AUSTRALIAN PRODUCT INFORMATION
Herceptin SC (trastuzumab) solution for injection

1. NAME OF THE MEDICINE
Trastuzumab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Herceptin SC vial contains 600mg/5mL of trastuzumab.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.

Clear to opalescent solution, colourless to yellowish.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

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

Metastatic Breast Cancer
Herceptin SC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

It is important to check the labels to ensure the correct formulation (intravenous or subcutaneous) is being administered to the patient as was prescribed**.** Switching treatment between Herceptin IV and Herceptin SC and vice versa, using a three-weekly (q3w) dosing regimen, was investigated in study MO22982 (PrefHER) (see section 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.

HER2 testing is mandatory prior to initiation of Herceptin SC therapy

Detection of HER2 Protein Overexpression or HER2 Gene Amplification

Herceptin should only be used in patients whose tumours have HER2 protein overexpression or HER2 gene amplification. Herceptin treatment is only appropriate if there is strong HER2 overexpression, as described by a 3+ score by immunohistochemistry (IHC) or a positive in situ hybridisation (ISH) result. For patients with an intensity score of 2+ on IHC, confirmation of HER2 positive status by ISH is mandatory.

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

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

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

For full instructions on 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.

Dosage

No loading dose is required.

The recommended fixed dose of Herceptin SC is 600 mg, irrespective of the patient's body weight, administered every three weeks.

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. The optimal dosage regimen and its associated treatment duration have not been defined. However, extending adjuvant treatment beyond one year is not recommended (see section 5.1 Pharmacodynamic Effects, Clinical Trials).

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

Missed Doses

If the patient misses a dose, it is recommended the next 600 mg dose is administered as soon as possible. The interval between subsequent Herceptin SC injections should not be less than 3 weeks.

Dose modification

No reductions in the dose of Herceptin were made during clinical trials. Patients may continue Herceptin therapy during periods of reversible, chemotherapy-induced myelosuppression, but they should be carefully monitored for complications of neutropenia during this time. The specific instructions to reduce or hold the dose of chemotherapy should be followed.

Special populations

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

Method of Administration
Herceptin SC solution is not to be used for intravenous administration and must be administered via a subcutaneous injection only.

The dose should be administered over 2 - 5 minutes.

The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the previous site in healthy skin and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Herceptin SC, other medications for SC administration should preferably be injected at different sites.

Patients should be observed for fever and chills or other administration-associated symptoms (see 4.8 Adverse Effects (Undesirable Effects)). Interruption of the injection and/or medication may help to control such symptoms.

Preparation for SC injection
Herceptin SC solution for injection is for single-use, in one patient only.

The 600 mg/5 mL ready-to-use solution does not need to be diluted. The solution should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Herceptin SC does not contain any antimicrobial-preservative; from a microbiological point of view, the medicine should be used immediately. If not being used immediately, preparation should take place in controlled and validated aseptic conditions, and storage of the prepared product should not exceed 24 hours at 2 °C to 8 °C and 6 hours in total at ambient temperature (do not store above 30°C); see also section 6.4 Special Precautions for Storage.

After transfer of the solution to the syringe, it is recommended to replace the transfer needle by a syringe closing cap to avoid drying of the solution in the needle and not compromise the quality of the medicinal product. The hypodermic injection needle must be attached to the syringe immediately prior to administration followed by volume adjustment to 5mL.

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
In the Phase III trial BO22227 (HANNAH), which compared the administration of Herceptin IV with Herceptin SC, subjects in the SC arm experienced a higher incidence of serious adverse events and discontinuation of treatment.

The potential impact of such effects should be considered for each patient when deciding to use Herceptin SC (see section 4.8 Adverse Effects (Undesirable Effects)**)**.

General
Herceptin therapy should only be initiated under the supervision of a physician experienced in the treatment of cancer patients. Herceptin should be administered by a healthcare professional prepared to manage anaphylaxis and adequate life support facilities should be available. Treatment may be administered in an outpatient setting.

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

Cardiac Dysfunction

General considerations

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

The median half-life of trastuzumab following SC administration is 26.5 days, which is similar to the half-life following IV administration (see section 5.2 Pharmacokinetic Properties). Patients who receive anthracycline after stopping Herceptin may also be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 27 weeks after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Candidates for treatment with Herceptin, especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, ECG and echocardiogram or MUGA scan. Monitoring may help to identify patients who develop cardiac dysfunction, including signs and symptoms of CHF. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin.

The concomitant usage of Herceptin SC with other agents which can affect left ventricular function has not been formally studied.

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

Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6 - 8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy unless the benefits for the individual patient are deemed to outweigh the risks.

The safety of continuation or resumption of Herceptin in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during Herceptin therapy, it should be treated with the standard medications for this purpose. In the pivotal trials, most patients who developed heart failure or asymptomatic cardiac dysfunction improved with standard heart failure treatment consisting of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a β-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on weekly therapy with Herceptin without additional clinical cardiac events.

