AUSTRALIAN PRODUCT INFORMATION
Herceptin (trastuzumab) powder for injection

1. NAME OF THE MEDICINE
Trastuzumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Herceptin 150 mg vial contains 150mg of trastuzumab
Herceptin 60mg vial contains 60 mg trastuzumab

The reconstituted Herceptin solution contains 21 mg/mL of trastuzumab.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
Powder for IV infusion.

Sterile, preservative-free lyophilized white to pale yellow powder.

Herceptin solution for subcutaneous (SC) injection (Herceptin SC) is a colourless to yellowish, clear to opalescent and contains 600 mg/5mL of trastuzumab (see separate Herceptin SC Product Information).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Early Breast Cancer
Herceptin is indicated for the treatment of HER2-positive early breast cancer following surgery, and in association with chemotherapy and, if applicable, radiotherapy.

Locally Advanced Breast Cancer
Herceptin is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin.

Metastatic Breast Cancer
Herceptin 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 taxanes for the treatment of those patients who have not received chemotherapy for their metastatic disease; or

c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor positive metastatic breast cancer.

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.

4.2 DOSE AND METHOD OF ADMINISTRATION
HER2 testing is mandatory prior to initiation of Herceptin therapy (see below Detection of HER2 Protein Overexpression and Gene Amplification).

Detection of HER2 Protein Overexpression or HER2 Gene Amplification
Herceptin should only be used in patients whose tumours have HER2 protein 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 protein overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks. HER2 gene amplification should be detected using in situ hybridization (ISH) of fixed tumour blocks. Examples of ISH include fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH) and silver in situ hybridization (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 the use of these assays and interpretation of the results 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.

General
In order to prevent medication errors, it is important to check the vial labels to ensure the medicine being prepared and administered is Herceptin (trastuzumab) and not Kadcyla® (trastuzumab emtansine).

It is important to check the labels to ensure the correct formulation (intravenous or subcutaneous) is being administered to the patient as was prescribed. Switching treatment between Herceptin IV and Herceptin SC and vice versa, using a three-weekly (q3w) dosing regimen, was investigated in study MO22982 (PrefHER) (see section 5.1 Pharmacodynamic Properties and section 4.8 Adverse Effects (Undesirable Effects)). In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded in the patient medical record.

Dosage
Early Breast Cancer
Three-weekly schedule: the recommended initial loading dose is 8 mg/kg body weight, followed by a maintenance dose of 6 mg/kg body weight administered at 3 weekly intervals.

Weekly schedule: the recommended initial loading dose is 4 mg/kg body weight, followed by a maintenance dose of 2 mg/kg body weight administered at weekly intervals.

Locally Advanced Breast Cancer
Three-weekly schedule: the recommended initial loading dose is 8 mg/kg body weight, followed by a maintenance dose of 6 mg/kg body weight administered at 3 weekly intervals.

Metastatic Breast Cancer
Three-weekly schedule: the recommended initial loading dose is 8 mg/kg body weight, followed by a maintenance dose of 6 mg/kg body weight administered at 3 weekly intervals.

Weekly schedule: the recommended initial loading dose is 4 mg/kg body weight, followed by a maintenance dose of 2 mg/kg body weight administered at weekly intervals.

Advanced Gastric Cancer
Three-weekly schedule: the recommended initial loading dose is 8 mg/kg body weight, followed by a maintenance dose of 6 mg/kg body weight administered at 3-weekly intervals.

Refer to section 5.1 Pharmacodynamic Properties, Clinical Trials (including Table 5 for early breast cancer) for the sequence and dosing of chemotherapy medicines used in the supporting pivotal trials. Refer also to the currently approved product information for the chemotherapy partners.

Missed Doses
If the patient has missed a dose of Herceptin by one week or less, then the usual maintenance dose of Herceptin (weekly regimen: 2 mg/kg; 3-weekly: 6 mg/kg) should be administered as soon as possible (do not wait until the next planned cycle). Subsequent maintenance doses should then be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; 3-weekly: 8 mg/kg) as soon as possible. Subsequent maintenance doses (weekly regimen: 2 mg/kg; 3-weekly: 6 mg/kg) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

Dose modification
If the patient develops an infusion-related reaction (IRR), the infusion rate of Herceptin IV may be slowed or interrupted (see section 4.4 Special Warnings and Precautions for Use). 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 carefully monitored for complications of neutropenia during this time. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Use in Elderly
In clinical trials, patients ≥ 65 years of age did not receive reduced doses of trastuzumab. Age has been shown to have no effect on the disposition of trastuzumab (see section 5.2 Pharmacokinetic Properties).

Method of Administration
Herceptin IV solution is not to be used for subcutaneous administration and must be administered as an IV infusion. Do not administer as an IV push or bolus.

Herceptin IV loading doses should be administered over approximately 90 minutes. If the loading dose was well tolerated, subsequent doses can be administered as a 30-minute infusion.

Patients should be observed for fever and chills or other infusion-associated symptoms (see section 4.8 Adverse Effects (Undesirable Effects)). Interruption of the infusion and/or medication may help to control such symptoms. The infusion may be resumed when symptoms abate.

Duration of Treatment

Patients with early or locally advanced breast cancer should be treated for 1 year or until disease recurrence or unmanageable toxicity, whichever occurs first. However, extending adjuvant treatment beyond one year is not recommended (see section 5.1 Pharmacodynamic Properties, Clinical Trials, Early Breast Cancer**)**.

Patients with metastatic breast cancer and advanced gastric cancer should be treated until progression of disease or unmanageable toxicity.

Preparation for IV infusion

Reconstituting the Powder
Appropriate aseptic technique should be used.

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.

Each 60 mg vial should be reconstituted with 3.0 mL of sterile water for injections as the solvent. The use of other solvents should be avoided. The resultant solution is 3.1 mL of approximately 21 mg/mL trastuzumab. A 7.5% overage is included to ensure withdrawal of the labelled dose of 60 mg.

Each 150 mg vial should be reconstituted with 7.2 mL of sterile water for injections as the solvent. The use of other solvents should be avoided. The resultant solution is 7.4 mL of approximately 21 mg/mL trastuzumab. A 4% overage is included to ensure withdrawal of the labelled dose of 150 mg.

Instructions for Reconstitution

1) Using a sterile syringe, slowly inject 7.2 mL (for 150 mg vial) or 3.0 mL (for 60 mg vial) of sterile water for injections in the vial containing the lyophilized Herceptin, directing the stream into the lyophilized cake.

