AUSTRALIAN PRODUCT INFORMATION

OGIVRI®

(trastuzumab (rch)) powder for injection

1 NAME OF THE MEDICINE

Trastuzumab.

OGIVRI is a biosimilar medicine to Herceptin. The evidence for comparability supports the use of OGIVRI for the listed indications.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OGIVRI contains trastuzumab as the active ingredient.

Each OGIVRI 150 mg single-dose vial contains 150 mg of trastuzumab.

Each OGIVRI 440 mg Pharmacy Bulk Pack contains 440 mg of trastuzumab.

Excipients with known effect: Sorbitol

OGIVRI contains 0.77 mg sorbitol/ 1.00 mg trastuzumab. There is 115.2 mg of sorbitol in the 150 mg vial and 337.9 mg of sorbitol in the 440 mg Pharmacy Bulk Pack.

Reconstitution of the 150 mg vial with 7.2 mL of sterile water for injection yields 7.4 mL of a single-dose solution containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overage of 4% ensures that the labelled dose can be withdrawn from each vial.

Reconstitution of the 440 mg vial with 20 mL of bacteriostatic water for injection yields a multiple-dose solution containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for IV infusion.

OGIVRI is a sterile, white to pale yellow, preservative-free lyophilized powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Early Breast Cancer

OGIVRI 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

OGIVRI is indicated for the treatment of HER2-positive locally advanced breast cancer in combination with neoadjuvant chemotherapy followed by adjuvant OGIVRI.

Metastatic Breast Cancer

OGIVRI 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

OGIVRI 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

General

HER2 testing is mandatory prior to initiation of trastuzumab therapy (refer to Detection of HER2 Protein Overexpression and Gene Amplification below as well as Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.1 PHARMACODYNAMIC PROPERTIES).

In order to prevent medication errors, it is important to check the vial labels to ensure the medicine being prepared and administered is **Trastuzumab** (OGIVRI) and not **Trastuzumab-containing product (e.g. trastuzumab emtansine** (KADCYLA®) or trastuzumab deruxtecan (ENHERTU®)).

OGIVRI IV solution is not to be used for subcutaneous administration and must be administered as an IV infusion only. Do not administer as an IV push or bolus. If an alternate route of administration is required, other trastuzumab products offering such an option should be used.

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 Trastuzumab IV and Trastuzumab SC and vice versa, using a three-weekly (q3w) dosing regimen, was investigated in study MO22982 (PrefHER) (see Sections 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials and 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.

Do not administer OGIVRI to patients with rare hereditary problems of fructose intolerance because it contains sorbitol as an excipient (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Detection of HER2 Protein Overexpression or HER2 Gene Amplification

OGIVRI 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

OGIVRI 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

OGIVRI 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.

Recommended Dosage

Refer to Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials (including Table 16 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 products.

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.

Refer to Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials for chemotherapy combination dosing. Refer also to the currently approved product information for the chemotherapy products.

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.

Missed Doses

If the patient has missed a dose of OGIVRI by one week or less, then the usual maintenance dose of OGIVRI (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 OGIVRI by more than one week, a re-loading dose of OGIVRI 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 Reduction

If the patient develops an infusion-related reaction (IRR), the infusion rate of OGIVRI may be slowed or interrupted (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

No reductions in the dose of trastuzumab were made during clinical trials. Patients may continue trastuzumab therapy during periods of reversible, chemotherapy-induced myelosuppression, but they should be carefully monitored for complications of neutropenia during this time.

Refer to the product information of chemotherapy products for specific information on dose reduction or delays. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Management of cardiac dysfunction: assess left ventricular function in all patients prior to and during treatment with trastuzumab (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Special populations

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

In clinical trials, elderly patients did not receive reduced doses of trastuzumab. In a population pharmacokinetic analysis, age and renal impairment has been shown to have no effect on the disposition of trastuzumab (see Section 5.2 PHARMACOKINETIC PROPERTIES, Pharmacokinetics in Special Populations).

Paediatric population

There is no relevant use of trastuzumab in the paediatric population.

Method of Administration

OGIVRI 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.

OGIVRI should be administered by a healthcare professional prepared to manage anaphylaxis and emergency kit and adequate life support facilities should be available.

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

Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-associated symptoms (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Interruption or slowing of the rate 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.

Preparation for IV infusion

Labelling of prepared solution

The label of the resulting solution must contain the following statement: THIS SOLUTION CONTAINS SORBITOL.

Reconstituting the Powder

Appropriate aseptic technique should be used.

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

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.

Each 440 mg vial should be reconstituted with 20 mL of bacteriostatic water for injection as the solvent. The use of other solvents should be avoided. The resultant multiple-dose solution contains approximately 21 mg/mL trastuzumab. In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water For Injection (SWFI) without preservative to yield a single use solution.

Instructions for Reconstitution

150 mg vial

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

2. Swirl vial gently to aid reconstitution. OGIVRI 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 clear to slightly opalescent solution and should be practically free of visible particulates.

440 mg vial with bacteriostatic water for injection

1. Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of OGIVRI. The stream of diluent should be directed into the lyophilized cake.

2. Swirl the vial gently to aid reconstitution. DO NOT SHAKE.

3. Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.

4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be practically free of visible particulates, clear to slightly opalescent and colourless to pale yellow.

5. Store reconstituted OGIVRI at 2°C to 8°C; discard unused OGIVRI after 24 hours.

6. Note: If OGIVRI is reconstituted with SWFI without preservative (for patients with hypersensitivity to benzyl alcohol), use immediately and discard any unused portion.

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:

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

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:

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

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. OGIVRI SHOULD NOT BE MIXED OR DILUTED WITH OTHER MEDICINES. No incompatibilities between OGIVRI 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. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration.

From a microbiological point of view, the OGIVRI infusion solution, if reconstituted with sterile water (SWFI) without preservative, should be used immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2°C to 8°C.

