2-arm, parallel-group, double-blind, single-dose study in healthy male subjects	HERZUMA® or HERCEPTIN®: 6 mg/kg, IV infusion for 90 minutes (± 5 minutes)	Randomized: 70 healthy subjects HERZUMA®: 35 HERCEPTIN®: 35	HERZUMA®: 36.2 (20 - 55) HERCEPTIN®: 34.1 (18 - 54)	Male: 70

CT-P6 3.2	Randomized, controlled, 2-arm, parallel-group, double-blind, multicentre, international study in patients with HER2-Positive EBC	**Neoadjuvant Period** HERZUMA® or HERCEPTIN®: • Loading dose of 8 mg/kg on Day 1 of Cycle 1, and then 6 mg/kg repeated every 3 weeks on Day 1 of Cycles 2-8 • 90-minute IV infusion (± 5 minutes) Docetaxel: • Immediately after the dose of study drug (Day 1 of each cycle), 3-weekly for 12 weeks (Cycles 1-4) • 75 mg/m^2 as a 1-hour IV infusion FEC: • Immediately after the dose of study drug (Day 1 of each cycle), 3-weekly for 12 weeks (Cycles 5-8) • Fluorouracil 500 mg/m^2 as a 3- to 5-minute IV bolus or as an infusion for 30 minutes (± 5 minutes); • Epirubicin 75 mg/m^2 as a 3- to 5-minute IV bolus or as an infusion for 30 minutes (± 5 minutes); • Cyclophosphamide 500 mg/m^2 as an IV bolus for 3 to 5 minutes **Adjuvant Period** HERZUMA® or	Randomized: 562 EBC patients HERZUMA®: 278 HERCEPTIN®: 284	HERZUMA®: 52.1 (24 - 79) HERCEPTIN®: 52.0 (22 - 74)	Female: 562

		HERCEPTIN®: ▪ 6 mg/kg, 3-weekly for up to 1 year from the first day of study drug administration in the Neoadjuvant Period, excluding surgery (or up to 10 cycles after surgery) ▪ 90-minute IV infusion (± 5 minutes)			

4.2 Comparative Study Results

4.2.1 Comparative Bioavailability Studies

4.2.1.1. Pharmacokinetics

Comparability criteria were met for the PK parameters C_{max} and AUC_T as the point estimate for the ratio of the geometric means for Herzuma® and Herceptin® for C_{max} and the 90% CI for the ratio of the geometric means for AUC_T were within the acceptance margins of 80.0% to 125.0% (see Table 17).

Table 17 Analysis of PK Parameters (from measured data) in Study CT-P6 1.5

Trastuzumab
(1 x 6 mg/kg)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Herzuma®	Herceptin® Roche (US)	Ratio (%) of Geometric LS Means	90% CI of Ratio (%)
AUC_T (h·µg/mL)	18183.7 18942.0 (19.3)	18312.5 19121.2 (18.8)	99.3	92.9 - 106.2
AUC_I (h·µg/mL)	19523.1 20307.5 (18.7)	19709.4 20519.9 (17.6)	99.1	93.0 - 105.5
C_{max} (µg/mL)	128.0 133.0 (17.9)	132.5 137.3 (15.5)	96.6	90.9 - 102.6
T_{max} (h)[1]	2.2 (43.3)	2.6 (63.7)		
$T_{1/2}$ (h)[1]	189.3 (19.0)	183.7 (20.4)		

Note: Number of subjects in each treatment group is 35.

[1] T_{max} and $T_{1/2}$ are expressed as the arithmetic mean (CV %) only.

AUC_I: Area under the serum concentration-time curve from time 0 to infinity; AUC_T: Area under the serum concentration-time curve from time 0 to the last measurable concentration; CI: Confidence interval; C_{max}: Observed maximum serum concentration; LS: Least squares; PK: Pharmacokinetics; $T_{1/2}$: Terminal half-life; T_{max}: Time to maximum serum concentration.

4.2.2 Comparative Safety and Efficacy

4.2.2.1 Efficacy

Early Breast Cancer

The comparative efficacy and safety study CT-P6 3.2 was designed to rule out any clinically meaningful differences between Herzuma® and Herceptin®, both given in combination with docetaxel (Cycles 1 through 4) followed by 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) (Cycles 5 through 8), in terms of efficacy as determined by pathological complete response (pCR), in patients with HER2-positive operable early breast cancer. The study included female patients 18 years of age or older with histologically confirmed and newly diagnosed breast cancer. Patients had HER2-positive status confirmed locally, defined as 3+ score by immunohistochemistry (IHC). When the IHC result was equivocal (defined as 2+ score), the patient had a positive fluorescence in situ hybridization (FISH) or a chromogenic in situ hybridization (CISH) result.
Demographic and baseline disease characteristics were similar between the Herzuma® arm and the Herceptin® arm with respect to age, race, height, weight, hormone receptor status and stage of disease. Overall, at screening 58.4% of study patients were hormone receptor positive (estrogen and/or progesterone), and the most frequently reported stage was Stage IIb (I: 10.0%, IIa: 29.2%, IIb: 36.7%, IIIa: 23.1%).
The primary efficacy endpoint was the proportion of patients achieving pCR, defined as the absence of invasive tumour cells in the breast and in axillary lymph nodes, regardless of the ductal carcinoma in situ (DCIS). The pCR was determined at the time of surgery, using hematoxylin and eosin evaluation of the resected specimen.
Comparability between Herzuma® and Herceptin® was demonstrated since the two-sided 95% confidence interval of the risk ratio for pCR after the Neoadjuvant Period was entirely contained within the pre-defined equivalence interval of [0.74 to 1.35].

