

# Data Sheet

## Herceptin<sup>®</sup>

*Trastuzumab 150 mg and 440 mg powder for concentrate for solution for infusion*

**Antineoplastic agent**

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### Pharmaceutical Form

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#### **Type of dosage form**

Powder for concentrate for solution for infusion.

#### **Route of administration**

Intravenous infusion.

#### **Sterile/radioactive statement**

Sterile product.

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### Qualitative and Quantitative Composition

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#### **Active ingredient**

Trastuzumab.

Dosage Preparations: 150 mg single-dose vial and 440 mg multi-dose vial containing powder for concentrate for solution for infusion. Reconstituted Herceptin concentrate contains 21 mg/mL of trastuzumab.

#### **Excipients**

Herceptin 150 mg and 440 mg vials:

L-histidine hydrochloride, L-histidine, α,α-trehalose dihydrate, polysorbate 20.

Solvent vial (for use with the 440 mg vial only):

Water for Injection containing 1.1% benzyl alcohol (Bacteriostatic Water for Injection).

#### **Appearance**

Herceptin is a white to pale yellow lyophilised powder. The solvent is a clear to slightly opalescent liquid.

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## Indications

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### Metastatic breast cancer

Herceptin is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

- as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease; or
- in combination with taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or
- in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.

### Early breast cancer

Herceptin is indicated for the treatment of patients with:

- HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy, followed by adjuvant Herceptin; or
- HER2-positive early breast cancer following surgery, sequentially or concurrently with chemotherapy and, if applicable, radiotherapy.

Herceptin should only be used in early breast cancer patients with a normal left ventricular ejection fraction.

### Advanced gastric cancer

Herceptin is indicated in combination with cisplatin and either capecitabine or 5-FU for the treatment of patients with HER2 positive advanced adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

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## Dosage and Administration

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HER2 testing is mandatory prior to initiation of Herceptin therapy (see Dosage and Administration, Detection of HER2 Overexpression or Gene Amplification). Herceptin should be administered by a healthcare professional prepared to manage anaphylaxis and adequate life support facilities should be available. Treatment may be administered in an outpatient setting.

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient medical record. Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Herceptin should be administered as an intravenous infusion.

**DO NOT ADMINISTER HERCEPTIN AS AN INTRAVENOUS PUSH OR BOLUS.**

## **Breast Cancer**

Herceptin may be used in **metastatic breast cancer** with the once weekly dose schedule, or the, alternative three-weekly schedule. The alternative schedule has been tested in clinical trials but has not been compared directly with the standard weekly regimen.

For treatment of **early breast cancer**, either the once weekly schedule or the three weekly schedule, with loading and subsequent doses, may be used.

### **Once Weekly Dose Schedule**

#### **Loading dose**

The recommended initial loading dose of Herceptin is 4 mg/kg body weight administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable Effects). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

#### **Subsequent doses**

The recommended weekly maintenance dose of Herceptin is 2 mg/kg body weight. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable Effects).

### **Three-Weekly Dose Schedule**

#### **Loading dose**

The recommended initial loading dose of Herceptin is 8 mg/kg body weight administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable Effects). Interruption of the infusion and/or medication may help to control such symptoms. The infusion may be resumed when symptoms abate.

#### **Subsequent doses**

The recommended three-weekly maintenance dose of Herceptin is 6 mg/kg body weight administered as a 90-minute intravenous infusion. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30 minute infusion. Patients should be observed for fevers and chills or other infusion-associated symptoms (see Undesirable Effects).

#### **Switching patients from established weekly schedule to three-weekly doses**

The first 6 mg/kg dose should be given a week after the last 2 mg/kg dose. As a precaution, all 6 mg/kg doses should be administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable Effects). Interruption of the infusion and/or medication may help to control such symptoms. The infusion may be resumed when symptoms abate. Subsequent maintenance doses of 6 mg/kg are given three-weekly.

## ***Advanced Gastric Cancer***

Initial loading dose of Herceptin is 8 mg/kg body weight, followed by 6 mg/kg body weight three 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.

In clinical trials, patients with advanced gastric cancer were treated with Herceptin until progression of disease.

Refer to Clinical Efficacy Studies, Advanced Gastric Cancer for chemotherapy combination dosing.

## ***Duration of treatment***

In clinical studies, patients with **metastatic breast cancer** or **advanced gastric cancer** were treated with Herceptin 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 early breast cancer beyond one year is not recommended.

## ***Missed doses***

If the patient misses a dose of Herceptin by one week or less, then the usual maintenance dose of Herceptin (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 Herceptin maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg respectively) should then be given according to the previous schedule.

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

## ***Dose reduction***

No reductions in the dose of Herceptin were made during clinical trials. Patients may continue Herceptin 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.

## ***Special Dosage Instructions***

### ***Elderly***

Data suggest that the disposition of Herceptin is not altered based on age (see Pharmacokinetics in Special Populations). In clinical trials, elderly patients did not receive reduced doses of Herceptin.

## Children

The safety and efficacy of Herceptin in paediatric patients have not been established.

## ***Detection of HER2 Overexpression or Gene Amplification***

Herceptin should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification.

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

HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks. HER2 gene amplification should be detected using in situ hybridisation (ISH) of fixed tumour blocks. Examples of ISH include fluorescence *in situ* hybridisation (FISH), chromogenic *in situ* hybridisation (CISH) and silver *in situ* hybridisation (SISH).

For any other method to be used for the assessment of HER2 protein or gene expression, the test method must be precise and accurate enough to demonstrate overexpression of HER2 (it must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) HER2 overexpression).

For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH, CISH and SISH assays. Official recommendations on HER2 testing may also apply.

## Breast Cancer

Herceptin treatment is only appropriate if there is strong HER2 overexpression, as described by a 3+ score by IHC or a positive ISH result. For patients with an intensity score of 2+ on IHC, confirmation of HER2 positive status by ISH is mandatory.

