# Herzuma™ 150 mg, 440 mg Powder for concentrate for solution for infusion

Trastuzumab

**Antineoplastic agent**

## 1. DESCRIPTION

### 1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent.

ATC code: L01 XC03

### 1.2 Type of Dosage Form

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.

**150 mg single dose vial** containing powder for concentrate for solution for infusion.

The lyophilised powder is of a white to pale yellow colour. The solvent is a clear, colourless liquid.

Reconstituted Herzuma concentrate contains 21 mg/ml of trastuzumab.

**440 mg multidose vial** containing powder for concentrate for solution for infusion.

Solvent vial: water for injection containing 1.1% benzyl alcohol as an antimicrobial preservative (bacteriostatic water for injection).

The lyophilised powder is of a white to pale yellow colour. The solvent is a clear, colourless liquid.

Reconstituted Herzuma concentrate contains 21 mg/ml of trastuzumab

*Excipients:* Herzuma vial: L-histidine HCl, L-histidine, α,α-trehalose dihydrate, polysorbate 20.

Herzuma has been developed as a biosimilar to Herceptin. Herzuma is not interchangeable or automatically substitutable with Herceptin.

## 2. CLINICAL PARTICULARS

### 2.1 Therapeutic Indications

**Breast Cancer**

*Metastatic Breast Cancer (MBC)*

Herzuma is indicated for the treatment of patients with metastatic breast cancer who have tumours 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 or docetaxel 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.

*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).
- 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, for locally advanced (including inflammatory) breast cancer or tumours >2cm in diameter.

**Metastatic Gastric Cancer (MGC)**

Herzuma in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with Human epidermal growth factor receptor 2 (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 immunohistochemistry (IHC2+) and a confirmatory SISH or FISH (fluorescence in situ hybridization) result, or by an IHC 3+ result. Accurate and validated assay methods should be used.

### 2.2 Dosage and Administration

**General**

HER2 testing is mandatory prior to initiation of Herzuma therapy.

Herzuma should be administered by a qualified health care professional.

It is important to check the product labels to ensure that the drug about to be administered is consistent with what has been prescribed for the patient.
Herzuma should be administered as intravenous infusion.
Do not administer as an intravenous push or bolus.

**MBC and EBC**

***Weekly schedule:***

*Loading dose:* The recommended initial loading dose is 4 mg/kg body weight Herzuma administered as a 90-minute IV infusion.

*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.

***Alternative 3-weekly schedule:***

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 prior dose was well tolerated, the dose can be administered as a 30-minute infusion.

**MGC**

***Three-weekly schedule:***

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 prior dose was well tolerated, the dose can be administered as a 30-minute infusion.

**Breast Cancer (MBC and EBC) and Gastric Cancer (MGC)**

*Duration of treatment*

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

*Missed doses*

If the patient misses a dose of Herzuma by one week or less, then the usual maintenance dose of Herzuma (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be given as soon as possible. Do not wait until the next planned cycle. Subsequent Herzuma maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg respectively) should then be given according to the original schedule.

If the patient misses a dose of Herzuma by more than one week, a re-loading dose of Herzuma should be given over approximately 90 minutes (weekly regimen: 4 mg/kg; three weekly regimen: 8 mg/kg). Subsequent Herzuma maintenance doses (weekly regimen: 2 mg/kg; three weekly regimen 6 mg/kg respectively) should then be given according to the original schedule.

*Dose modification*

If the patient develops an infusion-related reaction (IRR), the infusion rate of Herzuma may be slowed or interrupted (see section 2.4 Warnings and Precautions). 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

Herzuma has been developed as a biosimilar to Herceptin. Herzuma is not interchangeable or automatically substitutable with Herceptin.

### 2.2.1 Special Dosage Instructions

*Geriatric use*

Data suggest that the disposition of Herzuma is not altered based on age (see section 3.2.1 Pharmacokinetics in Special Populations). In clinical trials, patients ≥ 65 years of age did not receive reduced doses of trastuzumab.

*Peadiatric use*

The safety and efficacy of Herzuma in paediatric patients < 18 years of age have not been established.