Early and Locally Advanced Breast Cancer

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

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

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

Adjuvant treatment

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

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

Risk factors for a cardiac event, identified in 4 large adjuvant studies, included advanced age (> 50 years), low level of baseline and declining LVEF (< 55%), low LVEF prior to or following the initiation of paclitaxel treatment, Herceptin treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving Herceptin after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Herceptin and a high body mass index (> 25 kg/m^2).

Neoadjuvant-adjuvant treatment

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

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

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

Hypersensitivity Reactions including Anaphylaxis
Severe hypersensitivity reactions have been infrequently reported in patients treated with the Herceptin IV formulation. Signs and symptoms included 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. In the event of a hypersensitivity reaction, appropriate medical therapy should be administered, which may include adrenaline, corticosteroids, antihistamines, bronchodilators and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

Administration-Related Reactions (ARRs)
In BO22227 study, ARRs (known to occur with the administration of Herceptin SC (see section 4.8 Adverse Effects (Undesirable Effects)) occurred more frequently in the Herceptin SC arm when compared to the Herceptin IV arm (47.8% vs 37.2%) and the majority of events (97% of events in each treatment arm) were grade 1 or 2. The overall rate is in line with the results from other studies where IRR rates of up to 54% have been observed. Grade 3 ARRs were 1.7% and 2.0% in the Herceptin SC and Herceptin IV arms, respectively. Serious ARR's including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress and supraventricular tachyarrhythmia have been reported in trastuzumab trials (see section 4.8 Adverse Effects (Undesirable Effects)).

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

Patients should be observed for ARRs. Symptoms can be treated with an analgesic/antipyretic such as paracetamol and an antihistamine. Serious reactions have been treated successfully with supportive therapy such as oxygen, intravenous fluids, beta-agonists and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. In other patients with acute onset of signs and symptoms, initial improvement was followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours or up to one week following treatment.

Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy or co-morbidities may be at increased risk of a fatal reaction. Therefore, these patients should not be treated with Herceptin (see Pulmonary Reactions below).

Pulmonary Reactions

Severe pulmonary events leading to death have been reported with the use of Herceptin in the post-marketing setting. These events may occur as part of an ARR (see Administration-Related Reactions above) or with a delayed onset. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema, pulmonary hypertension, pulmonary fibrosis and respiratory insufficiency have been reported.

Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Herceptin.

Tumour lysis syndrome (TLS)

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

Paediatric Use

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

Use in the Elderly

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

Effects on laboratory tests

No data available

Use in Renal Impairment

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

Use in Hepatic Impairment

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

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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

Administration of paclitaxel in combination with IV 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 Herceptin regimen (n = 25) were not altered appreciably, relative to parameters determined during the initiation of paclitaxel, prior to introduction of Herceptin. Similarly, docetaxel pharmacokinetics determined during the first dose of Herceptin in the standard weekly regimen (n = 10) were not altered appreciably relative to those determined 2 weeks earlier for docetaxel-alone.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

A study in female cynomolgus monkeys revealed no evidence of impaired fertility at IV trastuzumab doses up to 25 mg/kg twice weekly, corresponding to serum trough levels (serum C_{min}) about 22 times higher than that in humans receiving the recommended 600 mg dose every 3 weeks. However, the binding affinity of trastuzumab to epidermal growth factor receptor 2 protein in cynomolgus monkeys is unclear.

Use in Pregnancy – Category D

Herceptin should be avoided during pregnancy and since trastuzumab may persist in the circulation for up to 7 months, pregnancy should be avoided for 7 months after the last dose of Herceptin, unless the anticipated benefit for the mother outweighs the unknown risk to the foetus.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin.

Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 7 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herceptin, or becomes pregnant within 7 months following the last dose of Herceptin, close monitoring by a multidisciplinary team is desirable.

Herceptin SC contains vorhyaluronidase alfa (see section 6.1 List of Excipients). Developmental toxicity studies in mice demonstrated reductions in foetal weight and increases in the number of resorptions following SC injections of vorhyaluronidase alfa. The no effect dose is estimated to be 160 times the dose (normalised to body surface area), to be administered to patients receiving Herceptin subcutaneous formulation.

Use in Lactation

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

It is not known whether trastuzumab is excreted in human milk. As human immunoglobulin G (IgG) is secreted into human milk and the potential for harm to the infant is unknown, breast-feeding should be avoided during Herceptin therapy and for 7 months after the last dose of Herceptin.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

. Herceptin has a minor influence on the ability to drive and use machines. Dizziness and somnolence may occur during treatment with Herceptin (see section 4.8 Adverse Effects (Undesirable Effects).Patients experiencing administration-related symptoms should be advised not to drive or use machines until symptoms resolve completely.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