4.3 CONTRAINDICATIONS

OGIVRI is contraindicated in patients with known hypersensitivity to the active substance (trastuzumab), murine proteins or to any of its excipients listed in Section 6.1 LIST OF EXCIPIENTS.

In the treatment of early or locally advanced breast cancer, OGIVRI 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

OGIVRI 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 OGIVRI therapy. OGIVRI should be administered by a healthcare professional prepared to manage anaphylaxis and emergency kit and adequate life support facilities should be available. Treatment may be administered in an outpatient setting.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures.

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

Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

Sorbitol

OGIVRI contains 0.77 mg sorbitol/ 1.00 mg trastuzumab. There is 115.2 mg of sorbitol in the 150 mg vial and 337.9 mg of sorbitol in the 440 mg Pharmacy Bulk Pack.

Patients with hereditary fructose intolerance (HFI) must not be given this medicine.

A detailed history with regards to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Cardiac Dysfunction

General considerations

Patients treated with trastuzumab are at increased risk of developing congestive heart failure (CHF) (New York Heart Association [NYHA] class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab therapy alone or in combination with a taxane (for example, paclitaxel or docetaxel) 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, LVEF of < 55%, diastolic dysfunction, older age.

Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment (see Section 5.2 PHARMACOKINETIC PROPERTIES). Patients who receive anthracycline after stopping trastuzumab may also be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

All candidates for treatment with trastuzumab, especially those with prior anthracycline and cyclophosphamide monohydrate (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop cardiac dysfunction, including signs and symptoms of CHF. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. A careful risk-benefit assessment should be made before deciding to treat with trastuzumab.

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients, cardiac function should be monitored during treatment (e.g. every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6 - 8 weeks).

Evaluate left ventricular function in all patients prior to and during treatment with trastuzumab. If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of trastuzumab therapy has been seen.

If left ventricular ejection fraction (LVEF) drops ≥ 10 percentage points from baseline and to below 50%, trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or clinically significant CHF has developed, discontinuation of trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

The safety of continuation or resumption of trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with 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 trastuzumab treatment continued on weekly therapy with trastuzumab 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 trastuzumab. In patients who receive anthracycline containing chemotherapy further monitoring is recommended and should occur yearly up to 5 years from the last administration of trastuzumab, or longer if a continuous decrease of LVEF is observed.

All patients should have a determination of LVEF prior to treatment. Use of trastuzumab 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 trastuzumab treatment.

Patients with history of myocardial infarction (MI), angina pectoris requiring medication, history of or present CHF (NYHA Class II–IV), LVEF of < 55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medication eligible), and haemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant breast cancer clinical trials with trastuzumab and therefore treatment cannot be recommended in such patients.

Adjuvant treatment

Trastuzumab 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 trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence was more marked when trastuzumab was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months.

Risk factors for a cardiac event, identified in 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, trastuzumab treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving trastuzumab after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of trastuzumab and a high body mass index (> 25 kg/m^2).

Neoadjuvant-adjuvant treatment

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

If patients have been treated concurrently with low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Metastatic breast cancer

Trastuzumab and anthracyclines should not be given concurrently in the metastatic breast cancer setting.

Patients with MBC who have previously received anthracyclines are also at risk of cardiac dysfunction with trastuzumab treatment, although the risk is lower than with concurrent use of trastuzumab and anthracyclines.

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 trastuzumab. 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, OGIVRI 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 (epinephrine), corticosteroids, antihistamines, bronchodilators and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Infusion-Related Reactions (IRRs)

IRRs are known to occur with the administration of trastuzumab (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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

Serious IRRs to trastuzumab infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, angioedema 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. The majority of patients experienced resolution of symptoms and subsequently received further infusions of trastuzumab.

The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued, or the rate of infusion slowed, and the patient should be monitored until resolution of all observed symptoms (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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.

On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the trastuzumab infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

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 trastuzumab (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Pulmonary Reactions).

Pulmonary Reactions

Severe pulmonary events have been reported with the use of trastuzumab in the post-marketing setting (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). These events have occasionally been fatal. These events may occur as part of an infusion-related reaction (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Infusion-Related Reactions) or with a delayed onset.

In addition, cases of interstitial lung disease including pulmonary 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 trastuzumab.

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 OGIVRI. 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 trastuzumab 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 trastuzumab in clinical trials. However, greater sensitivity to trastuzumab 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 trastuzumab in patients with hepatic impairment has not been studied.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Administration of paclitaxel in combination with trastuzumab 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 trastuzumab regimen (n = 25) were not altered appreciably, relative to parameters determined during the initiation of paclitaxel, prior to introduction of trastuzumab. Similarly, docetaxel pharmacokinetics determined during the first dose of trastuzumab 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.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There is no fertility data available in humans. 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 C_{min}) about 15 times higher than that in humans receiving the recommended weekly dose of 2 mg/kg.

Use in Pregnancy

Category D.

OGIVRI 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 OGIVRI, 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 OGIVRI.

Women of childbearing potential should be advised to use effective contraception during treatment with OGIVRI 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 OGIVRI, or becomes pregnant while receiving OGIVRI or within 7 months following the last dose of OGIVRI, 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 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 trastuzumab therapy and for 7 months after the last dose of trastuzumab.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

OGIVRI has a minor influence on the ability to drive and use machines. Dizziness and solmenence may occur during treatment with OGIVRI (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)

Summary of the safety profile

Amongst the most serious and/or common adverse reactions reported in trastuzumab usage (intravenous and subcutaneous formulations) to date are cardiac dysfunction, infusion-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

Tabulated list of adverse reactions

Table 1 summarises adverse drug reactions (ADRs) that have been reported in association with the use of trastuzumab alone, or in combination with chemotherapy in the below reference medicine pivotal clinical trials as well as in the post-marketing setting.