2) Swirl vial gently to aid reconstitution. Herceptin may be sensitive to shear-induced stress, e.g. agitation or rapid expulsion from a syringe. 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 preparation results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

Instructions for Dilution

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

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

Three-Weekly Regimen
Determine the volume of the reconstituted solution required based on a loading dose of trastuzumab 8 mg/kg body weight, or subsequent every 3 weeks dose of 6 mg/kg body weight:

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

Preparation and Stability of the Admixture
The appropriate amount of the reconstituted solution should be withdrawn from the vial using a sterile needle and syringe and added to an infusion bag containing 250 mL of 0.9% sodium chloride.

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

Herceptin SHOULD NOT BE MIXED OR DILUTED WITH OTHER MEDICINES.

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

The infusion bag should be gently inverted to mix the solution in order to avoid foaming. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-bacterial preservative or bacteriostatic agent, asceptic technique must be observed. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

From a microbiological point of view, the Herceptin infusion solution should be used immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2 to 8°C.

4.3 CONTRAINDICATIONS

Herceptin is contraindicated in patients with known hypersensitivity to trastuzumab, Chinese hamster ovary cell proteins or to any of its excipients.

In the treatment of early or locally advanced breast cancer, Herceptin is contraindicated in patients with a left ventricular ejection fraction of less than 45% and those with symptomatic heart failure.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Herceptin therapy should only be initiated under the supervision of a physician experienced in the treatment of cancer patients. Usual clinical care should be taken to prevent microbial contamination of the intravenous access sites used to deliver Herceptin therapy. 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.

If Herceptin is used concurrently with cytotoxic chemotherapy, the specific guidelines used to reduce or hold the dose of chemotherapy should be followed. Patients may continue Herceptin therapy during periods of reversible chemotherapy-induced myelosuppression, renal toxicity or hepatic toxicity.

Cardiac Dysfunction

General considerations

Patients treated with Herceptin are at increased risk of developing congestive heart failure (CHF) (New York Heart Association [NYHA] class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Herceptin therapy alone or in combination with a taxane following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. This may be moderate to severe and has been associated with death. In addition, caution should be exercised in treating patients with increased cardiac risk e.g. hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age.

Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping Herceptin treatment (see Section 5.2 Pharmacokinetic Properties). 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 7 months 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 anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, ECG and echocardiogram, 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 treatment until 24 months from the last administration of Herceptin.

If left ventricular ejection fraction (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, or clinically significant CHF has developed, 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 unless the benefits for the individual patient are deemed to outweigh the risks.

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. In the pivotal trials, most patients who developed heart failure or asymptomatic cardiac dysfunction improved with standard heart failure treatment consisting of 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 Herceptin treatment continued on weekly therapy with Herceptin without additional clinical cardiac events.

Early and Locally Advanced 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.

All patients should have a determination of LVEF prior to treatment. Use of Herceptin is contraindicated in patients with early or locally advanced disease and a LVEF of less than 45% and those with symptomatic heart failure (see section 4.3 Contraindications). Patients with a LVEF of 45 - 55% at baseline should be monitored regularly for symptoms of heart failure during Herceptin treatment.

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

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

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 4 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 (> 25 kg/m^2).

Neoadjuvant-adjuvant treatment
Herceptin neoadjuvant-adjuvant treatment concurrent with anthracyclines should be used with caution and only in chemotherapy-naive patients. The maximum cumulative doses of the low-dose anthracycline regimens should not exceed 180 mg/m^2 (doxorubicin) or 360 mg/m^2 (epirubicin).

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.

Metastatic breast cancer
Herceptin and anthracyclines 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, and baseline LVEF <50% (measured by echocardiography or MUGA) were excluded from Study BO18255 (ToGA) according to the study protocol.

Hypersensitivity Reactions including Anaphylaxis

Severe hypersensitivity reactions have been infrequently reported in patients treated with Herceptin. Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. The onset of symptoms generally occurred during an infusion, but there have also been reports of symptom onset after the completion of an infusion. Reactions were most commonly reported in association with the initial infusion.

Patients should be observed closely for hypersensitivity reactions. Herceptin infusion should be interrupted in all patients with severe hypersensitivity reactions. In the event of a hypersensitivity reaction, appropriate medical therapy should be administered, which may include adrenaline, corticosteroids, antihistamines, bronchodilators and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Infusion-Related Reactions (IRRs)

IRRs are known to occur with the administration of Herceptin (see section 4.8 Adverse Effects (Undesirable Effects)).

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

Serious IRRs to Herceptin infusion including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress and supraventricular tachyarrhythmia have been reported (see section 4.8 Adverse Effects (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 paracetamol and an antihistamine. Serious reactions have been treated successfully with supportive therapy such as oxygen, intravenous fluids, 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 co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Herceptin (see Pulmonary Reactions below).

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 above) 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, pulmonary hypertension, pulmonary fibrosis 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 Herceptin.

Tumour lysis syndrome (TLS)

Tumour lysis syndrome (TLS) refers to the constellation of metabolic disturbances that may be seen after initiation of effective cancer treatment. It usually occurs in patients with high grade, bulky, rapidly proliferating, treatment-responsive tumours and in patients with acute haematological malignancies. Cases of possible TLS have been reported in patients treated with Herceptin. Patients with significant tumour burden (e.g. bulky metastases) may be at a higher risk. Patients could present with hyperuricemia,

hyperphosphatemia, and acute renal failure which may represent possible TLS. Providers should consider additional monitoring and/or treatment as clinically indicated.

Paediatric Use
The safety and efficacy of Herceptin in patients under the age of 18 years have not been established.

Use in the Elderly
Clinical experience is limited in patients above 65 years of age. The risk of cardiac dysfunction may be increased in elderly patients. The reported clinical experience is not adequate to determine whether older patients respond differently from younger patients. Elderly patients did not receive reduced doses of Herceptin in clinical trials. However, greater sensitivity to Herceptin in some older patients cannot be ruled out.

Use in Renal Impairment
Formal PK studies have not been conducted in patients with renal impairment. Based on population PK analysis, renal impairment is not expected to influence trastuzumab exposure, however, limited data from patients with moderate to severe renal impairment were included in the population PK analysis (see section 5.2 Pharmacokinetic Properties).

Use in Hepatic Impairment
The use of Herceptin in patients with hepatic impairment has not been studied.