The corresponding frequency categories for each adverse drug reaction is based on 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): Herceptin IV arm (n=1678). Control arm (n=1708)
- B-31/N9831 Joint Analysis: Herceptin IV arms (n=2345). Control arm (n=1673)
- BCIRG 006: Herceptin IV arm (n=2133). Control arm (n=1041)
- BO16216 (TanDEM): Herceptin IV arm (n=161). Control arm (n=161)

Locally Advanced Breast Cancer

- MO16432 (NOAH): Herceptin IV arm (n=115). Control arm (n=116)
- BO22227 (HANNAH**):** Herceptin IV arm (n = 298). Herceptin SC arm (n = 297)

Metastatic Breast Cancer (MBC)

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

Advanced Gastric Cancer (Herceptin SC is not approved for this indication)

- BO18255 (ToGA): Herceptin IV arm (n=294). Control arm (n=290)

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

Table 1: Summary of adverse drug reactions occurring in patients treated with Herceptin in clinical trials and in the post market setting

System organ class	Adverse reaction[1]	Frequency
Infections and infestations	Nasopharyngitis	Very common
	Infection	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Herpes zoster	Common
	Influenza	Common
	Pharyngitis	Common

System organ class	Adverse reaction[1]	Frequency
	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	[3]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Dysgeusia	Very common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Peripheral neuropathy	Common
	Hypertonia	Common
	Somnolence	Common
	Ataxia	Common
	Paresis	Rare
	Brain oedema	Not known

System organ class	Adverse reaction[1]	Frequency
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
	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

System organ class	Adverse reaction[1]	Frequency
	[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
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	[3] Swelling face	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Nail disorder	Very common
	Alopecia	Very common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Acne	Common
	Onychoclasis	Common
	Pruritus	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common

System organ class	Adverse reaction[1]	Frequency
	Bone pain	Common
	Muscle spasms	Common
	Neck pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like illness	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Injection site pain[5]	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; [5] Injection site pain identified as an ADR in SC arm in Study BO22227.

Additional information for selected adverse drug reactions

The following information is relevant to all indications.

Subcutaneous Administration

In the neoadjuvant-adjuvant Study BO22227, subjects in the SC arm experienced a higher incidence of serious adverse events (21.5% vs. 14.1%). The higher incidence was predominantly due to a higher incidence of serious infections in the SC arm.

The incidence of discontinuation of Herceptin due to adverse effects was higher in the Herceptin SC arm (2.7 % (IV) vs. 5.7 % (SC)). The overall incidence of discontinuation due to left ventricular dysfunction (LVD) was 2.0% (SC) vs. 1.0 % (IV).

Herceptin SC administration was also associated with a higher incidence of administration-related reactions (ARRs) (48% vs. 37%) such as rash, erythema and cough. Antibodies to trastuzumab also developed more commonly in the Herceptin SC arm (14.6% vs. 7.1%). The clinical relevance of these antibodies is unknown. However, the pharmacokinetics, efficacy, or safety of Herceptin SC did not appear to be adversely affected by these antibodies and no relationship could be identified.

The potential impact of such effects should be considered for each patient when deciding to use Herceptin SC (see section 4.4 Special Warnings and Precautions for Use).

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

Herceptin SC safety and tolerability in EBC patients
In a study (Study MO28048 SafeHer) investigating the safety and tolerability of Herceptin SC as adjuvant therapy in 1868 patients with HER2 positive EBC no new safety signals were identified. Results were consistent with the known safety profile for Herceptin IV and Herceptin SC. In addition, treatment of lower body weight patients with Herceptin SC fixed dose in adjuvant EBC was not associated with increased safety risk, AEs and SAEs, compared to the higher body weight.

Infusion/Administration-Related Reactions (IRRs/ARRs) and Hypersensitivity
IRRs/ARRs such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress were seen in trastuzumab clinical trials (see section 4.4 Special Warnings and Precautions for Use).

In the neoadjuvant-adjuvant Study BO22227, the rate of ARRs was 47.8% in the HERECPTIN SC arm, compared to 37.2% in the Herceptin IV arm. Severe grade 3 events IRR/ARR events were 2.0% and 1.7% in the Herceptin IV and Herceptin SC arms, respectively. There were no grade 4 or 5 IRRs/ARRs.
IRRs may be clinically difficult to distinguish from hypersensitivity reactions.

Anaphylactoid reactions were observed in isolated cases (see section 4.4 Special Warnings and Precautions for Use).

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

Locally Advanced Breast Cancer (neoadjuvant –adjuvant setting)
In Study BO22227, when Herceptin was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300mg/m^2), at a median follow-up exceeding 70 months the incidence of cardiac failure/ congestive heart failure was 0.3% in the Herceptin IV arm and 0.7% in the Herceptin SC arm. In patients with lower body weights (<59 kg, the lowest body weight

quartile) the fixed dose used in the Herceptin SC arm was not associated with an increased risk of cardiac events or significant drop in LVEF.