### 2.3 Contraindications

Herzuma is contraindicated in patients with known hypersensitivity to trastuzumab or to any other component of the product.

### 2.4 Warnings and Precautions

### 2.4.1 General

**WARNING**
**CARDIOMYOPATHY:**
Trastuzumab administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with trastuzumab. Discontinuation of trastuzumab treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received trastuzumab in combination with anthracyclines and cyclophosphamide (see Warnings).

In order to improve traceability of biological medicinal products, the trade name 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.

**Infusion/Administration-related reactions (IRRs/ARRs)**

IRRs are known to occur with the trastuzumab IV formulation.
Pre-medication may be used to reduce risk of occurrence of IRRs.
Serious IRRs to trastuzumab infusion including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, supraventricular tachyarrhythmia and urticaria have been reported have been reported (see section 2.6 Undesirable Effects). 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. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. 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 who are experiencing dyspnoea at rest due to complications of advanced malignancy or comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with trastuzumab.

**Pulmonary reactions**

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 IRR or with a delayed onset. 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. Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with trastuzumab.

**Cardiac dysfunction**

***General considerations***

Patients treated with trastuzumab may be 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 pharmacokinetics model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment (see Pharmacology: Pharmacokinetics under Actions).
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. 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 drops 10 ejection 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 declined further, 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 unless the benefits for the individual patient are deemed to outweigh the risks.
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 an 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 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).

*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-naïve patients. The maximum cumulative doses of the low-dose anthracycline regimens should not exceed 180 mg/m$^2$ (doxorubicin) or 360 mg/m$^2$ (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.

**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 sensitivity 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 infusion-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 with the concomitant medication used in clinical trials have not been observed (see section 3.2 Pharmacokinetics Properties).

***Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents***

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

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.

Data from study JP16003, a single-arm study of trastuzumab (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m$^2$ IV) in Japanese women with HER2-positive MBC, suggest that concomitant administration of trastuzumab has no effect on the single dose pharmacokinetics of docetaxel. Study JP19959 was a substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer to study the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab. The results of this small substudy suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by

concurrent use of cisplatin plus 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.

***Effect of antineoplastic agents on trastuzumab pharmacokinetics***

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

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

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

## 2.5 Use in Special Populations

### 2.5.1 Pregnancy

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

### 2.5.2 Nursing Mothers

It is not known whether trastuzumab is secreted in human milk. As human immunoglobulin G (IgG) is secreted into human milk, and the potential for harm to the infant is unknown, breast-feeding should be avoided during trastuzumab therapy (see section 3.3.2 Other (Preclinical Safety)).

## 2.6 Undesirable Effects

### 2.6.1 Clinical Trials

Table 1 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Herceptin alone or in combination with chemotherapy in pivotal clinical trials. All the terms included are based on the highest percentage seen in pivotal clinical trials.

As Herceptin 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.

The corresponding frequency category for each adverse drug reaction is based on the following convention: 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.

**Table 1 Adverse Reactions Table**

| System organ class | Adverse reaction* | Frequency |
|---|---|---|
| Infections and infestations | Nasopharyngitis | Very common |
| | Infection | Very common |
| | Influenza | Common |
| | Pharyngitis | Common |
| | Sinusitis | Common |
| | Rhinitis | Common |
| | Upper respiratory tract infection | Common |
| | Urinary tract infection | Common |
| Blood and lymphatic system disorders | Anaemia | Very common |
| | Thrombocytopenia | Very common |
| | Febrile neutropenia | Very common |
| | White blood cell count decreased/leukopenia | Very Common |
| | Neutropenia | Common |
| Immune system disorders | Hypersensitivity | Common |
| Metabolism and nutrition disorders | Weight decreased | Very common |
| | Weight increased | Very common |
| | Decreased appetite | Very common |