## Advanced Gastric Cancer

Herceptin treatment is only appropriate if there is HER2 overexpression, as described by a 3+ IHC score. For cases with a score of less than 3+ by IHC, confirmation of HER2 positive status by ISH is mandatory.

Bright-field ISH technology is recommended for advanced gastric cancer samples to enable evaluation of tumour histology and morphology in parallel. Either FISH or SISH are recommended for detecting HER2 gene amplification in advanced gastric cancer tissue.

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## Contraindications

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Herceptin is contraindicated in patients with known hypersensitivity to trastuzumab or to any of its excipients.

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## Warnings and Precautions

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### **General**

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

### ***Infusion-related reactions (IRRs), Allergic reactions and Hypersensitivity***

Pre-medication may be used to reduce risk of occurrence of IRRs.

Serious adverse reactions to Herceptin infusion that have been reported infrequently include dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema (see Undesirable Effects). The majority of these events were associated with the initial infusion of Herceptin and generally occurred during or immediately following the infusion. Herceptin should be discontinued in the event of a severe infusion related reaction, until resolution of the symptoms. The majority of patients experience resolution of symptoms and subsequently receive further infusions of Herceptin. These symptoms can be treated with an analgesic/antipyretic such as pethidine 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. In other patients with acute onset of signs and symptoms, initial improvement was followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours or up to one week following an infusion.

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 Herceptin (see Pulmonary reactions).

### ***Pulmonary reactions***

Severe pulmonary events leading to death have been reported with the use of Herceptin in the post-marketing setting. These events may occur as part of an infusion-related reaction (see Infusion-related reactions (IRRs), Allergic reactions and Hypersensitivity) or with 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 comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Herceptin.

## ***Cardiac dysfunction***

### **General considerations**

Patients treated with Herceptin 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 Herceptin therapy alone or in combination with paclitaxel following anthracycline (doxorubicin or epirubicin)-containing chemotherapy. This may be moderate to severe and has been associated with death (see 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)

As the half-life of trastuzumab is approximately 28 – 38 days, trastuzumab may persist in the circulation for up to 27 weeks after stopping Herceptin treatment (see Pharmacokinetics). Patients who receive anthracycline after stopping Herceptin may also be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Candidates for treatment with Herceptin, especially those with prior exposure to anthracycline and cyclophosphamide (AC) exposure), should undergo baseline cardiac assessment including history and physical examination, ECG, echocardiogram, and/or 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 treatments until 24 months from the last administration of Herceptin.

If LVEF drops 10 percentage points from baseline and to below 50%, Herceptin should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, discontinuation of Herceptin 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 Herceptin therapy has been seen.

The safety of continuation or resumption of Herceptin in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during Herceptin therapy, it should be treated with the standard medications for this purpose. Discontinuation of Herceptin therapy should be strongly considered in patients who develop clinically significant heart failure unless the benefits for an individual patient are deemed to outweigh the risks. In the pivotal trials most patients who developed heart failure improved with standard heart failure treatment consisting of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a  $\beta$ -blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on weekly therapy with Herceptin without additional clinical cardiac events.

## Early breast cancer

For patients with early breast cancer, 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 Herceptin. In patients who receive anthracycline containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of Herceptin, 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 haemodynamic effective pericardial effusion were excluded from adjuvant breast cancer clinical trials with Herceptin.

### *Neoadjuvant-adjuvant treatment*

In patients with early breast cancer eligible for neoadjuvant-adjuvant treatment, Herceptin should only be used concurrently with anthracyclines in chemotherapy-naïve patients and only with low-dose anthracycline regimens i.e. with maximum cumulative doses of doxorubicin 180 mg/m<sup>2</sup> or epirubicin 360 mg/m<sup>2</sup>.

If patients have been treated concurrently with low-dose anthracyclines and Herceptin 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.

### *Adjuvant treatment*

Herceptin and anthracyclines should not be given concurrently in the adjuvant treatment setting.

In patients with early breast cancer an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence was more marked when Herceptin 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, Herceptin treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving Herceptin after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Herceptin and a high body mass index (BMI) (> 25 kg/m<sup>2</sup>).

## Metastatic breast cancer

Herceptin and anthracycline should not be given concurrently in the metastatic breast cancer setting.



## **Advanced Gastric Cancer**

In advanced gastric cancer, patients with a history of documented congestive heart failure, angina pectoris requiring medication, evidence of transmural myocardial infarction on ECG, poorly controlled hypertension (systolic BP >180 mmHg or diastolic BP >100 mmHg), clinically significant valvular heart disease, high risk uncontrollable arrhythmias, baseline LVEF <50% (measured by echocardiography or MUGA) were excluded from Study BO18255 (ToGA) according to the study protocol.

## ***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 Herceptin to a patient with a known sensitivity to benzyl alcohol, Herceptin should be reconstituted with water for injection, and only one dose per Herceptin vial should be used. Any unused portion must be discarded. Sterile water for injection, used to reconstitute the 150 mg single dose vials, does not contain benzyl alcohol.

## ***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.

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## **Interactions**

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No formal interaction studies have been performed with Herceptin in humans. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed. A comparison of serum levels of Herceptin given in combination with cisplatin, doxorubicin or epirubicin-plus-cyclophosphamide has not suggested the possibility of any interaction.

Administration of paclitaxel in combination with Herceptin resulted in a slightly less than two-fold decrease in trastuzumab clearance in a non-human primate study and in a 1.5-fold increase in Herceptin serum levels in clinical studies. Paclitaxel pharmacokinetics determined during the fourth cycle of the alternative 3-weekly Herceptin regimen ( $n = 25$ ) were not altered appreciably, relative to parameters determined during the initiation of paclitaxel, prior to introduction of Herceptin. Similarly, docetaxel pharmacokinetics determined during the first dose of Herceptin in the standard weekly regimen ( $n = 10$ ) were not altered appreciably relative to those determined 2 weeks earlier for docetaxel alone.