Effects on Laboratory Tests
No data available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No formal drug interaction studies have been performed with Herceptin in humans. Clinically significant interactions with 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 a 1.5-fold increase in trastuzumab 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 sub study 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.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility
A study in female cynomolgus monkeys revealed no evidence of impaired fertility at IV trastuzumab doses up to 25 mg/kg twice weekly, corresponding to serum trough levels (serum Cmin) about 15 times higher than that in humans receiving the recommended weekly dose of 2 mg/kg.

Use in Pregnancy – Category D
Herceptin should be avoided during pregnancy and since trastuzumab may persist in the circulation for up to 7 months, pregnancy should be avoided for 7 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 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 Herceptin, or becomes pregnant within 7 months following the last dose of Herceptin, close monitoring by a multidisciplinary team is desirable.

Use in Lactation
A study conducted in lactating cynomolgus monkeys dosed intravenously with trastuzumab at 25 mg/kg twice weekly (serum C_{min} about 15 times higher than that in humans receiving the recommended weekly dose of 2 mg/kg) demonstrated that trastuzumab is excreted in the milk. The exposure to trastuzumab in utero and the presence of trastuzumab in the serum of infant monkeys was not associated with adverse effects on their growth or development from birth to 1 month of age. However, the binding affinity of trastuzumab to epidermal growth factor receptor 2 protein in cynomolgus monkeys is unclear.

It is not known whether trastuzumab is excreted 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 Herceptin therapy and for 7 months after the last dose of Herceptin.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Herceptin has a minor influence on the ability to drive and use machines. Dizziness and somnolence may occur during treatment with Herceptin (see section 4.8 Adverse Effects (Undesirable Effects). Patients experiencing infusion-related symptoms should be advised not to drive or use machines until symptoms resolve completely.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)
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 the below pivotal clinical trials as well as in the post-marketing setting.

The corresponding frequency category for each adverse drug reactios 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 are presented in order of decreasing seriousness.

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)

Locally Advanced Breast Cancer

- **MO16432 (NOAH):** Herceptin arm (n=115). Control arm (n=116)

Metastatic Breast Cancer (MBC)

- **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: Summary of adverse drug reactions occurring in patients treated with Herceptin in clinical trials and the post market setting

System organ class	Adverse reaction[1]	Frequency
Infections and infestations	Nasopharyngitis	Very common
	Infection	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Herpes zoster	Common
	Influenza	Common
	Pharyngitis	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Erysipelas	Common
	Cellulitis	Common
	Sepsis	Uncommon
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile neutropenia	Very common
	Anaemia	Very common
	Thrombocytopenia	Very common
	White blood cell count decreased / leukopenia	Very common
	Neutropenia	Very common
	Hypoprothrombinaemia	Not known
	Immune Thrombocytopenia	Not Known
Immune system disorders	Hypersensitivity	Common
	[2]Anaphylactic reaction	Not known
	[2]Anaphylactic shock	Not known

System organ class	Adverse reaction[1]	Frequency
Metabolism and nutrition disorders	Weight Decreased/Weight Loss	Very common
	Weight Increased	Very common
	Decreased appetite	Very common
	Anorexia	Very common
	Hyperkalaemia	Not known
	Tumour lysis syndrome	Not known
Psychiatric disorders	Insomnia	Very common
	Depression	Common
	Anxiety	Common
	Thinking abnormal	Common
Nervous system disorders	[3]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Dysgeusia	Very common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Peripheral neuropathy	Common
	Hypertonia	Common
	Somnolence	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and Labyrinth Disorders	Deafness	Uncommon
Cardiac disorders	[3]Blood pressure decreased	Very common
	[3]Blood pressure increased	Very common
	[3]Heart beat irregular	Very common
	[3]Palpitation	Very common
	[3]Cardiac flutter	Very common
	[4]Ejection fraction decreased	Very common
	[2]Cardiac failure (congestive)	Common
	[2,3]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis	Not known

System organ class	Adverse reaction[1]	Frequency
	Bradycardia	Not known
	Gallop rhythm present	Not known
Vascular disorders	Lymphoedema	Very common
	Hot flush	Very common
	[2,3]Hypotension	Common
	Hypertension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	[2,3]Wheezing	Very common
	[2]Dyspnoea	Very common
	Cough	Very common
	Epistaxis	Very common
	Rhinorrhoea	Very common
	Oropharyngeal pain	Very common
	Asthma	Common
	Lung disorder	Common
	[2]Pleural effusion	Common
	[2]Pneumonia	Common
	Pneumonitis	Uncommon
	[2]Pulmonary fibrosis	Not known
	[2]Respiratory distress	Not known
	[2]Respiratory failure	Not known
	[2]Lung infiltration	Not known
	[2]Acute pulmonary oedema	Not known
	[2]Acute respiratory distress syndrome	Not known
	[2]Bronchospasm	Not known
	[2]Hypoxia	Not known
	[2]Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	[2]Orthopnoea	Not known
	Pulmonary oedema	Not known
	Interstitial lung disease	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	Lip swelling	Very common
	Abdominal pain	Very common
	Stomatitis	Very common
	Pancreatitis	Very common
	Constipation	Very common

System organ class	Adverse reaction[1]	Frequency
	Dyspepsia	Very common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular Injury	Common
	Hepatitis	Common
	Liver Tenderness	Common
	Jaundice	Rare
	Hepatic Failure	Not known
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	[3]Swelling face	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Nail disorder	Very common
	Alopecia	Very common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Acne	Common
	Onychoclasis	Common
	Pruritus	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known

System organ class	Adverse reaction[1]	Frequency
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like illness	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Mucosal inflammation	Very common
	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common
	Contusion	Common

[1] 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;[2] Denotes adverse reactions that have been reported in association with a fatal outcome;[3] Denotes adverse reactions that are reported largely in association with Infusion-related reactions. Specific percentages for these are not available;[4] Observed with combination therapy following anthracyclines and combined with taxanes

Additional information for selected adverse drug reactions

The following information is relevant to all indications.

Infusion-Related Reactions (IRRs) and Hypersensitivity

IRRs 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 section 4.4 Special Warnings and Precautions for Use).

IRRS may be clinically difficult to distinguish from hypersensitivity reactions.

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 (see section 4.4 Special Warnings and Precautions for Use).

Cardiac Dysfunction

Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to Herceptin. It has been associated with fatal outcome. Signs and symptoms of heart failure, such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, pulmonary hypertension and S3 gallop or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin (see section 4.4 Special Warnings and Precautions for Use).