| | | |
|---|---|---|
| Psychiatric disorders | Insomnia | Very common |
| | Depression | Common |
| | Anxiety | Common |
| Nervous system disorders | Dizziness | Very common |
| | Headache | Very common |
| | Paraesthesia | Very common |
| | Hypoaesthesia | Very common |
| | Dysgeusia | Very common |
| | Hypertonia | Common |
| | Peripheral neuropathy | Common |
| | Somnolence | Common |
| Eye disorders | Lacrimation increased | Very common |
| | Conjunctivitis | Very common |
| Ear and labyrinth disorder | Deafness | Uncommon |
| Cardiac disorders | Ejection fraction decreased | Very Common |
| | [+]Cardiac failure (congestive) | Common |
| | Cardiomyopathy | Common |
| | [+1]Supraventricular tachyarrhythmia | Common |
| | [1]Palpitation | Common |
| Vascular disorders | Lymphoedema | Very common |
| | Hot flush | Very Common |
| | [+1]Hypotension | Common |
| | Hypertension | Common |
| | Vasodilation | Common |
| Respiratory, thoracic and mediastinal disorders | [+]Dyspnoea | Very common |
| | Epistaxis | Very common |
| | Oropharyngeal pain | Very common |
| | Cough | Very common |
| | Rhinorrhoea | Very common |
| | Asthma | Common |
| | Lung disorder | Common |
| | [+]Pleural effusion | Common |
| | Pneumonia | Common |
| | Pneumonitis | Uncommon |
| | Wheezing | Uncommon |
| Gastrointestinal disorders | Diarrhoea | Very common |
| | Vomiting | Very common |
| | Nausea | Very common |
| | Abdominal pain | Very common |
| | Dyspepsia | Very common |
| | Constipation | Very common |
| | Stomatitis | Very common |
| Hepatobiliary disorder | Hepatocellular injury | Common |
| | Jaundice | Rare |
| Skin and subcutaneous disorders | Erythema | Very common |
| | Rash | Very common |
| | Alopecia | Very common |
| | Palmar-plantar erythrodysaesthesia syndrome | Very common |
| | Nail disorder | Very common |
| | Acne | Common |
| | Dermatitis | Common |
| | Dry skin | Common |
| | Hyperhydrosis | Common |
| | Maculopapular rash | Common |
| | Pruritus | Common |
| | Onychoclasis | Common |
| | Urticaria | Uncommon |

| | | |
|---|---|---|
| Musculoskeletal and connective tissue disorders | Arthralgia | Very common |
| | Myalgia | Very common |
| | Arthritis | Common |
| | Back pain | Common |
| | Bone pain | Common |
| | Muscle spasms | Common |
| | Neck pain | Common |
| | Pain in extremity | 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 |
| | Oedema | Common |
| | Malaise | Common |
| Injury, poisoning and procedural complications | Nail toxicity | Very common |

* Adverse drug reactions (ADRs) were identified as events that occurred with at least a 2% difference compared to the control arm in at least one of the major randomised clinical trials. 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.
[+] 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.

***Additional information for selected adverse drug reactions***

***Infusion-related reactions (IRRs)/ Administration-related reactions (ARRs)***

IRRs/ARRs reactions 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/ARRs 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.

***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, $S_3$ 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 subgroup, compared with 1% - 4% for the paclitaxel alone subgroup. 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 subgroup (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 to 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 AC→D and DCarbH 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 month. 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 III & IV) following 1 year of trastuzumab therapy was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%. Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥ 50% after the event) was evident for 71.4% of trastuzumab-treated patients.

Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of trastuzumab-treated patients. Approximately 17% 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.

In the pivotal trial BO22227, trastuzumab was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300mg/m$^2$); at a median follow-up exceeding 70 months, the incidence of cardiac failure/congestive cardiac failure was 0.3% in the trastuzumab arm.

***Metastatic Gastric Cancer***

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

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** | **Fluoropyrimidine/ Cisplatin (N = 290) (% of patients in each treatment arm)** | **Trastuzumab/ Fluoropyrimidine/ Cisplatin (N = 294)** |
|---|---|---|

| | | (% of patients in each treatment arm) |
|---|---|---|
| *LVEF decrease of ≥ 10% to a value of < 50% | 1.1% | 4.6% |
| Absolute value < 50% | 1.1% | 5.9% |
| *LVEF decrease of ≥ 10% to a value of ≥ 50% | 11.8% | 16.5% |

*Only includes patients whose method of assessment at that visit is the same as at initial assessments (FP, n = 187 and H +FP, n = 237)

**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 is infrequent following the administration of trastuzumab monotherapy in the metastatic setting, WHO Grade 3 leukopenia, 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). 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, 0.4% of trastuzumab-treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

***Metastatic 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 alone (7% compared with 15%). No WHO Grade 3 or 4 renal toxicity was observed.