A pharmacokinetic interaction substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer showed that co-administration of trastuzumab and capecitabine and cisplatin had no significant effects on the pharmacokinetics of the two chemotherapy agents compared with co-administration of the two agents without trastuzumab. The pharmacokinetics of trastuzumab were not evaluated in this study.

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## Use in Special Populations

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### Pregnancy

Pregnancy Category: D

Herceptin should be avoided during pregnancy and since trastuzumab may persist in the circulation for up to 27 weeks, pregnancy should be avoided for 6 months after the last dose of Herceptin, unless the anticipated benefit for the mother outweighs the unknown risk to the foetus.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin. Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 6 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 Herceptin, close monitoring by a multidisciplinary team is desirable.

### Nursing mothers

It is not known whether trastuzumab is secreted in human breast milk. As human IgG is secreted into human breast milk, and the potential for harm to the infant is unknown, breast-feeding should be avoided during Herceptin therapy and for 6 months after the last dose of Herceptin (See Preclinical Safety, Other).

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## Undesirable Effects

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The adverse drug reactions listed in this section fall into the following categories: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $<1/10$ ); uncommon ( $\geq 1/1,000$  to  $<1/100$ ); rare ( $\geq 1/10,000$  to  $<1/1,000$ ); very rare ( $<1/10,000$ ); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Presented in Table 1 below are adverse reactions that have been reported in association with the use of Herceptin alone, or in combination with chemotherapy in the below pivotal clinical trials as well as in the post-marketing setting.

#### *Early Breast Cancer*

- **BO16348 (HERA)**: Herceptin arm (n = 1678). Control arm (n = 1708)
- **B-31/N9831 Joint Analysis**: Herceptin arms (n = 2345). Control arm (n = 1673)
- **BCIRG 006**: Herceptin arm (n = 2133). Control arm (n = 1041)
- **BO16216 (TanDEM)**: Herceptin arm (n = 161). Control arm (n = 161)
- **MO16432 (NOAH)**: Herceptin arm (n = 115). Control arm (n = 116)

#### *Metastatic Breast Cancer*

- **H0648g / H0649g**: Herceptin arms (n = 469 and n = 222 respectively)
- **M77001**: Herceptin arm (n = 92). Control arm (n = 94).

*Advanced Gastric Cancer*

· **BO18255 (ToGA):** Herceptin arm (n = 294). Control arm (n = 290)

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

**Table 1: Adverse reactions**

<b>System organ class</b>	<b>Adverse reaction</b>	<b>Frequency</b>
Infections and infestations	+Pneumonia	Common (<1 %)
	Neutropenic sepsis	Common
	Cystitis	Common
	Herpes zoster	Common
	Infection	Common
	Influenza	Common
	Nasopharyngitis	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	Common
	Neutropenia	Common
	Thrombocytopenia	Common
	White blood cell count decreased / leukopenia	Common
	Hypoprothrombinaemia	Not known
Immune system disorders	Hypersensitivity	Common
	+Anaphylactic reaction	Not known
	+Anaphylactic shock	Not known
Metabolism and nutrition disorders	Weight Decreased/Weight Loss	Common
	Anorexia	Common

System organ class	Adverse reaction	Frequency
	Hyperkalaemia	Not known
Psychiatric disorders	Anxiety	Common
	Depression	Common
	Insomnia	Common
	Thinking abnormal	Common
Nervous system disorders	<sup>1</sup> Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Dysgeusia	Very common
	Peripheral neuropathy	Common
	Paraesthesia	Common
	Hypertonia	Common
	Somnolence	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very Common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and Labyrinth Disorders	Deafness	Uncommon
Cardiac disorders	<sup>1</sup> Blood pressure decreased	Very common
	<sup>1</sup> Blood pressure increased	Very common
	<sup>1</sup> Heart beat irregular	Very common
	<sup>1</sup> Palpitation	Very common
	<sup>1</sup> Cardiac flutter	Very common
	<sup>+</sup> Cardiac failure (congestive)	Common (2 %)
	<sup>+1</sup> Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Ejection fraction decreased <sup>^</sup>	Very Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis	Not known
	Bradycardia	Not known

System organ class	Adverse reaction	Frequency
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very Common
	<sup>+1</sup> Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	<sup>+1</sup> Wheezing	Very common
	<sup>+</sup> Dyspnoea	Very common (14 %)
	Cough	Very Common
	Epistaxis	Very Common
	Rhinorrhoea	Very Common
	Asthma	Common
	Lung disorder	Common
	Pharyngitis	Common
	<sup>+</sup> Pleural effusion	Uncommon
	Pneumonitis	Rare
	<sup>+</sup> Pulmonary fibrosis	Not known
	<sup>+</sup> Respiratory distress	Not known
	<sup>+</sup> Respiratory failure	Not known
	<sup>+</sup> Lung infiltration	Not known
	<sup>+</sup> Acute pulmonary oedema	Not known
	<sup>+</sup> Acute respiratory distress syndrome	Not known
	<sup>+</sup> Bronchospasm	Not known
	<sup>+</sup> Hypoxia	Not known
	<sup>+</sup> 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
	<sup>1</sup> Lip swelling	Very common
	Abdominal pain	Very common
	Pancreatitis	Common
	Dyspepsia	Common
	Haemorrhoids	Common
	Constipation	Common
	Dry mouth	Common

<b>System organ class</b>	<b>Adverse reaction</b>	<b>Frequency</b>
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
	<sup>1</sup> Swelling face	Very common
	Palmar-plantar erythrodysesthesia syndrome	Very common
	Acne	Common
	Alopecia	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhidrosis	Common
	Maculopapular rash	Common
	Nail disorder	Common
	Pruritus	Common
	Angioedema	Not known
	Dermatitis	Not known
Urticaria	Not known	
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	<sup>1</sup> Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	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

System organ class	Adverse reaction	Frequency
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	Common
	Malaise	Common
	Mucosal inflammation	Common
Oedema	Common	
Injury, poisoning and procedural complications	Contusion	Common

+ Denotes adverse reactions that have been reported in association with a fatal outcome.