In Study MO16432 (NOAH), Herceptin IV was administered concurrently with neoadjuvant chemotherapy containing 3-4 cycles of a neoadjuvant anthracycline (cumulative doxorubicin dose 180 mg/m^2) overall, the incidence of symptomatic cardiac dysfunction was 1.7 % in the Herceptin IV arm.

Early Breast Cancer (adjuvant setting)

In 3 pivotal clinical trials of adjuvant Herceptin IV given in combination with chemotherapy the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in patients who were administered Herceptin IV sequentially to a taxane (0.3 - 0.4%). The rate was highest in patients who were administered Herceptin IV concurrently with a taxane (2.0%). At 3 years, the cardiac event rate in patients receiving AC→ P (doxorubicin plus cyclophosphamide followed by paclitaxel) + H (Herceptin IV) was estimated at 3.2%, compared with 0.8% in AC→ P treated patients. No increase in the cumulative incidence of cardiac events was seen with further follow-up at 5 years.

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

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

After a median follow-up of 8 years the incidence of severe CHF (NYHA Class III & IV) following 1 year of Herceptin IV therapy (combined analysis of the two Herceptin IV treatment arms) was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥ 50% after the event) was evident for 71.4% of Herceptin IV-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of Herceptin IV treated patients. Approximately 17% of cardiac dysfunction related events occurred after completion of Herceptin IV.

In the joint analysis of studies NSABP B-31 and NCCTG N9831, with a median follow-up of 8.1 years for the AC→PH group (doxorubicin plus cyclophosphamide, followed by paclitaxel plus trastuzumab); in patients with a symptomatic CHF event in the AC→PH arm, while data are missing for 22.6%, 64.5% were known to recover, and 12.9% experienced no recovery. The median time to first recovery by LVEF status occurred at 8.3 months (range 1 – 104 months); 90.3% experienced a full or partial LVEF recovery.

Metastatic Breast Cancer

Depending on the criteria used to define cardiac dysfunction, the incidence in the pivotal metastatic trials varied between 9% and 12% in the Herceptin + paclitaxel subgroup, compared with 1% - 4% for the paclitaxel-alone subgroup. For Herceptin monotherapy, the rate was 6 - 9%. The highest rate of cardiac dysfunction was seen in patients receiving concurrent Herceptin + anthracycline / cyclophosphamide (27%), significantly higher than in the anthracycline / cyclophosphamide-alone subgroup (7 - 10%). In study M77001 with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving Herceptin and docetaxel, compared with 0% in patients receiving docetaxel-

alone. Most of the patients (79%) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for heart failure.

Haematological Toxicity

Monotherapy– Study H0649g

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

Combination Therapy – Studies H0648g and M77001

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

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

Early Setting – HERA Trial

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

Hepatic and Renal Toxicity

Monotherapy– Study H0649g

WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of Herceptin as monotherapy in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60% of these patients. No WHO Grade 3 or 4 renal toxicity was observed.

Combination Therapy – Study H0648g

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

WHO Grade 3 or 4 hepatic toxicity was less frequently observed among patients receiving Herceptin and paclitaxel than among patients receiving paclitaxel-alone (7% vs.15%). No WHO Grade 3 or 4 renal toxicity was observed.

Diarrhoea

Monotherapy– Study H0649g

Of patients treated with Herceptin monotherapy in the metastatic setting, 27% experienced diarrhoea.

Combination Therapy – Studies H0648g and M77001

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

Early Setting – HERA Study

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

Infection

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

BO22227, subjects in the SC arm experienced a higher incidence of serious infections with or without neutropenia (4.4% versus 8.1%).

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

Immunogenicity
In a neoadjuvant-adjuvant breast cancer trial (BO22227) at a median follow-up exceeding 70 months15.9% (47/295) of patients treated with Herceptin SC developed antibodies against trastuzumab.

Neutralising anti-trastuzumab antibodies were detected in post-baseline samples in 3 of 47 Herceptin patients. The clinical relevance of these antibodies is not known. The presence of anti-trastuzumab antibodies had no impact on pharmacokinetics, efficacy [determined by pathological complete response (pCR)] and event free survival (EFS) and safety [determined by the occurrence of administration related reaction (ARRs)] of trastuzumab IV or SC.

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

4.9 OVERDOSE
Single doses of up to 960 mg have been administered with no reported untoward effect.

Treatment of overdose should consist of general supportive measures.

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

5. PHARMACOLOGICAL PROPERTIES

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

Mechanism of Action
The HER2 (or c-erbB2) proto-oncogene encodes for a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor.

Trastuzumab has been shown, both in *in-vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. *In vitro*, trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2. In animal models *in vivo*, murine anti-HER2 antibody inhibited the growth of human tumours overexpressing HER2, indicating that the humanised antibody (trastuzumab) is likely also to have anti-proliferative activity *in vivo* against human breast tumours expressing high levels of HER2.