Table 18 Pathological Complete Response (pCR) Rate after the Neoadjuvant Period in Study CT-P6 3.2 (ITT set)

	ITT set	
	Herzuma® (n=278)	**Herceptin® (n=284)**
Primary endpoint: pCR		
Response rate (%) (95% CI)	120 (43.17%) (37.26 – 49.21)	134 (47.18%) (41.26 – 53.17)
Risk ratio estimate (95% CI)[1] for risk ratio estimate	0.9149 (0.7622 – 1.0981)	

Abbreviations: CI, Confidence interval; ITT, intent-to-treat; pCR, pathological complete response
[1] Asymptotic CI.

4.2.2.2 Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

4.2.2.3 Immunogenicity

In Study CT-P6 1.5, no subject tested positive for ADAs at any time point. In Study CT-P6 3.2, no patients tested positive for ADAs at any post-baseline time points during the Neoadjuvant and Adjuvant Periods.

5. PHARMACEUTICAL PARTICULARS

5.1 Storage

Store vials at 2°C–8°C.

This medicine should not be used after the expiry date (EXP) shown on the pack.

Shelf-life of the reconstituted solution 440 mg vials
Reconstituted solutions made with bacteriostatic water for injection for the 440mg vial of Herzuma®, as supplied, are stable for 28 days when stored refrigerated at 2°C-8°C. The reconstituted solution contains preservative and is therefore suitable for multiple use. Any remaining reconstituted solution should be discarded after 28 days.

When administering Herzuma® to a patient with a known hypersensitivity to benzyl alcohol (see section 2.4 Warnings and Precautions), Herzuma® should be reconstituted with sterile water for injection. In case Herzuma® is reconstituted with sterile water for injection, only one dose per Herzuma® vial should be used. The reconstituted solution should be used immediately. Any unused portion must be discarded.

Do not freeze the reconstituted solution.

150 mg vials (for single-dose use only)
The reconstituted product is physically and chemically stable for **48 hours at 2° C - 8° C** after dissolving with sterile water for injections.

From a microbiological point of view, the reconstituted solution should be further diluted immediately. If not further diluted immediately, in-use storage times and conditions prior to dilution are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product
The infusion solution (0.9% sodium chloride infusion solution) containing the reconstituted product is physically and chemically stable for **24 hours at 2°C - 8°C**.

From a microbiological point of view, the Herzuma® infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

5.2 Special Instructions for Use, Handling and Disposal
Appropriate aseptic technique should be used.

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

Instructions for Reconstitution - 440 mg vial:
Reconstitution is to be performed with bacteriostatic water for injection, containing 1.1% benzyl alcohol, as supplied. This yields a solution for multiple use, containing 21 mg/mL trastuzumab, at a pH of approximately 6.0. Use of other reconstitution solvents should be avoided except for sterile water for injection in case of a patient with a known hypersensitivity to benzyl alcohol.

1. Using a sterile syringe, slowly inject 20 ml of Bacteriostatic Water for Injection into the vial containing the lyophilized Herzuma®, directing the stream into the lyophilized cake.
2. Swirl vial gently to aid reconstitution. DO NOT SHAKE!

Instructions for Reconstitution – 150 mg vial:
1. Using a sterile syringe, slowly inject 7.2 ml of sterile water for injection into the vial containing the lyophilized Herzuma®, directing the stream into the lyophilized cake.
2. Swirl 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 Herzuma® results in a colorless to pale yellow transparent solution and should be essentially free of visible particles.

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

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

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

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

The appropriate amount of solution should be withdrawn from the vial and added to an infusion bag containing 250 ml of 0.9% sodium chloride. Dextrose (5%) solution should not be used (see Incompatibilities). The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately (see section 4.1 Storage).

Incompatibilities
No incompatibilities between Herzuma® and polyvinylchloride, polyethylene or polypropylene bags have been observed.

Dextrose (5%) solution should not be used since it causes aggregation of the protein. Herzuma® should not be mixed or diluted with other drugs.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines

should not be disposed of via wastewater and disposal through household waste should be avoided. Use established "collection systems", if available in your location. Local requirements should be followed for the disposal process of unused/expired medicines.

Disposal of syringes/sharps
The following procedures should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:
- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).
- Dispose of the full container according to local requirements.

5.3 Packs
150 mg vial
1 pack containing 1 vial with 150 mg trastuzumab
440 mg vial
1 pack containing 1 vial with 440 mg trastuzumab
+ 1 vial with 20 ml bacteriostatic water for injection containing benzyl alcohol

5.4 List of Excipients
L-histidine
L-histidine hydrochloride
α, α -trehalose dihydrate
Polysorbate 20
Water for injection

Medicine: keep out of reach of children

Current at 09 Sep 2019

Marketing Authorization Holder:
Celltrion Healthcare Singapore Pvt.,
Ltd. 1 Raffles Quay
#25-00 North Tower
Singapore 048583