1 Denotes adverse reactions that are reported largely in association with Infusion-related reactions. Specific percentages for these are not available.

^ Observed with combination therapy following anthracyclines and combined with taxanes

The following information is relevant to all indications:

### Infusion-related reactions (IRRs), Allergic reactions and Hypersensitivity

IRRs/hypersensitivity reactions such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress were seen in all Herceptin clinical trials (see Warnings and Precautions).

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

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

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

Anaphylactoid reactions were observed in isolated cases.

## Cardiac dysfunction

Signs and symptoms of cardiac dysfunction, such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ejection fraction, have been observed in patients treated with Herceptin (see Warnings and Precautions).

### **Early breast cancer**

#### *Neoadjuvant-adjuvant setting*

In the clinical trial setting, when Herceptin was administered concurrently with neoadjuvant chemotherapy containing three to four cycles of a neoadjuvant anthracycline (cumulative doxorubicin dose 180 mg/m<sup>2</sup> or epirubicin dose 360 mg/m<sup>2</sup>) overall, the incidence of symptomatic cardiac dysfunction was 1.7 % in the Herceptin arm.

#### *Adjuvant setting*

In 3 pivotal clinical trials of adjuvant Herceptin 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 Herceptin sequentially to a taxane (0.3 - 0.4%). The rate was highest in patients who were administered Herceptin 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 (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 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 Herceptin was administered after completion of adjuvant chemotherapy NYHA class III-IV heart failure was observed in 0.6% of patients in the 1-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 Herceptin therapy remained low at 0.8% and 9.8%, respectively. After a median follow-up of 8 years, the incidence of severe CHF (NYHA III & IV) following 1 year of Herceptin therapy (combined analysis of the two Herceptin treatment arms) was 0.89%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 6.35%.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values <sup>3</sup> 50% after the event) was evident for 70.0% of Herceptin-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 83.1% of Herceptin-treated patients. Approximately 10% of cardiac endpoints occurred after completion of Herceptin.



### **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 Herceptin + paclitaxel subgroup, compared with 1% - 4% for the paclitaxel alone subgroup. For Herceptin monotherapy, the rate was 6% - 9%. The highest rate of cardiac dysfunction was seen in patients receiving Herceptin + anthracycline/cyclophosphamide (27%), significantly higher than in the anthracycline/cyclophosphamide alone subgroup (7% - 10%). In study M77001 with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving Herceptin 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 heart failure.

### **Advanced Gastric Cancer**

In Study BO18255 (ToGA), at screening, the median LVEF value was 64% (range 48% - 90%) in the FP arm and 65% (range 50% - 86%) in the Herceptin + FP arm.

The majority of the LVEF decreases noted in BO18255 Study (ToGA) were asymptomatic, with the exception of 1 patient in the Herceptin arm whose LVEF decrease coincided with cardiac failure.

**Table 2: Summary of LVEF change from baseline (BO18255 Study)**

<b>LVEF Decrease<sup>#</sup>: Lowest Post-screening Value</b>	<b>FP (n = 290) (% of patients in each treatment arm)</b>	<b>FP + H (n = 294) (% of patients in each treatment arm)</b>
LVEF decrease <sup>3</sup> 10% to <50%	1.1%	4.6%
Absolute Value <50%	1.1%	5.9%
LVEF decrease <sup>3</sup> 10% to <sup>3</sup> 50%	11.8%	16.5%

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + Herceptin; <sup>#</sup>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 = 237)

**Table 3: Cardiac Adverse Events (BO18255 Study)**

	<b>FP (n = 290) (% of patients in each treatment arm)</b>	<b>FP +H (n = 294) (% of patients in each treatment arm)</b>
Total Cardiac Events	6%	6%
<sup>3</sup> Grade 3 NCI-CTC( v3.0) criteria	3% <sup>a</sup>	1% <sup>b</sup>

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + Herceptin; <sup>a</sup> 9 patients experienced 9 Events; <sup>b</sup> 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**

#### *Monotherapy – Study H0649g*

Haematological toxicity is infrequent following the administration of Herceptin monotherapy in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in < 1% of patients. No WHO Grade 4 toxicities were observed.

#### *Combination Therapy – Studies H0648g and M77001*

WHO Grade 3 or 4 haematological toxicity was observed in 63% of patients treated with Herceptin and an anthracycline/cyclophosphamide compared to an incidence of 62% in patients treated with the anthracycline/cyclophosphamide combination without Herceptin.

There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of Herceptin and paclitaxel compared with patients receiving paclitaxel alone (34% vs. 21%). Haematological toxicity was also increased in patients receiving Herceptin and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using HCl-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin + docetaxel (23% versus 17% for patients treated with docetaxel alone).

#### *Early breast cancer setting – BO16348 (HERA) Study*

Using NCI-CTC criteria, in the HERA trial, 0.4% of Herceptin-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 adverse events categorised under the Blood and Lymphatic System Disorders SOC (Grade ≥3) are shown below (Table 4) by trial treatment.

**Table 4: Blood and Lymphatic System Disorders (SOC) Adverse Events >1%**

	<b>FP (n=290) (% of patients in each treatment arm)</b>	<b>FP + H (n=294) (% of patients in each treatment arm)</b>
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile neutropenia	3%	5%
Thrombocytopenia	3%	5%

FP: Fluoropyrimidine/cisplatin; FP+H: Fluoropyrimidine/cisplatin + Herceptin

The total percentage of patients who experienced an adverse event of <sup>3</sup> Grade 3 NCI CTCAE v3.0 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 Herceptin 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 Herceptin and paclitaxel than among patients receiving paclitaxel (7% compared with 15%). No WHO Grade 3 or 4 renal toxicity was observed.