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

Herceptin IV in Combination with Adjuvant Chemotherapy
The use of adjuvant Herceptin IV in the setting of early breast cancer (after surgery and in association with chemotherapy and, if applicable, radiotherapy) has been studied in four multicentre randomised phase III trials of patients with HER2 positive breast cancer who have completed surgery. In these clinical trials, 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 summarised in Table 2 and efficacy results are presented in Tables 2-7.

Table 2: Clinical Trials in Early Breast Cancer

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

	HERA trial ***n* = 3386**	**NSABP B-31 and NCCTG N9831 trials (joint analysis)** ***n* = 3763**	**BCIRG 006** ***n* = 3222**
Timing of Herceptin IV in relation to chemotherapy	After completion of (neo)adjuvant [a]	Concurrent **(AC→PH)** or sequential **(AC→P→H)**	Concurrent **(AC→DH** and **DCarbH)**
Median follow-up	1 year (initial evaluation) [8 years (follow-up evaluation)]	2 years	3 years

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

The HERA trial was designed to compare 1 and 2 years of 3-weekly Herceptin IV treatment vs. observation in patients with HER2 positive breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of 2 years Herceptin IV treatment vs. 1 year Herceptin IV treatment was performed. Patients assigned to receive Herceptin IV 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 summarised in the following table:

Table 3: Efficacy Results from the HERA Trial at 12 months[1] and 8 years[2] of median follow up

Parameter	**Observation**	**Herceptin IV 1 yr treatment**	**p-value**	**HR (95% CI)**
<u>Disease free survival</u>				
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)
<u>Overall Survival</u>				
No. of patients with event (1 year[1])	2.4%	1.8%	0.24	0.75 (0.47, 1.21)
No. of patients with event (8 year[2])	20.6%	16.3%	0.0005	0.76 (0.65, 0.88)

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

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

In the final analysis (8 year median follow up) extending Herceptin IV 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 summarised in the following table:

Table 4: Summary of Efficacy Results from NSABP B-31 and NCCTG N9831 trials (joint analysis) at the time of the definitive DFS analysis*

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

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: Herceptin IV; 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 5: Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831

Parameter	AC→P (N=2032)	AC→PH (N=2031)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	< 0.0001	0.64 (0.55, 0.74)

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

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

Table 6: Overview of Efficacy Analyses BCIRG 006 AC→D versus AC→DH

Parameter	**AC→D** ***n* = 1073**	**AC→DH** ***n* = 1074**	**p-value**	**HR (95% CI)**
Disease-free survival (DFS)				
No. patients with event	195	134	<0.0001	0.61 (0.49, 0.77)
Death (OS event)				
No. patients with event	80	49	0.0024	0.58 (0.40,0.83)

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

Table 7: Overview of Efficacy Analyses BCIRG 006 AC→D versus DCarbH

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

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

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

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

Herceptin SC safety and tolerability in EBC patients
In a study (Study MO28048 SafeHer) investigating the safety and tolerability of Herceptin SC as adjuvant therapy in 1868 patients with HER2 positive EBC no new safety signals were identified. Results were consistent with the known safety profile for Herceptin IV and Herceptin SC. In addition, treatment of lower body weight patients with Herceptin SC fixed dose in adjuvant EBC was not associated with increased safety risk, AEs and SAEs, compared to the higher body weight (see section 4.8 Adverse Effects (Undesirable Effects)).

Locally Advanced Breast Cancer

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

Herceptin in Combination with Neoadjuvant-Adjuvant Chemotherapy

In the neoadjuvant-adjuvant setting Herceptin has been evaluated in 2 phase III studies;

Study BO22227 (HANNAH):

Study BO22227 (HANNAH) was conducted to demonstrate non-inferiority of Herceptin SC vs. Herceptin IV. Steady state (pre-dose Cycle 8) serum trastuzumab C_{trough} values and pCR were co-primary endpoints. Secondary endpoints included event free survival and overall survival for which the study was not powered to measure differences between treatment arms. Patients with HER2-positive operable or locally advanced breast cancer (LABC) including inflammatory breast cancer received 8 cycles of either Herceptin SC or Herceptin IV concurrently with chemotherapy (four cycles of docetaxel 75mg/m^2 followed by four cycles of a FEC combination regimen comprising fluorouracil 500 mg/m², epirubicin 75 mg/m², and cyclophosphamide 500 mg/m²), followed by surgery, and continued therapy with Herceptin SC or Herceptin IV, as originally randomised, for an additional 10 cycles for a total of 1 year of treatment. In HANNAH, in the majority of cases, it was retrospectively determined that the pathologist assessing the primary specimens and nodes was masked to treatment allocation and no supplemental independent review was performed.