***Metastatic Gastric Cancer***

In the 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 than those in the F+P 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 than those in the F+P arm (1% and <1% respectively).

***Diarrhoea***

***Breast Cancer***

Of patients treated with trastuzumab monotherapy 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, 8% of trastuzumab-treated patients experienced diarrhea during the first year of treatment.

***Metastatic Gastric Cancer***

In the 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 v3.0 severity criteria, the percentage of patients experiencing grade ≥ 3 diarrhoea was 4% in the FP arm versus 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.

### 2.6.2 Post Marketing

The following adverse drug reactions have been identified from postmarketing experience with trastuzumab (Table 5).

**Table 5 Adverse Reactions reported in the post-marketing setting**

| System organ class | Adverse reaction |
|---|---|
| Blood and lymphatic system disorders | Hypoprothrombinemia |
| | Immune thrombocytopenia |
| Immune system disorders | Anaphylactoid reaction |
| Metabolism and nutrition disorders | Tumour lysis syndrome |
| Eye disorders | Madarosis |
| Cardiac disorders | Cardiogenic shock |
| | Tachycardia |
| Respiratory, thoracic and mediastinal disorders | Bronchospasm |
| | Oxygen saturation decreased |
| | Respiratory failure |
| | Interstitial lung disease |
| | Lung infiltration |
| | Acute respiratory distress syndrome |
| | Respiratory distress |
| | Pulmonary fibrosis |
| | Hypoxia |
| | Laryngeal oedema |
| Renal and urinary conditions | Glomerulonephropathy |
| | Renal failure |
| Pregnancy, puerperium and perinatal disorders | Pulmonary hypoplasia |
| | Renal hypoplasia |
| | Oligohydramnios |

### 2.6.3 Adverse Events

Table 6 below indicates adverse events that historically have been reported in patients who have received trastuzumab. As no evidence of a causal association has been found between trastuzumab and these events, these events are not considered expected for the purposes of regulatory reporting.

**Table 6 Adverse Events**

| System organ class | Adverse Event |
|---|---|
| Infections and infestations | Cellulitis |
| | Erysipelas |
| | Sepsis |
| | Meningitis |
| | Bronchitis |
| | Herpes zoster |

| | |
|---|---|
| | Cystitis |
| Blood and lymphatic system disorders | Leukaemia |
| Immune system disorders | Anaphylaxis |
| | Anaphylactic shock |
| Psychiatric disorders | Thinking abnormal |
| Nervous system disorders | Ataxia |
| | Paresis |
| | Cerebrovascular disorder |
| | Brain oedema |
| | Lethargy |
| | Coma |
| Ear and labyrinth disorders | Vertigo |
| Cardiac disorders | Pericardial effusion |
| | Bradycardia |
| | Pericarditis |
| Respiratory, thoracic and mediastinal system disorders | Hiccups |
| | Dyspnoea, exertional |
| Gastrointestinal system disorders | Gastritis |
| | Pancreatitis |
| Hepatobiliary disorders | Hepatic failure |
| Musculoskeletal and connective tissue disorders | Musculoskeletal pain |
| Renal system disorders | Dysuria |
| Reproductive system and breast disorders | Breast pain |
| General disorders and administration site conditions | Chest discomfort |

## 2.7 Overdose

There is no experience with overdosage 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 humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an $IgG_1$ isotype that contains human framework regions with the complementarity-determining regions of a murine anti-p185 HER2 antibody that binds to human 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 25%-30% of primary breast and 6.8%-42.6 % metastatic gastric cancers. 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 protein.
Studies indicate that breast cancer patients whose tumours have amplification or overexpression of HER2 have a shortened disease-free survival compared to patients whose tumours 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 tumour 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 for Herceptin