### ***Advanced Gastric Cancer***

In Study BO18255 (ToGA) no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

NCI-CTCAE (v3.0) grade  $\geq 3$  renal toxicity was not significantly higher in patients receiving Herceptin than those in the fluoropyrimidine/cisplatin arm (3% and 2% respectively).

NCI-CTCAE (v3.0) grade  $\geq 3$  adverse events in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported adverse event and was not significantly higher in patients receiving Herceptin than those in the fluoropyrimidine/cisplatin arm (1% and <1% respectively).

## **Diarrhoea**

### ***Breast Cancer***

#### *Monotherapy – Study H0649G*

Of patients treated with Herceptin monotherapy in the metastatic setting, 27% experienced diarrhoea. In the HERA trial (median follow-up 1 year), 7% of Herceptin-treated patients had diarrhoea.

#### *Combination Therapy – Studies H0648g and M77001*

An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has been observed in patients receiving Herceptin in combination with chemotherapy compared with patients receiving chemotherapy-alone or Herceptin-alone.

#### *Early breast cancer setting – HERA Study*

In the HERA trial, 8% of Herceptin treated patients experienced diarrhoea during the first year of treatment.

### ***Advanced Gastric Cancer***

In Study BO18255 (ToGA), 109 patients (37%) in the Herceptin treatment arm versus 80 patients (28%) in the comparator arm experienced any grade diarrhoea. Four percent (4%) of patients in the fluoropyrimidine/cisplatin arm experienced Grade 3 diarrhoea vs. 9% in the Herceptin arm.

## **Infection**

An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed primarily in patients treated with Herceptin + paclitaxel compared with patients receiving paclitaxel alone or Herceptin-alone.

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## Overdosage

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

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre (in Australia call 13 11 26; in New Zealand call 0800 767 766).

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## Pharmacological Properties and Effects

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### ***Pharmacodynamic Properties***

#### **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<sub>1</sub> isotype 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 25% - 30% of primary breast cancers and 6.8% - 42.6% of advanced 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 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.

#### **Clinical efficacy studies**

##### **Early Breast Cancer**

###### *Herceptin in combination with neoadjuvant-adjuvant chemotherapy*

The use of Herceptin for the neoadjuvant-adjuvant treatment of locally advanced breast cancer has been studied in Study MO16432 (NOAH), a multicentre randomized trial, designed to investigate the concurrent administration of Herceptin with neoadjuvant chemotherapy, including both an anthracycline and a taxane, followed by adjuvant Herceptin, up to a total treatment duration of 1 year. The study

recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory breast cancer. Patients with HER2+ tumours were randomized to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant Herceptin (n = 116), or neoadjuvant chemotherapy alone (n = 118).

Herceptin was administered concurrently with 10 cycles of neoadjuvant chemotherapy as follows;

- Doxorubicin (60 mg/m<sup>2</sup>) and paclitaxel (150 mg/m<sup>2</sup>) in combination with Herceptin (8 mg/kg loading dose, followed by 6 mg/kg maintenance, administered 3-weekly) for 3 cycles, followed by
- Paclitaxel (175 mg/m<sup>2</sup>) and Herceptin (6mg/kg, administered 3-weekly) for 4 cycles, followed by
- CMF on day 1 and 8 every 4 weeks for 3 cycles, in combination with 4 cycles of Herceptin (6mg/kg administered 3-weekly), followed by
- up to 7 additional cycles of Herceptin (6mg/kg, administered 3-weekly) alone to complete 1 year after starting Herceptin

The primary endpoint for the study, event-free survival (EFS), was defined as the time from randomization to disease recurrence or progression (local, regional, distant or contralateral), or death of any cause. The efficacy results from NOAH (full analysis population, defined as all patients who were randomized in the study following the intent-to-treat principle, with the exception of 3 patients whose data could not be evaluated) are summarized in the table below. The median duration of follow-up in the Herceptin arm was 3.8 years.

**Table 5: Overview of Efficacy Analyses MO16432 (NOAH)**

Parameter	Chemo + Herceptin n = 115	Chemo only n = 116	p-value	HR (95% CI)
<b>Event-free survival (EFS)</b>				
No. patients with event	46	59	p = 0.0275	0.65 (0.44, 0.96)
<b>Total pathological complete response<sup>^</sup></b> (95% CI)	40% (31.0, 49.6)	20.7% (13.7, 29.2)	p = 0.0014	

<sup>^</sup> defined as absence of any invasive cancer both in the breast and axillary nodes; HR: hazard ratio

The addition of Herceptin to neoadjuvant chemotherapy, followed by adjuvant Herceptin 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.

To date, results are not available comparing the efficacy of Herceptin administered with chemotherapy in the adjuvant setting with that obtained in the neoadjuvant/adjuvant setting.

#### *Herceptin in combination with adjuvant chemotherapy*

The use of Herceptin in the setting of early breast cancer (after surgery and in association with chemotherapy and, if applicable radiotherapy) has been studied in four multicentre, randomised, phase III trials of patients with HER2 positive breast cancer who have completed surgery. In these clinical trials, localised breast cancer was limited to operable, primary adenocarcinoma of the breast with positive axillary nodes or node negative disease with additional indicators of a higher degree of risk.

The design of these studies is summarized in Table 6 and efficacy results are presented in Tables 7 - 10.