The adverse drug reactions listed in this section fall into the following categories: 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): trastuzumab arm (n=1678). Control arm (n=1708)
- B-31/N9831 Joint Analysis: trastuzumab arms (n=2345). Control arm (n=1673)
- BCIRG 006: trastuzumab arm (n=2133). Control arm (n=1041)
- BO16216 (TanDEM): trastuzumab arm (n=161). Control arm (n=161)

Locally Advanced Breast Cancer

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

Metastatic Breast Cancer (MBC)

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

Advanced Gastric Cancer

- BO18255 (ToGA): trastuzumab 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

System organ class	Adverse reaction[1]	Frequency
Infections and infestations	Nasopharyngitis	Very common
	Infection	Very common
	Neutropenic sepsis	Common

System organ class	Adverse reaction[1]	Frequency
	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
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	Tremor[3]	Very common
	Dizziness	Very common
	Headache	Very common

System organ class	Adverse reaction[1]	Frequency
	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
	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

System organ class	Adverse reaction[1]	Frequency
	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
	Dyspepsia	Very common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular Injury	Common
	Hepatitis	Common
	Liver Tenderness	Common
	Jaundice	Rare
	Hepatic Failure	Not known

System organ class	Adverse reaction[1]	Frequency
Skin and subcutaneous disorders	Erythema	Very common
	Rash	Very common
	Swelling face[3]	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 conditions	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal disorders	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common

System organ class	Adverse reaction[1]	Frequency
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Mucosal inflammation	Very common
	Malaise	Common
	Oedema	Common
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, respiratory distress, rash, nausea, vomiting and headache were seen in all trastuzumab 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 trastuzumab 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 trastuzumab 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 trastuzumab 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 trastuzumab 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 trastuzumab containing arm compared to 5% to 6% in the comparator arm.

Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of trastuzumab (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE) and have been associated with a fatal outcome. 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 trastuzumab. It has been associated with fatal outcome (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Signs and symptoms of cardiac dysfunction and 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 trastuzumab (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Locally Advanced Breast Cancer (neoadjuvant –adjuvant setting)

In the clinical trial setting, when trastuzumab 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 trastuzumab arm.

Early Breast Cancer (adjuvant setting)

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in patients who were administered trastuzumab sequentially to a taxane (0.3 - 0.4%). The rate was highest in patients who were administered trastuzumab concurrently with a taxane (2.0%). At 3 years, the cardiac event rate in patients receiving AC→P (doxorubicin plus cyclophosphamide monohydrate 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 monohydrate, followed by docetaxel), AC→DH (doxorubicin plus cyclophosphamide monohydrate, followed by docetaxel plus trastuzumab), and DCarbH (docetaxel, carboplatin and trastuzumab) treatment arms, respectively. For symptomatic CHF (NCI-CTC Grade 3 - 4), the 5-year rates were 0.6%, 1.9%, and 0.4% in the AC→D, AC→DH, and DCarbH treatment arms, respectively. The overall risk of developing symptomatic cardiac events was low and similar for patients in AC→D and DCarbH arms; relative to both the AC→D and DCarbH arms there was an increased risk of developing a symptomatic cardiac event for patients in the AC→DH arm, being discernable by a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events up to 2.3% compared to approximately 1% in the two comparator arms (AC→D and DCarbH).

When trastuzumab was administered after completion of adjuvant chemotherapy, NYHA class III-IV heart failure was observed in 0.6% of patients in the 1year 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 1year trastuzumab 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 trastuzumab therapy (combined analysis of the two trastuzumab 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 trastuzumab-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of trastuzumab-treated patients. Approximately 17% of cardiac dysfunction related events occurred after completion of trastuzumab.

In the joint analysis of studies NSABP B-31 and NCCTG N9831, with a median follow-up of 8.1 years for the AC→PH group (doxorubicin plus cyclophosphamide monohydrate, 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 trastuzumab + paclitaxel subgroup, compared with 1% - 4% for the paclitaxel-alone subgroup. For trastuzumab monotherapy, the rate was 6 - 9%. The highest rate of cardiac dysfunction was seen in patients receiving concurrent trastuzumab + anthracycline / cyclophosphamide

monohydrate (27%), significantly higher than in the anthracycline / cyclophosphamide monohydrate-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 trastuzumab and docetaxel, compared with 0% in patients receiving docetaxel-alone. Most of the patients (79%) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for 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 trastuzumab + FP arm.

The majority of the LVEF decreases noted in Study BO18255 (ToGA) were asymptomatic, with the exception of 1 patient in the trastuzumab 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) ***	**FP + H (*n* = 294) ***
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 + trastuzumab; [#]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). *% patients in each treatment arm

Table 3: Summary of LVEF Change from baseline (Study BO18255)

	FP (n = 290) *	**FP +H (n = 294) ***
Total Cardiac Events	6%	6%
≥ Grade 3 NCI CTCAE v3.0	3% a	1% b

FP: fluoropyrimidine/cisplatin; FP+H: fluoropyrimidine/cisplatin + trastuzumab; [a] 9 patients experienced 9 Events; [b] 4 patients experienced 5 Events; *% patients in each treatment arm

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

Haematological Toxicity

Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Immunogenicity

In a neoadjuvant-adjuvant breast cancer trial, 8.1% (24/296) of patients treated with trastuzumab developed antibodies against trastuzumab (regardless of antibody presence at baseline). Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 24 trastuzumab patients.

The clinical relevance of these antibodies is not known. However, the pharmacokinetics, efficacy [determined by pathological complete response (pCR)] or safety [determined by the occurrence of administration related reaction (ARRs)] of trastuzumab did not appear to be adversely affected by these antibodies.

There are no immunogenicity data available for trastuzumab in gastric cancer.

Breast Cancer

Monotherapy– Study H0649g

Haematological toxicity is infrequent following the administration of trastuzumab 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 trastuzumab and an anthracycline/cyclophosphamide monohydrate compared to an incidence of 62% in patients treated with the anthracycline/cyclophosphamide monohydrate combination without trastuzumab.