***Metastatic Breast Cancer***

Herceptin monotherapy has been used in clinical trials for patients with metastatic breast cancer who have tumours that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease.
Herceptin has also been used in clinical trials in combination with paclitaxel or an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide as first line therapy for patients with metastatic breast cancer who have tumours 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 Herceptin. Patients could be treated with Herceptin until progression of disease.
Herceptin monotherapy, when used as second- or third-line treatment of women with metastatic breast cancer which overexpresses HER2, results in an overall tumour response rate of 15% and a median survival of 13 months.
The use of Herceptin in combination with paclitaxel as first-line treatment of women with metastatic breast cancer that overexpresses HER2 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 Herceptin and paclitaxel is

3.9 months (6.9 months versus 3.0 months). Tumor response and one year survival rate are also increased for Herceptin in combination with paclitaxel versus paclitaxel alone.
Herceptin has also been studied in a randomised, controlled trial, in combination with docetaxel, as first-line treatment of women with metastatic breast cancer. The combination of Herceptin and docetaxel significantly increased response rate (61% versus 34%) and prolonged the median time to disease progression, (by 5.6 months) compared with patients treated with docetaxel alone. Median survival was also significantly increased in patients receiving the combination, compared with those receiving docetaxel alone (31.2 months versus 22.7 months).
*Combination treatment with Herceptin and anastrozole*
Herceptin has been studied in combination with anastrozole for first line treatment of metastatic breast cancer in HER2 overexpressing, hormone-receptor i.e. oestrogen-receptor (ER) and/or progesterone-receptor (PR) positive patients. Progression free survival was doubled in the t Herceptin 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 Herceptin containing regimen after progression of disease. Fifty two percent of the patients taking Herceptin plus anastrozole survived for at least 2 years compared to 45% taking anastrozole alone.
***Early Breast Cancer***
In the adjuvant setting, Herceptin was investigated in 4 large multicentre, randomised, phase 3 trials:

- Study BO16348 was designed to compare one and two years of three-weekly Herceptin 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 Herceptin treatment versus one year Herceptin treatment was performed. Patients assigned to receive Herceptin 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 NCCTG N9831 and NSAPB-B31 that comprise the joint analysis were designed to investigate the clinical utility of combining Herceptin IV treatment with paclitaxel following AC chemotherapy; additionally the NCCTG N9831 study investigated adding Herceptin sequentially to AC-paclitaxel chemotherapy in patients with HER2-positive early breast cancer following surgery.
- Study BCIRG 006 was designed to investigate combining Herceptin 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 BO16348 study 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 7 Efficacy Results (BO16348 study): Results at 12 months* and 8 years** of median follow-up**

| | Median follow-up 12 months | | Median follow-up 8 years | |
|---|---|---|---|---|
| Parameter | Observation N=1693 | Trastuzumab 1 Year N= 1693 | Observation N= 1697*** | Trastuzumab 1 Year N= 1702*** |
| Disease-free survival | | | | |
| No. patients with event | 219 (12.9%) | 127 (7.5%) | 570 (33.6%) | 471 (27.7%) |
| No. patients without event | 1474 (87.1%) | 1566 (92.5%) | 1127 (66.4%) | 1231 (72.3%) |
| P-value versus Observation | < 0.0001 | | < 0.0001 | |
| Hazard Ratio versus Observation | 0.54 | | 0.76 | |
| Recurrence-free survival | | | | |
| No. patients with event | 208 (12.3%) | 113 (6.7%) | 506 (29.8%) | 399 (23.4%) |
| No. patients without event | 1485 (87.7%) | 1580 (93.3%) | 1191 (70.2%) | 1303 (76.6%) |
| P-value versus Observation | < 0.0001 | | < 0.0001 | |
| Hazard Ratio versus Observation | 0.51 | | 0.73 | |

| | | | | |
|---|---|---|---|---|
| Distant disease- free survival | | | | |
| No. patients with event | 184 (10.9%) | 99 (5.8%) | 488 (28.8%) | 399 (23.4%) |
| No. patients without event | 1508 (89.1%) | 1594 (94.6%) | 1209 (71.2%) | 1303 (76.6%) |
| P-value versus Observation | < 0.0001 | | < 0.0001 | |
| Hazard Ratio versus Observation | 0.50 | | 0.76 | |
| Overall survival (death) | | | | |
| No. patients with event | 40 (2.4%) | 31 (1.8%) | 350 (20.6%) | 278 (16.3%) |
| No. patients without event | 1653 (97.6%) | 1662 (98.2%) | 1347 (79.4%) | 1424 (83.7%) |
| P-value versus Observation | 0.24 | | 0.0005 | |
| Hazard Ratio versus Observation | 0.75 | | 0.76 | |