**Table 6: Clinical Trials in Early Breast Cancer**

	<b>HERA trial</b> <b>n = 3386</b>	<b>NSAPB B-31 and NCCTG N9831 trials (joint analysis)</b> <b>n = 3763</b>	<b>BCIRG 006</b> <b>n = 3222</b>
<b>Eligible patients</b>	Node positive or node negative [n = 1098] and tumour size >1 cm;  <i>Protocol initially unrestricted but amended and node negative patients with tumours ≤1 cm [n =93, 8.5%] and node negative patients with tumours &gt;1 and ≤2 cm [n = 509,46.4%] were included</i>	Node positive or node negative [n = 190] and tumour size  · >2 cm regardless of hormonal status; or · >1 cm and ER–ve  [n = 63 node-negative and tumour size ≤2 cm])	Node positive or node negative and at least 1 of the following:  · tumour size > 2 cm and ER and PR -ve, or · histologic and/or nuclear grade 2-3, or · age < 35 years.
<b>Herceptin dosage regimen</b>	Loading dose 8 mg/kg, followed by 6 mg/kg (q3w)	Loading dose 4 mg/kg, followed by 2 mg/kg (q1w)	Loading dose 4 mg/kg, followed by 2 mg/kg (q1w). After chemo, 6 mg/kg (q3w)
<b>Duration of Herceptin treatment</b>	1yr or 2yrs	52 weeks	52 weeks
<b>Chemotherapy regimen(s)</b>	Various	AC (q3w) followed by IV paclitaxel as a continuous IV infusion (AC→P).  Paclitaxel: 80 mg/m <sup>2</sup> q1w for 12 weeks or 175 mg/m <sup>2</sup> q3w for 4 cycles (day 1 of each cycle)	AC followed by docetaxel (AC→D) or docetaxel and carboplatin (DCarb)  Docetaxel (IV infusion over 60 min): (AC→D): 100 mg/m <sup>2</sup> q3w for 4 cycles or (DCarb): 75 mg/m <sup>2</sup> q3w for 6 cycles Carboplatin (at target AUC): 6 mg/mL/min (IV infusion over 30 - 60 min) q3w for a total of 6 cycles.
<b>Timing of Herceptin in relation to chemotherapy</b>	After completion of (neo)adjuvant <sup>a</sup>	Concurrent (AC→PH) or sequential (AC→P→H)	Concurrent (AC→DH and DCarbH)
<b>Median follow-up</b>	1 year (initial evaluation) 8 years (follow-up evaluation )	2 years	3 years

AC = doxorubicin + cyclophosphamide; q3w = every 3 weeks; q1w = weekly chemo = chemotherapy; <sup>a</sup> 89% of subjects received adjuvant chemotherapy; 5% received neoadjuvant chemotherapy and 6% received a combination of neoadjuvant and adjuvant chemotherapy..

The HERA trial was designed to compare 1 and 2 years of 3-weekly Herceptin treatment vs. observation in patients with HER2 positive breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of 2 years Herceptin treatment vs. 1 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 3 weeks for either 1 or 2 years. The efficacy results from the HERA trial are summarized in the following table:

**Table 7: Efficacy Results from the HERA Trial at 12 months<sup>1</sup> and 8 years<sup>2</sup> of median follow up**

Parameter	Observation	Herceptin 1yr treatment	p-value	HR (95% CI)
<b><u>Disease free survival</u></b>				
No. of patients with event (1 year <sup>1</sup> )	12.9%	7.5%	<0.0001	0.54 (0.44,0.67)
No of patients with event (8 year <sup>2</sup> )	33.6%	27.7%	<0.0001	0.76 (0.67, 0.86)
<b><u>Overall Survival</u></b>				
No. of patients with event (1 year <sup>1</sup> )	2.4%	1.8%	0.24	0.75 (0.47,1.21)
No. of patients with event (8 year <sup>2</sup> )	20.6%	16.3%	0.0005	0.76 (0.65, 0.88)

HR: Hazard ratio; <sup>1</sup> co-primary endpoint of DFS of 1 year vs. observation met the pre-defined statistical boundary; <sup>2</sup> final analysis (includes crossover of 52% of patients from the observation arm to Herceptin).

The HERA study included a subgroup of patients ( $n = 602$ ) with small tumours (<2 cm) and node-negative disease. In this subgroup, the relative risk reduction was similar to the overall trial population (HR = 0.50; 95% CI 0.21 - 1.15). However, the benefit in terms of absolute difference in rate of recurrence after 1 year of follow-up was smaller (2.7% recurrence rate with Herceptin vs. 5.5% with observation).

In the final analysis (8 year median follow up) extending Herceptin treatment for a duration of 2 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% vs. 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%).

The efficacy results from the joint analysis of the NCCTG 9831 and NSABP B-31 trials are summarized in the following table:

**Table 8: Efficacy Results from NSABP B-31 and NCCTG N9831 trials (joint analysis)**

Parameter	AC→P	AC→PH	p-value	HR (95% CI)
<b><u>Disease recurrence</u></b>				
Rate (Herceptin vs. observation)	15.5%	8.0%	< 0.0001	0.48 (0.39, 0.59)
<b><u>Survival</u></b>				
Deaths (Herceptin vs. observation)	5.5%	3.7%	0.014	0.67 (0.48, 0.92)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: Herceptin; HR: Hazard ratio

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

**Table 9: Overview of Efficacy Analyses BCIRG 006 AC→D versus AC→DH**

Parameter	AC→D n = 1073	AC→DH n = 1074	p-value	HR (95% CI)
<b><u>Disease-free survival (DFS)</u></b>				
No. patients with event	195	134	<0.0001	0.61 (0.49, 0.77)
<b><u>Death (OS event)</u></b>				
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 BCIRG 006 AC→D versus DCarbH**

Parameter	AC→D n = 1073	DCarbH n = 1075	p-value	HR (95% CI)
<b><u>Disease-free survival (DFS)</u></b>				
No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
<b><u>Death (OS event)</u></b>				
No. patients with event	80	56	0.00182	0.66 (0.47,0.93)

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

### **Metastatic Breast Cancer**

#### *Herceptin monotherapy or in combination with chemotherapy*

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 (AC) 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<sup>2</sup> 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 paclitaxel is 3.9 months (6.9 months vs. 3.0 months). Tumour



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% vs. 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 vs. 22.7 months).