There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of trastuzumab and paclitaxel compared with patients receiving paclitaxel-alone (34% vs. 21%). Haematological toxicity was also increased in patients receiving trastuzumab 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 trastuzumab + 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 trastuzumab treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

Advanced Gastric Cancer

The most frequently reported 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)*	**FP + H (n = 294)***
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile neutropenia	3%	5%
Thrombocytopenia	3%	5%

FP: fluoropyrimidine/cisplatin; FP+H: fluoropyrimidine/cisplatin + trastuzumab; * % patients in each treatment arm

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.

Pulmonary events

Severe pulmonary adverse reactions occur in association with the use of trastuzumab and have been associated with a fatal outcome.

These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 trastuzumab 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 trastuzumab and an anthracycline/cyclophosphamide monohydrate compared with an incidence of 8% in patients treated with the anthracycline/cyclophosphamide monohydrate combination without trastuzumab. No WHO Grade 3 or 4 renal toxicity was observed.

WHO Grade 3 or 4 hepatic toxicity was less frequently observed among patients receiving trastuzumab 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 trastuzumab 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 trastuzumab than those in the fluoropyrimidine/cisplatin arm (1% and <1% respectively).

Diarrhoea

Breast Cancer

Monotherapy– Study H0649g

Of patients treated with trastuzumab 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 trastuzumab in combination with chemotherapy compared with patients receiving chemotherapy-alone or trastuzumab-alone.

Early Setting – HERA Study

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

Advanced Gastric Cancer

In Study BO18255 (ToGA), 109 patients (37%) in the trastuzumab 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 trastuzumab 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 trastuzumab + chemotherapy compared with patients receiving chemotherapy-alone or trastuzumab-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.

Switching treatment from Trastuzumab IV to Trastuzumab SC and vice versa

Reference medicine study MO22982 (PrefHER) investigated switching from Trastuzumab IV to Trastuzumab SC, and vice versa, in patients with HER2 positive EBC, with a primary objective to evaluate patient preference for either Trastuzumab IV infusion or Trastuzumab SC injection. This trial investigated using a 2-arm, cross-over design with patients being randomized to one of two different q3w Trastuzumab treatment sequences (Trastuzumab IV (Cycles 1-4) → Trastuzumab SC (Cycles 5-8), or Trastuzumab SC (Cycles 1-4) → Trastuzumab 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 Trastuzumab in their planned treatment regimen, therefore patients were either naïve to Trastuzumab IV treatment (20.3%) or pre-exposed to Trastuzumab IV (79.7%) as part of ongoing adjuvant treatment for HER2 positive EBC. Overall, switches from Trastuzumab IV to Trastuzumab 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 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Reporting Suspected Adverse Effects

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 overdose 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 on 13 11 26 (Australia)

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

The following clinical trial information has been generated on the reference medicine.

Early Breast Cancer

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

Trastuzumab in Combination with Adjuvant Chemotherapy

The use of trastuzumab 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**	**NSAPB 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.
Trastuzumab 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 trastuzumab 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)** 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 trastuzumab	After completion of (neo)adjuvant [a]	Concurrent (**AC→PH**) or sequential (**AC→P→H**)	Concurrent (**AC→DH** and **DCarbH**)

	HERA trial n = 3386	NSAPB B-31 and NCCTG N9831 trials (joint analysis) n = 3763	BCIRG 006 n = 3222
in relation to chemotherapy			
Median follow-up	1 year (initial evaluation) [8 years (follow-up evaluation)]	2 years	3 years

AC = doxorubicin + cyclophosphamide monohydrate; 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 trastuzumab 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 trastuzumab treatment vs. 1 year trastuzumab treatment was performed. Patients assigned to receive trastuzumab were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every 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	Trastuzumab 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 trastuzumab)

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 trastuzumab vs. 5.5% with observation).

In the final analysis (8 year median follow up) extending trastuzumab 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 NSAPB 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 (trastuzumab vs. observation)	15.5%	8.0%	< 0.0001	0.48 (0.39, 0.59)
Survival Deaths (trastuzumab vs. observation)	5.5%	3.7%	0.014**	0.67 (0.48, 0.92)

A: doxorubicin; C: cyclophosphamide monohydrate; P: paclitaxel; H:trastuzumab; 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 monohydrate; 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 monohydrate, followed by docetaxel; AC→DH = doxorubicin plus cyclophosphamide monohydrate, 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 monohydrate, 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 - Duration of Treatment).

Switching treatment from Trastuzumab IV to Trastuzumab SC and vice versa

Study MO22982 (PrefHER) investigated switching from Trastuzumab IV to Trastuzumab SC, and vice versa, in patients with HER2 positive EBC, with a primary objective to evaluate patient preference for either Trastuzumab IV infusion or Trastuzumab SC injection. This trial investigated using a 2-arm, cross-over design with patients being randomized to one of two different q3w Trastuzumab treatment sequences (Trastuzumab IV (Cycles 1-4) → Trastuzumab SC (Cycles 5-8), or Trastuzumab SC (Cycles 1-4) → Trastuzumab 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 Trastuzumab in their planned treatment regimen, therefore patients were either naïve to Trastuzumab IV treatment (20.3%) or pre-exposed to Trastuzumab IV (79.7%) as part of ongoing adjuvant treatment for HER2 positive EBC. Overall, switches from Trastuzumab IV to Trastuzumab 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 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.

Trastuzumab in Combination with Neoadjuvant-Adjuvant Chemotherapy

The use of trastuzumab 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 trastuzumab with neoadjuvant chemotherapy, including both an anthracycline and a taxane, followed by adjuvant trastuzumab, 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 trastuzumab (*n* = 116), or neoadjuvant chemotherapy alone (*n* = 118).

Trastuzumab 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 trastuzumab (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 trastuzumab (6 mg/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 OGIVRI (6mg/kg administered 3-weekly), followed by

- up to 7 additional cycles of trastuzumab (6 mg/kg, administered 3-weekly) alone to complete 1 year after starting trastuzumab

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 trastuzumab arm was 3.8 years.