* Co-primary endpoint of DFS of 1 year 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 randomised 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 Herceptin vs. observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (95% CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8% versus 78.2%) in favour of the Herceptin arm.
A final analysis was performed after a median follow-up of 8 years, which showed that 1 year Herceptin 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 Herceptin treatment.
In this final analysis, extending Herceptin 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=0.89 and OS HR=0.98 (0.83, 1.15); p-value= 0.7846]. 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 NCCTG N9831 and NSAPB B31 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). Herceptin 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 8 Summary of Efficacy Results (joint analysis of the NCCTG 9831 and NSABP B-31 trials) at the time of the definitive DFS analysis:**

| Parameter | AC→P (N=1697) | AC→PH (N=1672) | p-value versus AC→P | Hazard Ratio versus AC→P (95% CI) |
|---|---|---|---|---|
| Disease-free survival<br>No. patients with event (%) | 261 (15.5) | 133 (8.0) | < 0.0001 | 0.48 (0.39, 0.59) |
| Distant recurrence<br>No. patients with event (%) | 193 (11.5) | 96 (5.7) | < 0.0001 | 0.47 (0.37, 0.60) |
| Death (OS event):<br>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
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 Herceptin 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 (Herceptin) 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 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 9 Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG 9831:**

| 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, HER2-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, oestrogen receptor- and progesterone receptor-negative, histologic and/or nuclear grade 2 - 3, or age < 35 years.
Herceptin 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 10 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 | 195 | 134 | < 0.0001 | 0.61 (0.49, 0.77) |
| Distant recurrence No. patients with event | 144 | 95 | < 0.0001 | 0.59 (0.46, 0.77) |
| Overall Survival (Death) No. patients with event | 80 | 49 | 0.0024 | 0.58 (0.40, 0.83) |

AC→D = doxorubicin + cyclophosphamide, followed by docetaxel; AC→DH = doxorubicin + cyclophosphamide, followed by docetaxel + trastuzumab; CI = confidence interval

**Table 11 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 + 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 (Herceptin) arm and 4.6 percentage points (85.5% versus 80.9%) in favour of the DCarbH (Herceptin) 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 randomised 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 setting, Herceptin was evaluated in: Study MO16432 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 Herceptin, or neoadjuvant chemotherapy alone, followed by adjuvant Herceptin 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 efficacy results from MO16432 are summarized in the table below. The median duration of follow-up in the trastuzumab arm was 3.8 years.

**Table 12 Overview of Efficacy Analyses (MO16432 study)**

| Parameter | Chemo + Trastuzumab (N=115) | Chemo only (N=116) | |
|---|---|---|---|
| Event-free survival<br>No. patients with event | 46 | 59 | Hazard Ratio (95% CI)<br>0.65 (0.44, 0.96) p=0.0275 |
| Total pathological complete response* (95% CI) | 40%<br>(31.0,49.6) | 20.7%<br>(13.7, 29.2) | p=0.0014 |

* Defined as absence of any invasive cancer both in the breast and axillary nodes

For the primary endpoint, EFS, the addition of Herceptin 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 Herceptin arm.

**Metastatic Gastric Cancer**
The efficacy results from the BO18255 study are summarized in table 12. Patients with 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 were recruited. 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.
The overall survival was significantly improved in the Herceptin + capecitabine/5-FU and cisplatin arm compared to the capecitabine/5-FU and cisplatin arm (p = 0.0046, Log-Rank test). The median survival time was 11.1 months with capecitabine/5-FU and cisplatin and 13.8 months with trastuzumab + capecitabine/5-FU and cisplatin. The risk of death was decreased by 26% (Hazard Ratio [HR] 0.74 95% CI [0.60-0.91]) for patients in the Herceptin arm compared to the capecitabine/5-FU arm.
Post-hoc subgroup analyses indicate that targeting tumors with higher levels of HER2 protein (IHC 2+/FISH+ and IHC 3+/regardless of the FISH status) results in a greater treatment effect. 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 capecitabine/5-FU and cisplatin and Herceptin + capecitabine/5-FU and cisplatin respectively.
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.