#### *Herceptin in combination with anastrozole*

The TAnDEM trial was a multi-centre, randomised, open-label, phase III study comparing Herceptin + anastrozole with anastrozole alone for the first-line treatment of metastatic breast cancer in HER2 overexpressing, hormone-receptor (i.e. oestrogen-receptor (ER) and/or progesterone-receptor (PR)) positive post-menopausal patients. Two hundred and seven patients were randomised to receive oral anastrozole (1 mg/day) with or without Herceptin (4 mg/kg loading dose, followed by 2 mg/kg weekly). Patients who had previously received Herceptin were excluded from this trial.

Median progression free survival was doubled in the Herceptin + anastrozole arm compared to the anastrozole alone arm (4.8 months vs. 2.4 months;  $p = 0.0016$ ). For the other parameters, the improvements seen for Herceptin + anastrozole were; overall response (16.5% vs. 6.7%); clinical benefit rate (42.7% vs. 27.9%); time to progression (4.8 months vs. 2.4 months). For time to response and duration of response no difference could be recorded between the arms. There was no significant difference in overall survival, however, more than half of the patients in the anastrozole alone arm crossed over to a Herceptin-containing regimen after progression of disease.

#### **Advanced Gastric Cancer**

Study BO18255 (ToGA) was a randomised, open-label, multicentre phase III study investigating Herceptin in combination with a fluoropyrimidine and cisplatin (FP) versus chemotherapy alone as first-line therapy in patients with HER2 positive, inoperable, locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.

Patients were eligible if they had 3+ levels of HER2 overexpression based on a 0 - 3+ scale by IHC assessment of tumour tissue and/or those whose tumours had HER2 gene amplification as determined by a FISH test (see Dosage and Administration, Detection of HER2 Overexpression or Gene Amplification).

After satisfying the screening eligibility criteria, including assessment of HER2 status, patients were randomly assigned (1:1) to receive either Herceptin (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) + fluoropyrimidine/cisplatin (FP+H) or FP alone. The chemotherapy regimen was chosen between 5-FU/cisplatin and capecitabine/cisplatin at the investigator's discretion and could be determined on an individual patient basis.

The efficacy results from ToGA are summarised in Table 11. The primary endpoint was overall survival, defined as the time from the date of randomization to the date of death from any cause. At the time of analysis a total of 349 randomised 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.

Overall survival was significantly improved in the FP + H arm compared to the FP arm ( $p = 0.0046$ , log-rank test). The median survival time was 11.1 months with FP and 13.8 months with FP + H. The risk of death was decreased by 26% (HR = 0.74; 95% CI 0.60 - 0.91) for patients in the FP + H arm compared to the FP arm.

Post-hoc subgroup analyses indicate that targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ and IHC 3+/regardless of 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 vs. 7.6 months, HR = 0.64 (95% CI 0.51 - 0.79).

**Table 11: Summary of Efficacy from Study BO18255**

Herceptin dosage regimen	Every 3 weeks			
<b>Chemotherapy regimens (FP)</b>	<ul style="list-style-type: none"> <li>Capecitabine: 1000 mg/m<sup>2</sup> orally twice daily for 14 days every 3 weeks for 6 cycles (Days 1 to 15 of each cycle).</li> <li>5-FU: 800 mg/m<sup>2</sup>/day as a continuous IV infusion over 5 days, given every 3 weeks for 6 cycles (Days 1 to 5 of each cycle). The 5-FU infusion could be started at the same time as the cisplatin infusion on Day 1.</li> <li>Cisplatin: 80 mg/m<sup>2</sup> every 3 weeks for 6 cycles (on Day 1 of each cycle) as a 2h IV infusion with hydration and premedication (steroids and anti-emetics).</li> </ul>			
<b>Efficacy Parameters</b>	<b>FP n = 290</b>	<b>FP+H n = 294</b>	<b>HR (95% CI)</b>	<b>p-value</b>
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 <sup>a</sup> (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; FP+H: Fluoropyrimidine/cisplatin + Herceptin; <sup>a</sup> Odds ratio

*Progression-free-survival*: time between day of randomization and first documentation of progressive disease (PD) or date of death, whichever occurred first. *Time to disease progression*: time between randomization and first occurrence of PD. *Overall response*: occurrence of either a confirmed complete (CR) or a partial (PR) best overall response as determined by RECIST criteria from confirmed radiographic evaluations of target and non-target lesions. *Duration of response*: time from when response (CR or PR) was first documented to the first documented disease progression. This was only calculated for patients who had a best overall response of CR or PR.

### ***Immunogenicity***

Human anti-trastuzumab antibodies were detected in 1 of 903 patients, who had no allergic manifestations.

## ***Pharmacokinetic Properties***

The pharmacokinetics of trastuzumab has been studied in patients with breast cancer (metastatic and early breast cancer) and advanced gastric cancer. Formal drug-drug interaction studies have not been performed for Herceptin.

### **Breast cancer**

Short duration intravenous infusions of 10, 50, 100, 250 and 500 mg trastuzumab once weekly in patients demonstrated dose-dependent pharmacokinetics. Mean half-life increased and clearance decreased with increased dose level.

### ***Steady State Pharmacokinetics in Breast Cancer***

A population pharmacokinetic method, using data from Phase I, Phase II and pivotal Phase III studies, was used to estimate the steady state pharmacokinetics in metastatic breast cancer patients. For a typical patient (body weight 68 kg the clearance of trastuzumab was 0.241 L/day and volume of distribution of the central ( $V_c$ ) and peripheral ( $V_p$ ) compartments were 3.02 L, and 2.68 L respectively, with a corresponding elimination half-life ranging from approximately 28-38 days. These indicate steady state pharmacokinetics should therefore be reached by approximately 27 weeks, with mean predicted AUC at steady state (over a three week period) of 1822mg•day/L with weekly dosing and 1912 mg•day/L with 3-weekly (once every three weeks) dosing. The estimated mean peak and trough concentrations were 113 mg/L and 69.9 mg/L (weekly) and 184 mg/L and 52.9 mg/L (3-weekly) respectively. Comparable steady state mean  $C_{max}$  of 225  $\mu\text{g/mL}$  and mean  $C_{min}$  of 68.9  $\mu\text{g/mL}$  at day 21 of cycle 18, the last cycle of 1 year treatment, have been reported in localised breast cancer patients administered Herceptin 3-weekly.