Table 11: Overview of Efficacy Analyses MO16432 (NOAH)

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

To date, results are not available comparing the efficacy of trastuzumab 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 trastuzumab 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 trastuzumab 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 - Dose Reduction**,** Detection of HER2 Overexpression or HER2 Gene Amplification).

Trastuzumab in Combination with Chemotherapy

Study H0648g was an open-label, randomized controlled, multinational trial of chemotherapy-alone and in combination with trastuzumab. 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 trastuzumab or paclitaxel (175 mg/m^2 infused over 3 hours) with or without trastuzumab. Patients on trastuzumab 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 trastuzumab 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 trastuzumab 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 trastuzumab treatment, although the effect appeared to be greater in the paclitaxel stratum. The efficacy of trastuzumab 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 trastuzumab + 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 trastuzumab + 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)

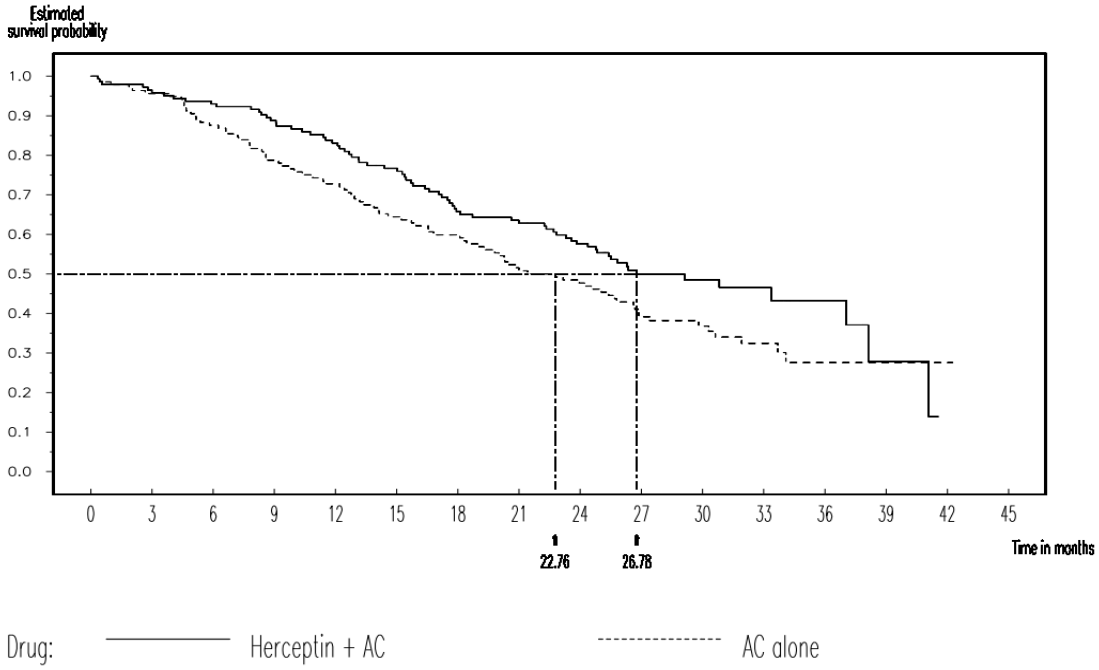
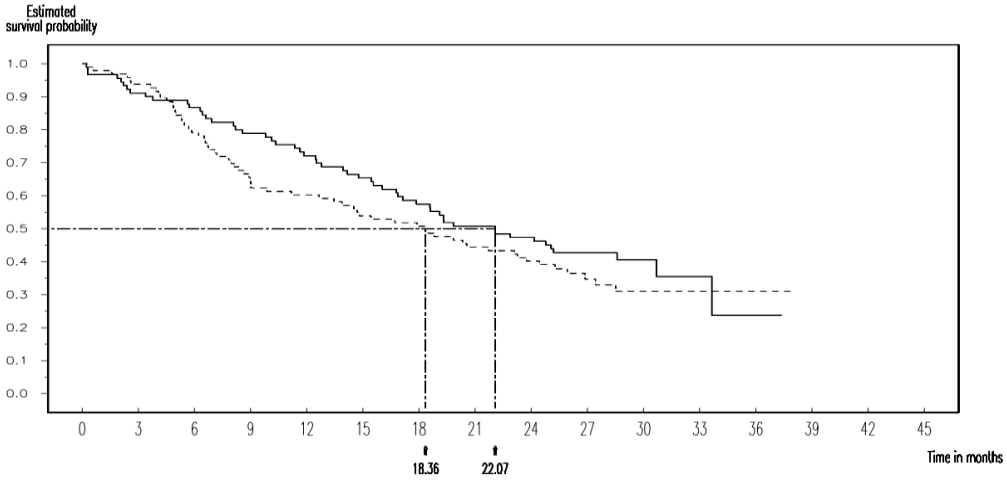


Figure 2 Survival Time: Paclitaxel ± HERCEPTIN (Study H0648g)

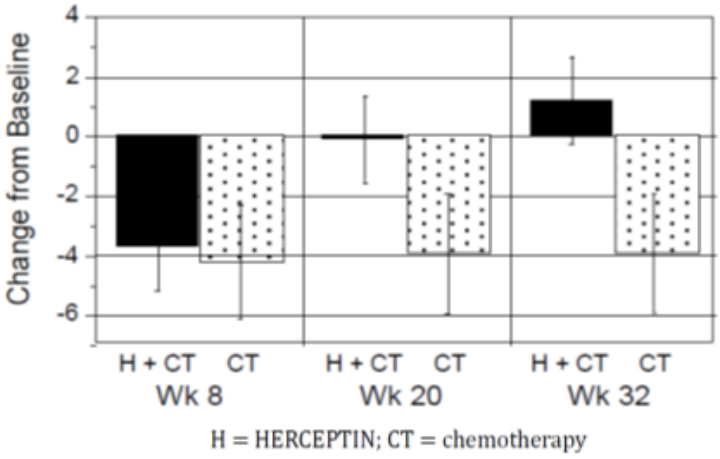


The relative overall survival advantage with the addition of trastuzumab was observed in both subgroups: AC [26.8 months (H + AC) vs. 22.8 months (AC-alone); p=0.052] and paclitaxel [22.1 months (H + P) vs. 18.4