The co-primary endpoint, pCR as defined by the absence of invasive neoplastic cells in the breast, resulted in rates of 40.7% (95% CI: 34.7, 46.9) in the Herceptin IV arm and 45.4% (95% CI: 39.2%, 51.7%) in the Herceptin SC arm, a difference of 4.7% in favour of the Herceptin SC arm. The lower boundary of the 1-sided 97.5% CI for the difference in pCR rates was -4.0, whereas the pre-defined non-inferiority margin was -12.5%, confirming the non-inferiority of Herceptin SC compared to the Herceptin IV based on this endpoint. The PK co-primary endpoint was C_{trough}, at pre-dose cycle 8 selected to ensure that the minimum serum concentration after the Herceptin SC fixed dosing should be at least as high as that after Herceptin IV weight-based dosing (i.e. comparable receptor saturation). For the results of the PK co-primary endpoint refer above to section 5.2 Pharmacokinetic Properties*).*

Analyses with longer term follow-up of a median duration exceeding 40 months supported the non-inferior efficacy of Herceptin SC compared to Herceptin IV with comparable results of both EFS and OS (3-year EFS rates of 73% in the Herceptin IV arm and 76% in the Herceptin SC arm, and 3-year OS rates of 90% in the Herceptin IV arm and 92% in the Herceptin SC arm). The final analysis at a median follow-up exceeding 70 months showed similar EFS and OS between patients who received Herceptin IV and those who received Herceptin SC. The 6-year EFS was 65% in both arms (ITT population: HR=0.98[95% CI: 0.74; 1.29]) and the OS rate 84% in both arms (ITT population: HR=0.94 [95% CI: 0.61; 1.45]).

Study MO16432 (NOAH):

Study MO16432 (NOAH) is a multicentre randomised trial, designed to investigate the concurrent administration of Herceptin IV with neoadjuvant chemotherapy, including both an anthracycline and a taxane, followed by adjuvant Herceptin IV, 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 randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant Herceptin IV (n = 116), or neoadjuvant chemotherapy alone (n = 118). Herceptin IV was administered concurrently with 10 cycles of neoadjuvant chemotherapy as follows;

- Doxorubicin (60 mg/m^2) and paclitaxel (150 mg/m^2) ^{in} combination with Herceptin IV (8 mg/kg loading dose, followed by 6 mg/kg maintenance, administered 3-weekly) for 3 cycles, followed by

- Paclitaxel (175 mg/m^2) and Herceptin IV (6mg/kg, administered 3-weekly) for 4 cycles, followed by
- CMF on day 1 and 8 every 4 weeks for 3 cycles, in combination with 4 cycles of Herceptin IV (6mg/kg administered 3-weekly), followed by
- up to 7 additional cycles of Herceptin IV (6mg/kg, administered 3-weekly) alone to complete 1 year after starting Herceptin

The primary endpoint for the trial, event-free survival (EFS), was defined as the time from randomisation 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 randomised in the trial following the intent-to-treat principle, with the exception of 3 patients whose data could not be evaluated) are summarised in the table below. The median duration of follow-up in the Herceptin IV arm was 3.8 years.

Table 8: Overview of Efficacy Analyses MO16432 (NOAH)

Parameter	**Chemo + Herceptin IV** ***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^	40%	20.7%		
(95% CI)	(31.0, 49.6)	(13.7, 29.2)	p = 0.0014	

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

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

Metastatic Breast Cancer

There are no data available to establish the efficacy of Herceptin for the treatment of metastatic disease in patients who have previously received the medicine for the treatment of localised disease.

The safety and efficacy of Herceptin IV has been studied in randomised, 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 Hybridisation (FISH) test (see section 4.2 Dose and Method of Administration).

Herceptin IV in Combination with Chemotherapy

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

The prospectively defined, primary intent-to-treat analysis indicated that the combination of Herceptin and chemotherapy significantly prolonged time to disease progression (progression-free survival) compared with

chemotherapy-alone as first-line treatment of women with metastatic breast cancer who had tumours that overexpressed HER2. The addition of Herceptin to chemotherapy extended the median time to disease progression by 2.8 months representing a 61% increase (p=0.0001).

Both anthracycline-treated and paclitaxel-treated patients benefited from Herceptin treatment, although the effect appeared to be greater in the paclitaxel stratum. The efficacy of Herceptin treatment was further supported by the secondary endpoints of response rate, duration of response and one-year survival (see Table 9 below).