Locally Advanced Breast Cancer (neoadjuvant –adjuvant setting)
In the clinical trial setting, when Herceptin was administered concurrently with neoadjuvant chemotherapy containing 3-4 cycles of a neoadjuvant anthracycline (cumulative doxorubicin dose 180 mg/m^2 or epirubicin dose 360 mg/m^2) overall, the incidence of symptomatic cardiac dysfunction was up to 1.7 % in the Herceptin arm.

Early Breast Cancer (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 (Herceptin) 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 Herceptin) treatment arms, respectively. For symptomatic CHF (NCI-CTC Grade 3 - 4), the 5-year rates were 0.6%, 1.9%, and 0.4% in the AC→D, AC→DH, and DCarbH treatment arms, respectively. The overall risk of developing symptomatic cardiac events was low and similar for patients in 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 Class III & IV) following 1 year of Herceptin therapy (combined analysis of the two Herceptin treatment arms) 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 Herceptin-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of Herceptin-treated patients. Approximately 17% of cardiac dysfunction related events occurred after completion of Herceptin.

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): in patients with a symptomatic CHF event, while data are missing for 22.6%, 64.5% were known to recover, and 12.9% experienced no recovery. The median time to first recovery by LVEF status occurred at 8.3 months (range 1 – 104 months); 90.3% experienced a full or partial LVEF recovery.

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 concurrent 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 fluoropyrimidine/cisplatin (FP) arm and 65% (range 50% - 86%) in the Herceptin + FP arm.

The majority of the LVEF decreases noted in Study BO18255 (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 (Study BO18255)

LVEF Decrease[#]: Lowest Post-screening Value	**FP (*n* = 290) (% patients in each treatment arm)**	**FP + H (*n* = 294) (% patients in each treatment arm)**
LVEF decrease ≥10% to <50%	1.1%	4.6%
Absolute Value <50%	1.1%	5.9%
LVEF decrease ≥ 10% to ≥ 50%	11.8%	16.5%

FP: fluoropyrimidine/cisplatin; FP+H: fluoropyrimidine/cisplatin + Herceptin; [#]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 (Study BO18255)

	FP (*n* = 290) (% patients in each treatment arm)	**FP +H (*n* = 294) (% patients in each treatment arm)**
Total Cardiac Events	6%	6%
≥ Grade 3 NCI CTCAE v3.0	3% [a]	1% [b]

FP: fluoropyrimidine/cisplatin; FP+H: fluoropyrimidine/cisplatin + Herceptin; [a] 9 patients experienced 9 Events; [b] 4 patients experienced 5 Events

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

Haematological Toxicity

Breast Cancer

Monotherapy– Study H0649g

Haematological toxicity is infrequent following the administration of Herceptin as 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 vs. 22%, using NCI-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin + docetaxel (23% vs. 17% for patients treated with docetaxel-alone).

Early Setting – HERA Trial
Using NCI-CTC criteria, in the BO16348 (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 categorized under the Blood and Lymphatic System Disorders SOC (Grade ≥3) are shown below by trial treatment.

Table 4: Frequently reported adverse events grade > 3 in blood and lymphatic System Disorders (SOC)

	FP (*n* = 290) (% patients in each treatment arm)	**FP + H (*n* = 294) (% patients in each treatment arm)**
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 ≥ Grade 3 NCI CTCAE v3.0 categorized 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
Monotherapy– Study H0649g
WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of Herceptin as monotherapy in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60% of these patients. No WHO Grade 3 or 4 renal toxicity was observed.

Combination Therapy – Study H0648g
WHO Grade 3 or 4 hepatic toxicity was observed in 6% of patients treated with Herceptin and an anthracycline/cyclophosphamide compared with an incidence of 8% in patients treated with the anthracycline/cyclophosphamide combination without Herceptin. No WHO Grade 3 or 4 renal toxicity was observed.

WHO Grade 3 or 4 hepatic toxicity was less frequently observed among patients receiving Herceptin and paclitaxel than among patients receiving paclitaxel-alone (7% vs.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 ≥ 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 ≥ 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.

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 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 + chemotherapy compared with patients receiving chemotherapy-alone or Herceptin-alone.

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

Immunogenicity
In a neoadjuvant-adjuvant EBC trial (BO22227) at a median follow-up exceeding 70 months, 10.1% (30/296) of patients treated with Herceptin IV and 15.9% (47/295) of patients receiving Herceptin SC developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the Herceptin IV arm and 3 of 47 patients in the Herceptin SC arm.

The clinical relevance of these antibodies is not known. The presence of anti-trastuzumab antibodies had no impact on pharmacokinetics, efficacy [determined by pathological complete response (pCR)] and event free survival (EFS) and safety [determined by the occurrence of administration related reaction (ARRs)] of Herceptin IV and Herceptin SC.

Switching treatment from Herceptin IV to Herceptin SC and vice versa
Study MO22982 (PrefHER) investigated switching from Herceptin IV to Herceptin SC, and vice versa, in patients with HER2 positive EBC, with a primary objective to evaluate patient preference for either Herceptin IV infusion or Herceptin SC injection. This trial investigated using a 2-arm, cross-over design with patients being randomized to one of two different q3w Herceptin treatment sequences (Herceptin IV (Cycles 1-4) → Herceptin SC (Cycles 5-8), or Herceptin SC (Cycles 1-4) → Herceptin IV (Cycles 5-8)). Patients participating in this trial could be enrolled at any time as long as there were at least 10 remaining cycles of Herceptin in their planned treatment regimen, therefore patients were either naïve to Herceptin IV treatment (20.3%) or pre-exposed to Herceptin IV (79.7%) as part of ongoing adjuvant treatment for HER2 positive EBC. Overall, switches from Herceptin IV to Herceptin SC and vice versa were well tolerated. Pre-switch rates (Cycles 1-4) for SAEs, Grade 3 AEs and treatment discontinuations due to AEs were low (<5%) and similar to post-switch rates (Cycles 5-8). No Grade 4 or Grade 5 AEs were reported. The effect of multiple switches back and forth was not investigated (see also section 5 Pharmacological Properties, Clinical Trials).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE
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).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

Mechanism of Action
The HER2 (or c erbB2) proto oncogene encodes for a single transmembrane spanning, receptor like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor.
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. In animal models in vivo, murine anti-HER2 antibody inhibited the growth of human tumours overexpressing HER2, indicating that the humanized antibody (trastuzumab) is likely also to have anti-proliferative activity in vivo against human breast tumours expressing high levels of HER2.