months (P-alone); p=0.273] (see also Figures 1 and 2). The analysis of overall survival was, however, greatly confounded by subsequent trastuzumab 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 trastuzumab). Hence, the survival advantage seen above, for trastuzumab + chemotherapy treatment versus chemotherapy-alone (which includes patients who subsequently received trastuzumab) 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 trastuzumab + 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 trastuzumab + 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 trastuzumab 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 trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg weekly). Sixty percent of patients had received prior anthracycline based adjuvant chemotherapy. Trastuzumab with docetaxel was shown to be efficacious in patients whether or not they had received prior adjuvant anthracyclines and regardless of their estrogen and/or progesterone receptor status.

The combination of trastuzumab + 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 ± trastuzumab (Study M77001)

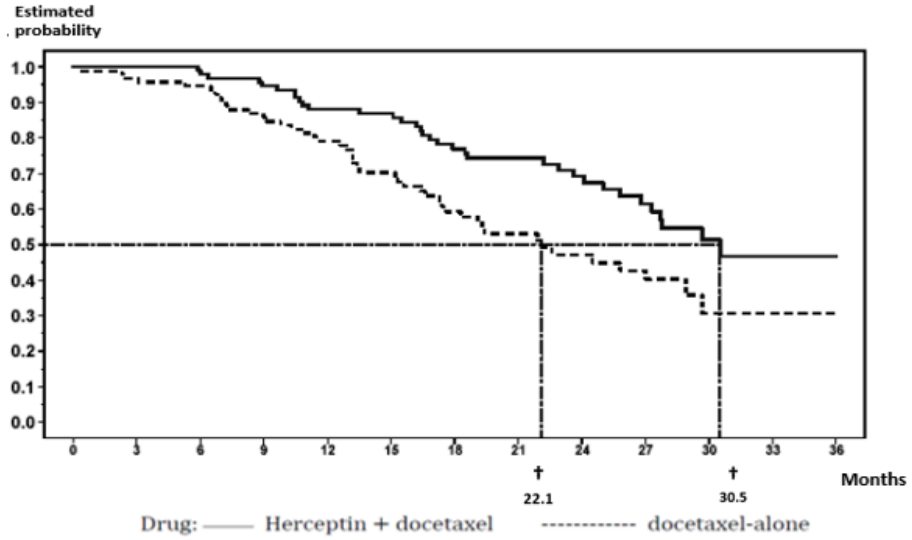


Table 12: Efficacy Outcomes with Combination Therapy for Metastatic Breast Cancer

	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 = trastuzumab; Chemo = chemotherapy; AC = anthracycline + cyclophosphamide monohydrate; P = paclitaxel; D = docetaxel

[a] p = log-rank test; [b] p = Chi-square test, ne = could not be estimated or not yet reached.

Trastuzumab in Combination with Anastrozole

The TAnDEM trial was a multi-centre, randomized, open-label, phase III trial comparing trastuzumab + anastrozole with anastrozole-alone for the first-line treatment of metastatic breast cancer in HER2 overexpressing, hormone-receptor (i.e. estrogen-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 trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg weekly). Patients who had received trastuzumab for early disease were excluded from this trial.

Median progression free survival (PFS) was doubled in the trastuzumab + 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 trastuzumab + 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 trastuzumab-containing regimen after progression of disease.

Trastuzumab Monotherapy

Study H0649g was a multinational, multi-centre, single arm trial of trastuzumab 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 trastuzumab 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.

Trastuzumab 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 trastuzumab 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 trastuzumab 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 trastuzumab 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 - Dose Reduction**,** Detection of HER2 Overexpression or HER2 Gene Amplification).

After satisfying the screening eligibility criteria, including assessment of HER2 status, patients were randomly assigned (1:1) to receive either trastuzumab (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

Trastuzumab 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

Trastuzumab dosage regimen	Every 3 weeks			
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 + trastuzumab; 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.

Comparative clinical trials

Three clinical studies were conducted to support similarity between OGIVRI and trastuzumab reference medicine (Herceptin):

- Two comparative pivotal bioavailability studies performed in healthy volunteers
- A clinical study performed in patients with metastatic breast cancer.

Table 15: Summary of OGIVRI clinical studies

Study Number	Study Design	Dosage, Route of Administration and Duration	Study population
MYL-Her-1001	Single-center, single-dose, 2-period, double-blind, crossover study	OGIVRI or EU-Herceptin 8 mg/kg single IV dose administered over 90 min	Healthy male subjects 22 randomized, 19 completed
MYL-Her-1002	Single-center, single-dose, randomized, double-blind, 3-arm, parallel-group study	OGIVRI or EU-Herceptin or US-Herceptin 8 mg/kg single IV dose administered over 90 min	Healthy male subjects 132 randomized, 121 completed
MYL-Her-3001	Multicenter, double-blind, randomized, parallel-group study	OGIVRI or EU-Herceptin 8 mg/kg IV loading dose followed by 6 mg/kg maintenance plus taxane, every 3 weeks for 8 cycles (Part 1) Patients with at least stable disease continued with maintenance monotherapy until disease progression, unacceptable toxicity, or death.	Patients with HER2+ metastatic breast cancer 500 randomized (OGIVRI: 249 Herceptin: 251) 356 completed part 1 (OGIVRI: 185, Herceptin: 171)

MYL-Her-3001 (Heritage Study) is a double-blind, randomized clinical trial designed to evaluate comparative efficacy and safety of OGIVRI vs Herceptin. Eligible patients (pts) had centrally confirmed, measurable HER2+ MBC without prior chemotherapy or trastuzumab for metastatic disease. Pts were randomized to receive either OGIVRI or Herceptin with docetaxel or paclitaxel for a minimum of 8 cycles. Trastuzumab was continued until progression. The primary endpoint was overall response rate (ORR) at Week 24 by blinded central evaluation using RECIST 1.1. Secondary endpoints include progression free survival (PFS), overall survival, and safety. A sample size of 456 pts was calculated to demonstrate equivalence in ORR at Week 24 for OGIVRI vs Herceptin, defined as a 90% confidence interval (CI) for the ratio of best ORR within the equivalence margin (0.81, 1.24).