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

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

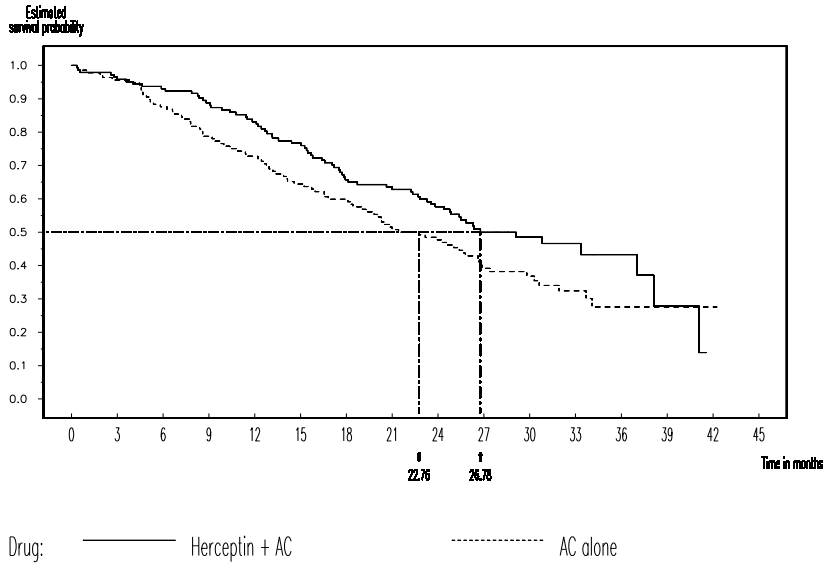
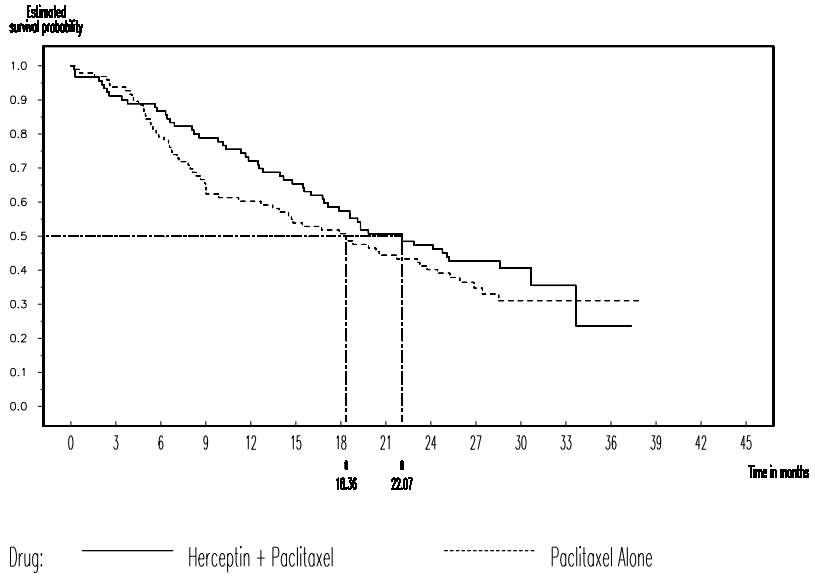


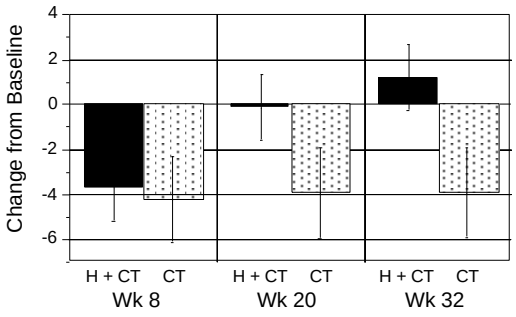
Figure 2: Survival Time: Paclitaxel ± Herceptin (Study H0648g)



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

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

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

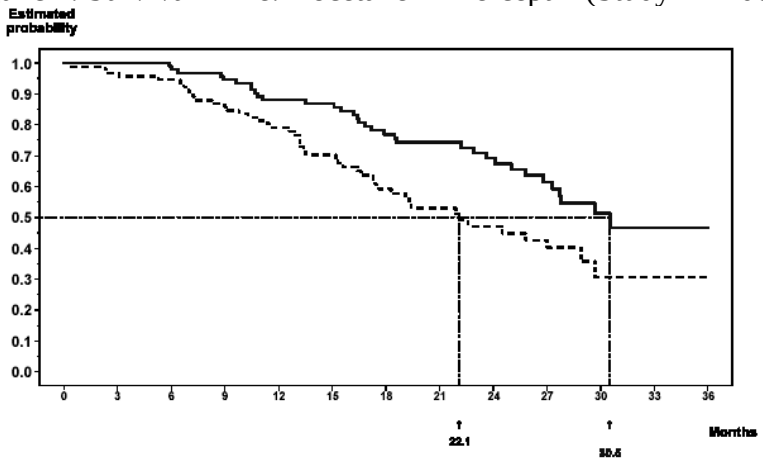


H = Herceptin; CT = chemotherapy

Study M77001 was a multinational, multi-centre, randomised, controlled trial investigating the safety and efficacy of Herceptin in combination with docetaxel, as first-line treatment in HER2 positive metastatic breast cancer patients. One hundred and eighty six patients received docetaxel (100 mg/m^2 infused over 1 hour on Day 2) with or without Herceptin IV (4 mg/kg loading dose, followed by 2 mg/kg weekly). Sixty percent of patients had received prior anthracycline based adjuvant chemotherapy. Herceptin IV with docetaxel was shown to be efficacious in patients whether or not they had received prior adjuvant anthracyclines and regardless of their oestrogen and/or progesterone receptor status.

The combination of Herceptin IV + 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 9). Median survival was also significantly increased in patients receiving the combination therapy compared with those receiving docetaxel-alone (30.5 months vs. 22.1 months) (see Figure 4).