It is expected that serum trastuzumab levels will fall to less than 5% of the trough levels at steady state approximately 27 weeks (190 days or 5 elimination half-lives) after a dose discontinuation.

### **Gastric cancer**

Short duration IV infusions of 8 mg/kg followed by 6 mg/kg Herceptin every 3 weeks in patients with advanced gastric cancer demonstrated concentration-dependent clearance comprised of predominantly linear and non-linear components. At very low serum concentrations (below 10 $\mu\text{g/mL}$ ) non-linear clearance comprises nearly all of the total clearance (7-fold higher than linear clearance). At higher concentrations (25  $\mu\text{g/mL}$ ) the non-linear clearance component decreases to approximately one-half of total clearance, whilst at higher concentrations (> 75 $\mu\text{g/L}$ ) clearance becomes predominantly linear.

### ***Steady State Pharmacokinetics in Advanced Gastric Cancer***

A two compartment population pharmacokinetic method, using data from the Phase III study BO18255 (ToGA) was used to estimate the steady state pharmacokinetics in patients with advanced gastric

cancer administered Herceptin 3-weekly at a loading dose of 8 mg/kg followed by a 3-weekly maintenance dose of 6 mg/kg. At high serum concentrations, total clearance is dominated by linear clearance and the half-life is approximately 26 days. Steady state  $C_{\min}$  is reached in approximately 168 days, due to the non-linear clearance component. The mean predicted steady-state AUC value (over a period of 3 weeks at steady state) is approximately 1213 mg•day/L, and the mean steady-state  $C_{\max}$  and  $C_{\min}$  values are approximately 132 mg/L and 27.6 mg/L respectively. It is expected that serum trastuzumab levels will fall to less than 5% of the trough levels at steady state, approximately 19 weeks after a dose discontinuation.

There are no data on the level of circulating extracellular domain of the HER2 receptor (shed antigen) in the serum of gastric cancer patients.

### **Special Populations**

Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. The data from Study H0649g suggest that the disposition of trastuzumab is not altered by patient characteristics such as age or serum creatinine. The population pharmacokinetic analysis also shows that the estimated creatinine clearance (Cockcroft and Gault) does not correlate with the pharmacokinetics of trastuzumab.

#### ***Elderly***

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

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## **Preclinical Safety**

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### ***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 Herceptin and have revealed no evidence of impaired fertility or 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.

### ***Other***

#### **Lactation**

A study conducted in lactating cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin 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.

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## Pharmaceutical Particulars

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### Storage

#### Vials

Store vials at 2 °C – 8 °C.

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

#### Shelf-life of the reconstituted solution

##### *Herceptin 440 mg vial*

Reconstituted solutions made with Bacteriostatic Water for Injection for the 440 mg vial of Herceptin, 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. If sterile water is used to reconstitute the 440 mg vial, the solution is stable for only **24 hours**, and must be discarded thereafter.

Do not freeze the reconstituted solution.

##### *Herceptin 150 mg vial*

The 150 mg vials are reconstituted with sterile water for injection and are for single use only.

The reconstituted product is physically and chemically stable for **48 hours at 2 °C – 8 °C** (refrigerate, do not freeze) after dissolving with 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. The shelf-life of the reconstituted solution is **24 hours at 2 °C – 8 °C**, unless reconstitution has taken place in controlled and validated aseptic conditions in which case the shelf-life is **48 hours at 2 °C – 8 °C**.

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

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

From a microbiological point of view, the Herceptin 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.

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## Special Instructions for Use, Handling and Disposal

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Appropriate aseptic technique should be used.

The 440 mg vial of Herceptin is reconstituted with 20 mL of 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.

The 150 mg vial of Herceptin is reconstituted with 7.2 mL of sterile water for injection.

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

### Instructions for reconstitution – 440 mg vial:

1. Using a sterile syringe, slowly inject 20 mL of sterile Bacteriostatic Water for Injection into the vial containing the lyophilised Herceptin, directing the stream into the lyophilised 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 lyophilised Herceptin, directing the stream into the lyophilised 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 Herceptin results in a colourless to pale yellow transparent solution and should be essentially free of visible particles.

### Instructions for dilution

#### **Weekly schedule**

Determine the volume of the reconstituted solution required based on a loading dose of 4 mg trastuzumab/kg body weight, or a maintenance dose of 2 mg trastuzumab/kg body weight:

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

#### **Three-weekly schedule**

Determine the volume of the reconstituted solution required based on a loading dose of 8 mg trastuzumab/kg body weight, or a maintenance dose of 6 mg trastuzumab/kg body weight:

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

### **Preparation and Stability of the Admixture**

The appropriate amount of reconstituted 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 medicines should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately (see Storage).

### **Incompatibilities**

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

Dextrose (5%) solution should not be used since it causes aggregation of the protein.

Herceptin should not be mixed or diluted with other medicines.

### **Disposal**

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

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## **Medicine Classification**

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Prescription medicine.

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## **Packs**

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*Herceptin 150 mg single-dose vials:* each pack contains one vial of Herceptin (150 mg trastuzumab).

*Herceptin 440 mg multi-dose vials:* each pack contains one vial of Herceptin (440 mg trastuzumab) and one 20 mL vial of Bacteriostatic Water for Injection.

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## **Name and Address**

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Roche Products (New Zealand) Limited  
PO Box 109113 Newmarket  
Auckland 1149  
NEW ZEALAND

Customer enquiries: 0800 656 464

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## Date of Preparation

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16 January 2014