A total of 500 patients were randomized, 458 were evaluable for efficacy. Of these 203 (44%) had hormone receptor positive MBC, 385 (84%) received docetaxel. Week 24 ORR was 69.6% for OGIVRI compared to 64% for Herceptin. The ratio of ORR was 1.09; both 90% CI (0.974-1.211) and 95% CI (0.954-1.237) were within the pre-defined equivalence margin. The efficacy results for PFS, OS, and DR were comparable without any marked difference at Month 36 across the MYL-14010 and Herceptin groups.

Immunogenicity was assessed by measuring the ADA levels in blood samples collected at baseline and during each treatment period. Among all patients tested positive for ADAs at least once at any timepoint post-baseline regardless of the ADA result at baseline, the overall ADA rate was 3.9% (9/247) in the OGIVRI arm and 4.4% (10/246) in the Herceptin arm. Titers were low in both arms across all timepoints.

The types, frequency and severity of adverse events were comparable between OGIVRI and Herceptin.

Table 16: Best Overall Response Rate (ORR) at Week 24 and Ratio of Best ORR (ITT1 Population; Study MYL-Her-3001)

Response		**OGIVRI + Taxane (N = 230)**	**Herceptin + Taxane (N = 228)**
Complete response (CR)	n (%)	3 (1.3)	0 (0.0)
Partial response (PR)	n (%)	157 (68.3)	146 (64.0)
Stable disease (SD)	n (%)	48 (20.9)	49 (21.5)
Progressive disease (PD)	n (%)	9 (3.9)	20 (8.8)
N/A	n (%)	13 (5.7)	13 (5.7)
Overall response rate	n (%)	160 (69.6)	146 (64.0)
90% CI		(64.57, 74.56)	(58.81, 69.26)
95% CI		(63.62, 75.51)	(57.81, 70.26)
Ratio OGIVRI:Herceptin		1.09	
90% CI		(0.974, 1.211)	
95% CI		(0.954, 1.237)	

CI: confidence interval, ITT: intent-to-treat, N: number of patients in treatment arm, n: number of patients with data available, N/A: not applicable. Percentages are based on the number of patients in the ITT1 population.

Equivalence was declared if the 90% CI of the ratio is completely within the equivalence range of (0.81, 1.24). The 90% and 95% CI was calculated on the natural log scale and back transformed using the exponential function to the original scale.

5.2 PHARMACOKINETIC PROPERTIES

The following pharmacokinetic property information has been generated on the reference medicine.

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 from 18 Phase I, II and III trials receiving trastuzumab 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 5^{th} - 95^{th} 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 17 (Cycle 1) and Table 18 (steady-state) below.

Table 17: Population Predicted Cycle 1 PK Exposure Values (with 5^{th} - 95^{th} Percentiles) for IV Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumor type	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC (µg.day/mL)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	29.4 (5.8 – 59.5)	178.0 (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 18: Population Predicted Steady State PK Exposure Values (with 5_{th} - 95_{th} Percentiles) for trastuzumab IV Dosing Regimens in Breast Cancer and AGC Patients

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

Comparative PK studies

MYL-Her-1001 was a single-dose, 2-period, randomized, double-blind, 2-way crossover study to assess the bioequivalence, safety, and tolerability of OGIVRI versus Herceptin (EU) in healthy male volunteers. 22 subjects were randomized to receive an 8 mg/kg single dose of both products.

The results of this study showed that C_{max} and $AUC_{0-\infty}$, were similar for OGIVRI and Herceptin as demonstrated by the point estimates of the ratio of the geometric mean of OGIVRI and Herceptin (92.18% and 93.70%, respectively) which were within the prespecified equivalence margins of 80% to 125% for both C_{max} and AUC_{0-inf} indicating bioequivalence between OGIVRI and Herceptin.

Table 19: Primary PK Parameters (PP Population; Study MYL-Her-1001)

Parameter	OGIVRI (N=19)	EU-Herceptin (N=19)	Point Estimate (90% CI)
Primary parameters			
C_{max} normalized (µg/mL)	165 (15.7)	178 (15.6)	0.9218 (0.8760; 0.9699)
$AUC_{0-\infty}$ normalized (µg.h/mL)	45486 (22.7)	48350 (28.5)	0.9368 (0.8874; 0.9889)

Data is presented as Geo Mean (Geo CV%) unless otherwise specified. aParameters adapted to 70 kg body weight.
Point estimate as a ratio of geometric means of MYL-1401O versus Herceptin (difference of adjusted means after back transformation). Normalized AUC0-∞=area under the serum concentration-time curve from time zero to infinity (normalized to a dose of 8.0 mg/kg); Normalized Cmax=maximum observed serum concentration (normalized to a dose of 8.0 mg/kg); CI=confidence interval; PP=per-protocol

In the second study, MYL-Her-1002, designed as a single-dose, randomized, double-blind, 3-arm parallel-group study to assess the bioequivalence of OGIVRI versus Herceptin (EU and US sourced) as well as Herceptin EU source versus US source, 132 healthy male volunteers received a 8 mg/kg single dose. The results demonstrated that OGIVRI is bioequivalent to EU-Herceptin and US-Herceptin, and that EU-Herceptin is bioequivalent to US-Herceptin, as the 90% CIs for the natural log-transformed parameters, $LNAUC_{0-last}$, $LNAUC_{0-\infty}$, and LNC_{max} for trastuzumab were within 80% to 125% for the test to reference ratio.