Clinical trials
Early Breast Cancer
Early breast cancer is defined as non-metastatic, primary, invasive carcinoma of the breast.

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 randomized phase III trials of patients with HER2 positive breast cancer who have completed surgery. In these clinical trials, early 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 5 and efficacy results are presented in Tables 6-10.

Table 5: Clinical Trials in Early Breast Cancer

	HERA trial ***n* = 3386**	**NSABP B-31 and NCCTG N9831 trials (joint analysis)** ***n* = 3763**	**BCIRG 006** ***n* = 3222**
Eligible patients	Node positive or node negative [*n* = 1098] and tumour size >1 cm; *Protocol initially unrestricted but amended and node negative patients with tumours ≤1 cm [n =93, 8.5%] and node negative patients with tumours >1 and ≤2 cm [n = 509,46.4%] were included*	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.
Herceptin dosage regimen	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)
Duration of Herceptin treatment	1 yr or 2 yrs	52 weeks	52 weeks
Chemotherapy regimen(s)	Various	AC (q3w) followed by IV paclitaxel as a continuous IV infusion (**AC→P)**. Paclitaxel: 80 mg/m^2 q1w for 12 weeks or 175 mg/m^2 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^2 q3w for 4 cycles or **(DCarb):** 75 mg/m^2 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.
Timing of Herceptin in relation to chemotherapy	After completion of (neo)adjuvant [a]	Concurrent **(AC→PH)** or sequential (**AC→P→H)**	Concurrent **(AC→DH** and **DCarbH)**
Median follow-up	1 year (initial evaluation) [8 years (follow-up evaluation)]	2 years	3 years

AC = doxorubicin + cyclophosphamide; q3w = every 3 weeks; q1w = weekly chemo = chemotherapy; [a] 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 6: Efficacy Results from the HERA Trial at 12 months[1] and 8 years[2] of median follow up

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

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

The HERA trial 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 tables:

Table 7: Summary of Efficacy Results from NSABP B-31 and NCCTG N9831 trials (joint analysis) at the time of the definitive DFS analysis*

Parameter	AC→P	AC→PH	p-value	HR (95% CI)
Disease recurrence				
Rate (Herceptin vs. observation)	15.5%	8.0%	< 0.0001	0.48 (0.39, 0.59)
Survival				
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

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

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

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). At 8 years, the survival rate was estimated to be 86.9% in the AC→P H arm and 79.4% in the AC→P arm, an absolute benefit of 7.4% (95% CI 4.9%, 10.0%. The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in the following table:

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

Parameter	AC→P (N=2032)	AC→PH (N=2031)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)

Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	< 0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

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)**
Disease-free survival (DFS) No. patients with event	195	134	<0.0001	0.61 (0.49, 0.77)
Death (OS event) 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)**
Disease-free survival (DFS) No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
Death (OS event) 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

Based on studies to date, the optimal duration of adjuvant trastuzumab therapy is 1 year and may be clarified in further randomized trials. However, extending adjuvant treatment beyond 1 year is not recommended (see section 4.2 Dose and Method of Administration).

Switching treatment from Herceptin IV to Herceptin SC and vice versa
Study MO22982 (PrefHER) investigated switching from Herceptin IV to Herceptin SC, and vice versa, in patients with HER2 positive EBC, with a primary objective to evaluate patient preference for either Herceptin IV infusion or Herceptin SC injection. This trial investigated using a 2-arm, cross-over design with patients being randomized to one of two different q3w Herceptin treatment sequences (Herceptin IV (Cycles 1-4) → Herceptin SC (Cycles 5-8), or Herceptin SC (Cycles 1-4) → Herceptin IV (Cycles 5-8)). Patients participating in this trial could be enrolled at any time as long as there were at least 10 remaining cycles of Herceptin in their planned treatment regimen, therefore patients were either naïve to Herceptin IV treatment (20.3%) or pre-exposed to Herceptin IV (79.7%) as part of ongoing adjuvant treatment for HER2 positive EBC. Overall, switches from Herceptin IV to Herceptin SC and vice versa were well tolerated. Pre-switch rates (Cycles 1-4) for SAEs, Grade 3 AEs and treatment discontinuations due to AEs were low (<5%) and similar to post-switch rates (Cycles 5-8). No Grade 4 or Grade 5 AEs were reported. The effect of multiple switches back and forth was not investigated (see section 4.8 Adverse Effects (Undesirable Effects)).

Locally Advanced Breast Cancer
Locally advanced breast cancer is defined as the absence of metastatic disease and meeting one or more of the following criteria: inflammatory breast cancer, a primary tumour that extends to the chest wall or skin, tumour > 5 cm with any positive lymph node(s), any tumour with disease in supraclavicular nodes, infraclavicular nodes or internal mammary nodes, any tumour with axillary lymph nodes fixed to one another or other structures.

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 trial 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^2) and paclitaxel (150 mg/m^2) 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^2) 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 trial, 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 trial 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 11: Overview of Efficacy Analyses MO16432 (NOAH)

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

^ 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.

Metastatic Breast Cancer
There are no data available to establish the efficacy of Herceptin for the treatment of metastatic disease in patients who have previously received the medicine for the treatment of early disease.
The safety and efficacy of Herceptin has been studied in randomized, controlled clinical trials in combination with chemotherapy (Studies H0648g, M77001 and TaNDEM) and in an open-label monotherapy clinical trial (Study H0649g) for the treatment of metastatic breast cancer. All trials studied patients with metastatic breast cancer whose tumours overexpress HER2. Patients were eligible if they had 2+ or 3+ levels of overexpression based on a 0 - 3+ scale by immunohistochemical (IHC) assessment of tumour tissue or whose tumours have HER2 gene amplification as determined by Fluorescence In Situ Hybridization (FISH) test (see section 4.2 Dose and Method of Administration).

Herceptin in Combination with Chemotherapy
Study H0648g was an open-label, randomized controlled, multinational trial of chemotherapy-alone and in combination with Herceptin. Patients with previously untreated metastatic breast cancer were treated with either an anthracycline (doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2) plus cyclophosphamide (600 mg/m^2) with or without Herceptin or paclitaxel (175 mg/m^2 infused over 3 hours) with or without Herceptin. Patients on Herceptin treatment received 4 mg/kg intravenous loading dose on Day 0, followed by weekly infusions of 2 mg/kg from Day 7, which they could continue to receive until evidence of disease progression. Patients who had previously received anthracycline based adjuvant therapy were treated with paclitaxel whereas those who were anthracycline naïve were treated with an anthracycline + cyclophosphamide.