**Table 13 Summary of Efficacy (BO18255 study)**

| **Parameter** | **FP N = 290** | **H+FP 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% | 1.70[a] (1.22, 2.38) | 0.0017 |
| Duration of Response, Median months | 4.8 | 6.9 | 0.54 (0.40-0.73) | < 0.0001 |

FP: Fluoropyrimidine/cisplatin
H+ FP: Fluoropyrimidinecisplatin + trastuzumab
[a] Odds ratio

### 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 intravenous 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 MGC. The nonlinear elimination parameter values 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 5th - 95th Percentiles) and PK parameter values at clinically relevant concentrations (Cmax and Cmin) for breast cancer and MGC patients treated with the approved Q1W and Q3W dosing regimens are shown in Table 14(Cycle 1) and Table 15 (steadystate) below.

**Table 14: Population Predicted Cycle 1 PK Exposure Values (with 5th - 95th Percentiles) in Breast Cancer and MGC 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) |
| | MGC | 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) | 88.3 (58 - 144) |

Table 15: Population Predicted Steady State PK Exposure Values (with 5th - 95$^{th}$ Percentiles) in Breast Cancer and MGC Patients

| Regimen | Primary tumor type | N | Cmin,ss (µg/mL) | Cmax,ss (µg/mL) | AUCss (µg.day/ mL) | Time to steadystate (week) | Total CL range at steady-state (L/day) |
|---|---|---|---|---|---|---|---|
| 8mg/kg + 6mg/kg q3w | MBC/ EBC | 1195 | 47.4 (5 - 115) | 179 (107 - 309) | 1794 (673 -3618) | 12 | 0.173 - 0.283 |
| | MGC | 274 | 32.9 (6.1 -88.9) | 131 (72.5 - 251) | 1338 (557 - 2875) | 9 | 0.189 - 0.337 |
| 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 intravenous administration using the respective population PK models. The results of these simulations indicate that at least 95% of patients will reach serum trastuzumab concentrations that are <1 µg/mL (approximately 3% of the population predicted Cmin,ss, or about 97% washout) by 7 months after the last dose. In early breast cancer patients administered at an initial loading dose of 8 mg/kg followed by a three weekly maintenance dose of 6 mg/kg for 1 year achieved steady state mean Cmax.

### 3.2.1 Pharmacokinetics in Special Populations

Detailed pharmacokinetic studies in the geriatric population 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.

*Geriatric Population*

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

## 3.3 Preclinical Safety

### 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 foetus. 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) foetal 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.

# 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®:<br>6 mg/kg, IV infusion for 90 minutes (± 5 minutes) | Randomized : 70 healthy subjects<br>HERZUMA®: 35<br>HERCEPTIN®: 35 | HERZUMA®: 36.2 (20 - 55)<br>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**<br>HERZUMA® or HERCEPTIN®:<br>▪ 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<br>▪ 90-minute IV infusion (± 5 minutes)<br>Docetaxel:<br>▪ Immediately after the dose of study drug (Day 1 of each cycle), 3-weekly for 12 weeks (Cycles 1-4)<br>▪ 75 mg/m$^2$ as a 1-hour IV infusion<br>FEC:<br>▪ Immediately after the dose of study drug (Day 1 of each cycle), 3-weekly for 12 weeks (Cycles 5-8)<br>▪ Fluorouracil 500 mg/m$^2$ as a 3- to 5-minute IV bolus or as an infusion for 30 minutes (± 5 minutes);<br>▪ Epirubicin 75 mg/m$^2$ as a 3- to 5-minute IV bolus or as an infusion for 30 minutes (± 5 minutes);<br>▪ Cyclophosphamide 500 mg/m$^2$ as an IV bolus for 3 to 5 minutes<br><br>**Adjuvant Period**<br>HERZUMA® or HERCEPTIN®:<br>▪ 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)<br>▪ 90-minute IV infusion (± 5 minutes) | Randomized: 562 EBC patients<br>HERZUMA®: 278<br>HERCEPTIN®: 284 | HERZUMA®: 52.1<br>(24 - 79)<br>HERCEPTIN®: 52.0<br>(22 - 74) | Female: 562 |