Table 20: Dose-Normalized Pharmacokinetic Parameters of OGIVRI and EU-Herceptin (Study MYL-Her-1002)

Parameter	OGIVRI (N=42) (A)	EU-Herceptin (N=41) (B)	LSMEANS Ratio (A/B)	90% CI[a]
AUC_{0-last} (µg•hr/mL)	48055 (15.92)	49823 (19.61)	0.97	91.31% — 103.05%
$AUC_{0-\infty}$ (µg•hr/mL)	48241 (16.19)	50075 (19.81)	0.97	91.17% — 102.97%
C_{max} (µg/mL)	200.4 (12.34)	192.6 (14.13)	1.04	99.00% —109.82%

Data are presented as mean (%CV) unless otherwise specified.

aUsed Natural Log Transformed Parameter

AUC0-∞=area under the serum concentration-time curve from time zero to infinity (normalized to a dose of 8.0 mg/kg); Cmax=maximum observed serum concentration (normalized to a dose of 8.0 mg/kg); CI=confidence interval

Table 21: Dose-Normalized Pharmacokinetic Parameters of OGIVRI and US-Herceptin (Study MYL-Her-1002)

Parameter	OGIVRI (N=42) (A)	US-Herceptin (N=37) (C)	LSMEANS Ratio (A/C)	90% CI*
AUC_{0-last} (µg•hr/mL)	48055 (15.92)	49826 (13.98)	0.96	90.34% — 102.29%

$AUC_{0-\infty}$ (µg•hr/mL)	48241 (16.19)	50181 (13.86)	0.96	89.96% — 101.94%
C_{max} (µg/mL)	200.4 (12.34)	197.9 (16.25)	1.02	96.42% — 107.26%

Data are presented as mean (%CV) unless otherwise specified.

aUsed Natural Log Transformed ParameterAUC0-∞=area under the serum concentration-time curve from time zero to infinity (normalized to a dose of 8.0 mg/kg); Cmax=maximum observed serum concentration (normalized to a dose of 8.0 mg/kg); CI=confidence interval

Table 22: Dose-Normalized Pharmacokinetic Parameters of EU-Approved Herceptin and US-Licensed Herceptin (Study MYL-Her-1002)

Parameter	EU-Herceptin (N=41) (B)	US-Herceptin (N=37) (C)	LSMEANS Ratio (C/B)	90% CI*
AUC_{0-last} (µg•hr/mL)	49823 (19.61)	49826 (13.98)	1.01	94.79% —107.41%
$AUC_{0-\infty}$ (µg•hr/mL)	50075 (19.81)	50181 (13.86)	1.01	95.01% —107.74%
C_{max} (µg/mL)	192.6 (14.13)	197.9 (16.25)	1.03	97.18% —108.17%

Data are presented as mean (%CV) unless otherwise specified.

aUsed Natural Log Transformed Parameter.

AUC0-∞=area under the serum concentration-time curve from time zero to infinity (normalized to a dose of 8.0 mg/kg); Cmax=maximum observed serum concentration (normalized to a dose of 8.0 mg/kg); CI=confidence interval

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 trastuzumab have been conducted to date.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

OGIVRI 150 mg single-dose vial and OGIVRI 440 mg Pharmacy Bulk Pack contain the following excipients: L-histidine hydrochloride monohydrate, L-histidine, sorbitol and Macrogol 3350; and hydrochloric acid and/or sodium hydroxide to buffer and adjust pH.

6.2 INCOMPATIBILITIES

Glucose solutions (for example, Dextrose (5%) solution) should not be used since it causes aggregation of the protein.

OGIVRI SHOULD NOT BE MIXED OR DILUTED WITH OTHER MEDICINES.

No incompatibilities between OGIVRI 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 OGIVRI 150 mg and 440 mg vials at 2°C to 8°C. Refrigerate. Do not freeze. Do not use beyond the expiration date stamped on the vial.

Reconstituted Solution

150 mg

A vial of OGIVRI reconstituted with sterile Water for Injections (SWFI) without preservative should be used immediately and any unused portion must be discarded. OGIVRI 150 mg is for single use in one patient only. Do not freeze the reconstituted solution.

440 mg

When reconstituted with BWFI, USP (1.1% benzyl alcohol) the Pharmacy Bulk Pack solution may be kept for no longer than 24 hours when stored at 2°C to 8°C or 6 hours at room temperature or above.

Diluted Solution for Infusion

From a microbiological point of view, the OGIVRI infusion solution, when reconstituted with sterile water (SWFI) without preservative, should be diluted and used immediately. The product is not intended to be stored after dilution.

Solutions of OGIVRI for infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing 0.9% sodium chloride at 2°C to 8°C for 24 hours, or 6 hours at room temperature or above.

6.5 NATURE AND CONTENTS OF CONTAINER

OGIVRI trastuzumab (rch) 150mg: Type I, clear, glass vial containing 150mg trastuzumab. Each carton contains 1 vial of OGIVRI 150mg.

OGIVRI trastuzumab (rch) 440mg with bacteriostatic water for injection: Type I, clear, glass vial containing 440mg trastuzumab and Type I, clear glass vial containing bacteriostatic water for injection. Each carton contains 1 vial of OGIVRI 440mg and 1 vial of bacteriostatic water for injection.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 288222 – OGIVRI trastuzumab (rch) 150 mg powder for injection vial

AUST R 288223 – OGIVRI trastuzumab (rch) 440 mg powder for injection vial with bacteriostatic water for injection

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

Chemical name:

Immunoglobulin G1, anti-human p185 neu receptor human-mouse monoclonal recombinant human monoclonal antibody (r-hu-MAb) human epidermal growth factor receptor 2 (HER2) g1-chain, disulfide with human-mouse monoclonal r-hu-MAb HER2 light chain, dimer

Molecular Formula: $C_{6460}H_{9972}N_{1724}O_{2014}S_{44}$

CAS Registry Number:

180288-69-1

OGIVRI is a biosimilar medicine to Herceptin.

OGIVRI (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)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION

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Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes

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