The prospectively defined, primary intent-to-treat analysis indicated that the combination of Herceptin and chemotherapy significantly prolonged time to disease progression (progression-free survival) compared with chemotherapy-alone as first-line treatment of women with metastatic breast cancer who had tumours that overexpressed HER2. The addition of Herceptin to chemotherapy extended the median time to disease progression by 2.8 months representing a 61% increase (p=0.0001).

Both anthracycline-treated and paclitaxel-treated patients benefited from Herceptin treatment, although the effect appeared to be greater in the paclitaxel stratum. The efficacy of Herceptin treatment was further supported by the secondary endpoints of response rate, duration of response and one-year survival (see Table 12 below).

One-year survival rates (the prospectively defined survival endpoint) were significantly better for the Herceptin + chemotherapy versus chemotherapy-alone (79% vs. 68%; p=0.008). With a median follow-up of approximately two years, overall survival is improved for patients initially treated with Herceptin + chemotherapy compared with those receiving chemotherapy-alone (25.4 vs. 20.3 months; p=0.025) with a relative risk of death of 0.769 (95% CI 0.607 - 0.973; p=0.028).

Figure 1 Survival Time: Anthracycline ± Herceptin (Study H0648g)

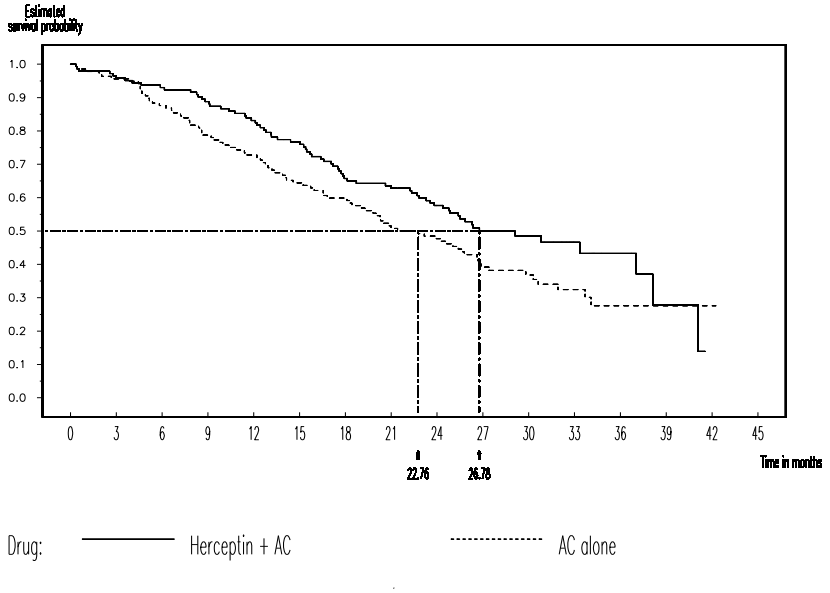
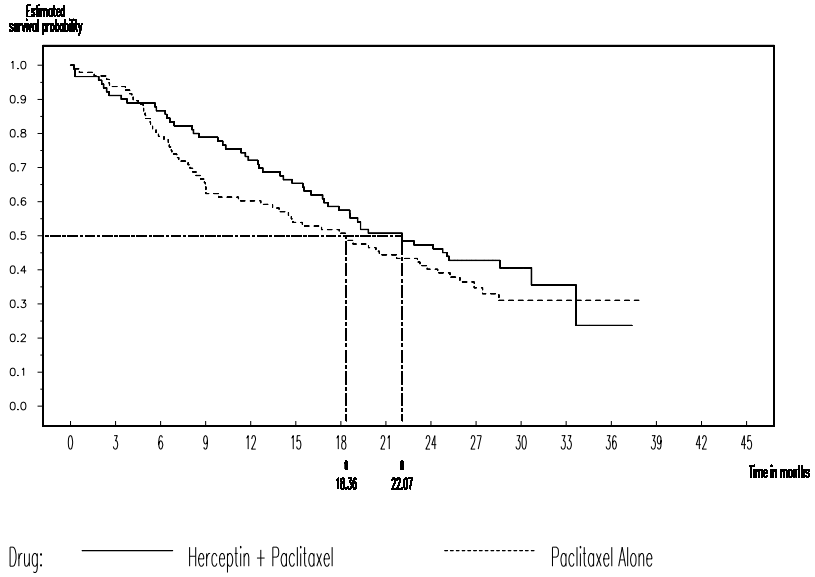


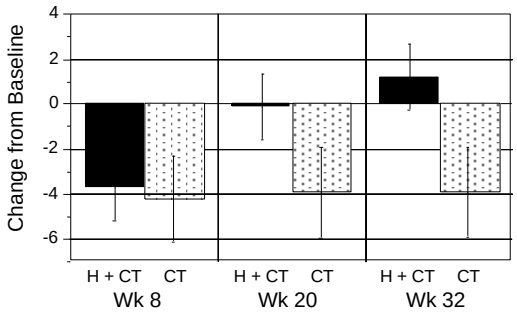
Figure 2 Survival Time: Paclitaxel ± Herceptin (Study H0648g)



The relative overall survival advantage with the addition of Herceptin was observed in both subgroups: AC [26.8 months (H + AC) vs. 22.8 months (AC-alone); *p*=0.052] and paclitaxel [22.1 months (H + P) vs. 18.4 months (P-alone); *p*=0.273] (see also Figures 1 and 2). The analysis of overall survival was, however, greatly confounded by subsequent Herceptin treatment of each of control arms' patients, following disease progression, in the open-label extension study, H0659g (59% of patients in the AC-alone group, and 75% of patients in the paclitaxel-alone group subsequently received Herceptin). Hence, the survival advantage seen above, for Herceptin + chemotherapy treatment versus chemotherapy-alone (which includes patients who subsequently received Herceptin) may underestimate the benefit to patients.

Importantly, the efficacy described above was obtained without a significant negative impact on the quality of life. Global quality of life decreased equally in both the chemotherapy-alone group and the Herceptin + chemotherapy group and was most likely related to the effects of cytotoxic chemotherapy. However, at weeks 20 and 32, the global quality of life score had returned to baseline or better than baseline in the group receiving Herceptin + chemotherapy, while it remained low in the chemotherapy-alone arm (see Figure 3 below).