## 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<br>(1 x 6 mg/kg)<br>From measured data<br><br>Geometric Mean<br>Arithmetic Mean (CV %) |
|---|

| Parameter | Herzuma® | Herceptin®<br>Roche (US) | Ratio (%) of<br>Geometric LS Means | 90% CI of<br>Ratio (%) |
|---|---|---|---|---|
| $AUC_T$<br>(h·µg /mL) | 18183.7<br>18942.0 (19.3) | 18312.5<br>19121.2 (18.8) | 99.3 | 92.9 - 106.2 |
| $AUC_I$<br>(h·µg /mL) | 19523.1<br>20307.5 (18.7) | 19709.4<br>20519.9 (17.6) | 99.1 | 93.0 - 105.5 |
| $C_{max}$<br>(µg/mL) | 128.0<br>133.0 (17.9) | 132.5<br>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®<br>(n=278)** | **Herceptin®<br>(n=284)** |
| **Primary endpoint: pCR** | | |
| Response rate (%)<br>(95% CI) | 120 (43.17%)<br>(37.26 – 49.21) | 134 (47.18%)<br>(41.26 – 53.17) |
| Risk ratio estimate<br>(95% CI)[1] for risk ratio estimate | 0.9149<br>(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.
Human anti-trastuzumab antibodies (ADA) were detected in 1 of 903 MBC patients, who had no allergic manifestations.

Randomized clinical trials have not been conducted to compare Herceptin and Herzuma in patients with MBC and MGC. Clinical efficacy and safety have been conducted in EBC to demonstrate clinical comparability between Herceptin and Herzuma. The extrapolation of these data to support uses of Herzuma in MBC and MGC is based on the demonstrated comparability, in terms of product quality, non-clinical, human pharmacokinetic and clinical characteristics.

## 5. PHARMACEUTICAL PARTICULARS

### 5.1 Storage
This medicine should not be used after the expiry date (EXP) shown on the pack.
Store vials at 2°C - 8°C.

- *440 mg vials (multidose vials)*

*Shelf-life of the reconstituted solution*
Reconstituted solutions made with bacteriostatic water for injection for the 440 mg 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.
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.

*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 **48 hours (do not store above 30°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 is 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.
Do not freeze the reconstituted solution.

- *150 mg vial (single-dose vials)*

*Shelf-life of the reconstituted solution*
The infusion solution (0.9% sodium chloride infusion solution) containing the reconstituted product is physically and chemically stable for **7 days at *2°C - 8°C***
From a microbiological point of view, the reconstituted solution should be further diluted in infusion solution immediately. If not, in-use storage times and conditions prior to use is 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.
*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 **48 hours (do not store above 30°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 is 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 Instruction for Use, Handling and Disposal
Appropriate aseptic technique should be used.
***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.

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 trastuzumab results in a colourless 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:*

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

- *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 section 4.3 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).

**5.3 Incompatibilities**

No incompatibilities between trastuzumab and polyvinylchloride, polyethylene or polypropylene bags have been observed. Dextrose (5%) solution should not be used since it causes aggregation of the protein.

Trastuzumab 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.

The following points 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.

**5.4 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

| Medicine: keep out of reach of children |
|---|

Date of Revision: April 2026

*Vials 150 mg*

Manufactured and released by CELLTRION, Inc. Incheon, Republic of Korea.

Product Registration Holder: Celltrion Healthcare Malaysia Sdn. Bhd. Bangsar South, Kuala Lumpur, Malaysia.

*Vials 440 mg*

Manufactured and released by CELLTRION, Inc. Incheon, Republic of Korea.

Product Registration Holder: Celltrion Healthcare Malaysia Sdn. Bhd. Bangsar South, Kuala Lumpur, Malaysia.