Figure 3 Changes from Baseline in Health-Related Quality-of-Life Scores in Study H0648g

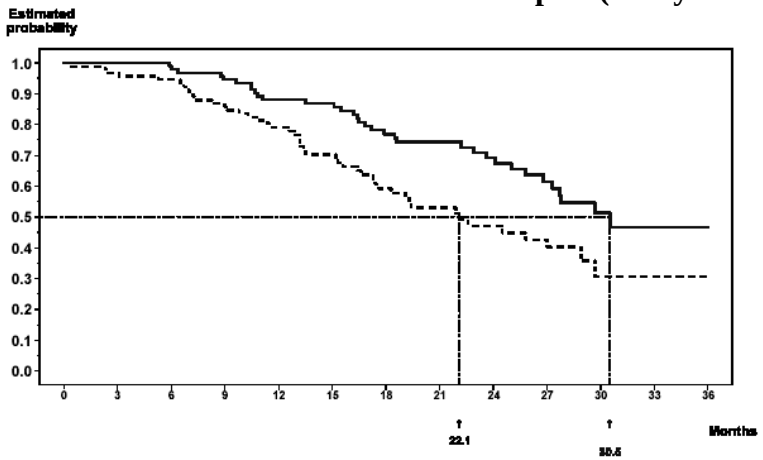


H = Herceptin; CT = chemotherapy

Study M77001 was a multinational, multi-centre, randomized, controlled trial investigating the safety and efficacy of Herceptin in combination with docetaxel, as first-line treatment in HER2 positive metastatic breast cancer patients. One hundred and eighty six patients received docetaxel (100 mg/m^2 infused over 1

hour on Day 2) with or without Herceptin (4 mg/kg loading dose, followed by 2 mg/kg weekly). Sixty percent of patients had received prior anthracycline based adjuvant chemotherapy. Herceptin with docetaxel was shown to be efficacious in patients whether or not they had received prior adjuvant anthracyclines and regardless of their oestrogen and/or progesterone receptor status.
The combination of Herceptin + docetaxel significantly increased response rate (61% vs. 34%) and prolonged the median time to disease progression by 4.9 months compared with patients treated with docetaxel-alone (see Table 12). Median survival was also significantly increased in patients receiving the combination therapy compared with those receiving docetaxel-alone (30.5 months vs. 22.1 months) (see Figure 4).

Figure 4 Survival Time: Docetaxel ± Herceptin (Study M77001)



Drug: ——— Herceptin + docetaxel ---------- docetaxel-alone

Table 12: Efficacy Outcomes with Combination Therapy for Metastatic Breast Cancer

	H0648g						**M77001**	
	H + chemo ***n* = 235**	**Chemo alone** ***n* = 234**	**H + AC** ***n* = 143**	**AC alone** ***n* = 138**	**H + P** ***n* = 92**	**P alone** ***n* = 96**	**H + D** ***n* = 92**	**D alone** ***n* = 94**
Median Time to Disease Progression (months, 95% CI)	7.4 (7.0, 9.0)	4.6 (4.4, 5.4)	7.8 (7.3, 9.4)	6.1 (4.9, 7.1)	6.9 (5.3, 9.9)	3.0 (2.1, 4.3)	10.6 (7.6, 12.9)	5.7 (5, 6.5)
***p*-value** [a]	*p*=0.0001		*p*=0.0004		*p*=0.0001		*p*=0.0001	
Response Rate (%)	50	32	56	42	41	17	61	34
***p*-value** [b]	*p*<0.0001		*p*=0.0197		*p*=0.0002		*p*=0.0002	
Median Duration of Response (months, 95% CI)	9.1 (7.7,11)	6.1 (5.5,7.8)	9.1 (7.4,12.2)	6.7 (5.8, 8.2)	10.5 (7.3, 12.5)	4.5 (3.9, 6.4)	11.4 (8.3, 15.0)	5.5 (4.4, 6.2)
***p*-value** [a]	*p*=0.0002		*p*=0.0047		*p*=0.0124		*p*=0.0002	
Overall Survival (months, 95% CI)	24.8 (22.3,33.7)	20.5 (17.9,25.3)	33.4 (22.8,38.1)	22.8 (18.3,29.8)	22.1 (16.9,33.7)	18.4 (12.7,23.8)	30.5 (26.8, ne)	22.1 (17.6, 28.9)
***p*-value** [a]	*p*=0.0540		*p*=0.1021		*p*=0.2597		*p*=0.0062	

H = Herceptin; Chemo = chemotherapy; AC = anthracycline + cyclophosphamide; P = paclitaxel; D = docetaxel
[a] *p* = log-rank test; [b] *p* = Chi-square test, ne = could not be estimated or not yet reached.

Herceptin in Combination with Anastrozole
The TAnDEM trial was a multi-centre, randomized, open-label, phase III trial 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 randomized 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 received Herceptin for early disease were excluded from this trial.

Median progression free survival (PFS) 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.

Herceptin Monotherapy
Study H0649g was a multinational, multi-centre, single arm trial of Herceptin as monotherapy in 222 women with HER2 overexpressing metastatic breast cancer. All patients had relapsed following treatment with the best available agents (e.g. anthracyclines and taxanes) and were heavily pre-treated. Two-thirds of the patients had prior adjuvant chemotherapy and all patients had tumour progression following at least one prior regimen of cytotoxic chemotherapy for metastatic disease. Ninety-four percent of the patients had prior anthracycline therapy, approximately 60% had prior paclitaxel therapy and 26% had prior bone marrow or stem cell transplants. Together with HER2 overexpression, which is associated with poorer clinical outcomes, aggressive disease was also suggested by nodal status at diagnosis and by the disease-free interval. Twenty-seven percent of patients had 10 or more positive nodes at the time of diagnosis. Thirty-eight percent of patients had a disease-free interval of less than one year prior to enrolment.

Patients received an intravenous loading dose of 4 mg/kg Herceptin on Day 0, followed by weekly intravenous infusions of 2 mg/kg until there was evidence of disease progression. Patients who developed progressive disease could stop treatment, continue on the 2 mg/kg weekly dose or receive an increased intravenous dose of 4 mg/kg, as the investigator deemed appropriate. The primary efficacy parameter was tumour response rate.
Herceptin as second- or third-line therapy induced objective, durable tumour responses in women with metastatic breast cancer who had tumours that overexpressed HER2. There were 8 complete responses and 26 partial responses yielding an overall response rate of 15%. The durability of the responses was particularly notable. The median duration of the responses was 9.1 months at the cut-off date for analysis (see Table 13 below).

Table 13: Efficacy Outcomes with Monotherapy Study H0649g

Outcome Measure	n	Time (months) Kaplan-Meier Estimate of Median (range)
Duration of response	34	9.1 (2–26+)
Time to disease progression	213	3.1 (0–28+)
Time to Treatment Failure	213	2.4 (0–28+)
Survival Time	213	12.8 (0.5–30+)

The clinical significance of the objective tumour responses in this group of patients was supported by the quality-of-life and survival data. Responders had clinically meaningful improvements in physical function, role function, social function, global quality of life and fatigue scale scores during Herceptin treatment. Most responders were still alive at data cut-off (28/34; 82%). The Kaplan-Meier estimate of median survival for all treated patients at the data cut-off date was 12.8 months.

Evidence of efficacy for Herceptin monotherapy is based upon response rates. No data are available to demonstrate improvement in survival or quality of life.

Advanced Gastric Cancer

Study BO18255 (ToGA) was a randomized, open-label, multicentre phase III trial 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 section 4.2 Dose and Method of Administration).

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 summarized in Table 14. 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 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.

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 PFS was 5.5 months vs. 7.6 months, HR = 0.64 (95% CI 0.51 - 0.79).

Table 14: Summary of Efficacy from Study BO18255

Herceptin dosage regimen	Every 3 weeks			
Chemotherapy regimens (FP)	• Capecitabine: 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (Days 1 to 15 of each cycle). • 5-FU: 800 mg/m^2/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. • Cisplatin: 80 mg/m^2 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).			
Efficacy Parameters	**FP** ***n*** **= 290**	**FP+H** ***n*** **= 294**	**HR (95% CI)**	***p*-value**
Overall Survival, Median months	11.1	13.8	0.74 (0.60-0.91)	0.0046
Progression-Free Survival, Median months	5.5	6.7	0.71 (0.59-0.85)	0.0002
Time to Disease Progression, Median months	5.6	7.1	0.70 (0.58-0.85)	0.0003
Overall Response Rate, %	34.5	47.3	1.70[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; FP+H: fluoropyrimidine/cisplatin + Herceptin; [a] 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.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of trastuzumab have been studied in patients with breast cancer (metastatic and early) and advanced gastric cancer (AGC).

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 patients from 18 Phase I, II and III trials receiving Herceptin IV to treat a range of cancers, but mostly breast and gastric cancer. 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 (metastatic and early) and 0.176 L/day for AGC. 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 (C_{max} and C_{min}) for breast cancer and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 15 (Cycle 1) and Table 16 (steady-state) below.

Table 15: Population Predicted Cycle 1 PK Exposure Values (with 5th - 95th Percentiles) for IV Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumour 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)	178.0 (116.5 – 290.5)	1372.5 (735.8 – 2245.0)
	AGC	274	23.1 (6.1 - 50.3)	131.9 (84.2 – 225.2)	1108.5 (588.2 – 1937.9)
4mg/kg + 2mg/kg qw	MBC/EBC	1195	37.7 (12.3 - 70.9)	88.3 (58.0 – 144.4)	1066.0 (585.6 – 1754.2)

Table 16: Population Predicted Steady State PK Exposure Values (with 5th - 95th Percentiles) for Herceptin IV Dosing Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumour type	N	Cmin,ss (µg/mL)	Cmax,ss (µg/mL)	AUCss (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	47.4 (5.0 - 114.7)	179.4 (107.3 – 308.8)	1794.2 (673.0 – 3618.4)	12	0.173 - 0.283
	AGC	274	32.9 (6.1 - 88.9)	131.0 (72.5 - 250.5)	1338.2 (557.0- 2875.4)	9	0.189 - 0.337
4mg/kg + 2mg/kg qw	MBC/EBC	1195	66.1 (14.9 – 142.3)	108.8 (51.0 - 208.6)	1765.3 (647.3 – 3578.1)	12	0.201 - 0.244

Pharmacokinetics in Special Populations

Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. However, in a population PK analysis, age and renal impairment were not shown to affect trastuzumab disposition. The population PK analysis showed that the estimated creatinine clearance (Cockcroft and Gault) does not correlate with the pharmacokinetics of trastuzumab.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Trastuzumab did not induce gene mutations in bacteria, nor did it cause chromosomal damage *in vitro* (chromosome aberration assay in human lymphocytes) or *in vivo* (mouse micronucleus test).

Carcinogenicity

No studies on the carcinogenic potential of Herceptin have been conducted to date.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine hydrochloride monohydrate
Histidine
Trehalose dihydrate
Polysorbate 20

6.2 INCOMPATIBILITIES

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

Herceptin SHOULD NOT BE MIXED OR DILUTED WITH OTHER MEDICINES.

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store Herceptin 60 mg and 150 mg vials at 2 to 8°C. Refrigerate. Do not freeze. Do not use beyond the expiration date stamped on the vial.

Reconstituted Solution

A vial of Herceptin reconstituted with sterile Water for Injections without preservative should be used immediately and any unused portion must be discarded. Product is for single use in one patient only. Do not freeze the reconstituted solution.

Diluted Solution for Infusion

From a microbiological point of view, the Herceptin infusion solution should be diluted and used immediately. The product is not intended to be stored after dilution. Solutions of Herceptin for infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing 0.9% sodium chloride at 2 to 8°C for 24 hours. Diluted Herceptin has been shown to be stable for up to 24 hours at temperatures up to 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Herceptin vial

Clear glass type I vial containing 60 mg or 150mg trastuzumab.

Each carton contains one vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimized. 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.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number

180288-69-1

Herceptin (trastuzumab) is a recombinant DNA derived humanized monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG1 kappa that contains human framework regions with the complementarity determining regions of a murine anti-p185 HER2 antibody that binds to HER2. Trastuzumab is composed of 1,328 amino acids and has a molecular weight of ~148 kDa.

The humanized antibody against HER2 is produced by recombinant mammalian cells (Chinese hamster ovary (rch)) in suspension culture in a nutrient medium and purified by affinity chromatography and ion exchange, including specific viral inactivation and removal procedures.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

Herceptin 150mg – 14 September 2000
Herceptin 60mg – 3 December 2010

10. DATE OF REVISION OF THE TEXT

7 May 2021

Summary table of changes

Section Changed	Summary of new information
4.2	Addition of instruction to use sterile needle and syringe for dilution