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



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

Table 9: Efficacy Outcomes with Combination Therapy for Metastatic Breast Cancer

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

H = Herceptin IV; Chemo = chemotherapy; AC = anthracycline + cyclophosphamide; P = paclitaxel; D = docetaxel

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

Herceptin IV in Combination with Anastrozole

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

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

however more than half of the patients in the anastrozole-alone arm crossed over to a Herceptin-containing regimen after progression of disease.

Herceptin IV Monotherapy

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

Patients received an intravenous loading dose of 4 mg/kg Herceptin IV on Day 0, followed by weekly IV infusions of 2 mg/kg until there was evidence of disease progression. Patients who developed progressive disease could stop treatment, continue on the Herceptin IV 2 mg/kg weekly dose or receive an increased IV dose of 4 mg/kg, as the investigator deemed appropriate. The primary efficacy parameter was tumour response rate.

Herceptin as second- or third-line therapy induced objective, durable tumour responses in women with metastatic breast cancer who had tumours that overexpressed HER2. There were 8 complete responses and 26 partial responses yielding an overall response rate of 15%. The durability of the responses was particularly notable. The median duration of the responses was 9.1 months at the cut-off date for analysis (see Table 10 below).

Table 10: Efficacy Outcomes with Monotherapy Study H0649g

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

Subcutaneous (SC) formulation

The pharmacokinetics of trastuzumab in Herceptin IV and SC formulations were compared in the phase III trial BO22227 (HANNAH) (SC formulation: fixed dose of 600 mg administered 3-weekly; IV formulation: 8 mg/kg loading dose, 6 mg/kg maintenance dose every 3 weeks). The pharmacokinetic results for the co-primary endpoint, C_{trough} pre-dose Cycle 8, showed non-inferiority of steady-state C_{trough} values for the Herceptin SC arm (fixed dosing) compared to the Herceptin IV arm (body-weight adjusted dosing).

The mean observed steady-state trough serum trastuzumab concentration during the neoadjuvant treatment phase, at the pre-dose Cycle 8-time point, was higher in the Herceptin SC arm than the IV arm, with mean observed values of 78.7 µg/mL (standard deviation (SD): 43.9 µg/mL) as compared to 57.8 µg/mL SD: (30.3 µg/mL). During the adjuvant phase of treatment, at the pre-dose Cycle 13-time point, the mean observed trastuzumab concentration values, were 90.4 µg/mL (SD: 41.9 µg/mL) and 62.1 µg/mL (SD: 37.1 µg/mL), respectively for the Herceptin SC and Herceptin IV arms. While approximate steady state concentrations with the Herceptin IV or Herceptin SC formulations were reached at pre-dose cycle 8, observed concentrations with the Herceptin SC formulation tended to increase slightly up to pre-dose cycle 13. The mean observed serum trastuzumab concentration at pre-dose cycle 18 was: 90.7 µg/mL, similar to that at pre-dose cycle 13, suggesting no further increase after cycle 13.

The median T_{max} following Herceptin SC Cycle 7 administration was approximately 3 days, with high variability (range 1-14 days). The mean C_{max} was expectedly lower in the Herceptin SC arm (149 µg/mL) than in the Herceptin IV arm (end of infusion value: 221 µg/mL).

The mean observed $AUC_{0\text{-}21\ days}$ following the Cycle 7 dose was approximately 10% higher with Herceptin SC as compared to the Herceptin IV formulation. With the Herceptin IV and Herceptin SC formulations, body weight had an influence on the pre-dose cycle 8 serum trastuzumab concentration and $AUC_{0\text{-}21days}$ values. In patients with body weight (BW) below 51 kg (10th percentile), the mean steady state AUC of trastuzumab following the Cycle 7 dose was about 80% higher after Herceptin SC than after Herceptin IV treatment. Whereas in the highest BW group, above 90 kg (90th percentile) AUC was 20% lower after Herceptin SC than after Herceptin IV treatment. Across BW subsets, patients who received Herceptin SC had a pre-dose trastuzumab concentration and $AUC_{0\text{-}21days}$ values that were comparable to, or higher than observed in patients who received Herceptin IV. Multiple logistic regression analyses showed no correlation of trastuzumab exposure values to efficacy (pCR) or safety results, and dose adjustment for body weight is not needed.

A population PK model with parallel linear and nonlinear elimination from the central compartment was constructed using pooled Herceptin SC and Herceptin IV PK data from the HANNAH (BO22227) study. The model described the observed PK profiles following Herceptin IV and Herceptin SC administration in the study's patient population: operable or locally advanced breast cancer (LABC). Bioavailability of the subcutaneous formulation was estimated to be 77.1%. Linear elimination clearance (linear CL) was 0.111 L/day and the central compartment volume (Vc) was 2.91 L.

The population predicted PK exposure parameter values (with 5th - 95th Percentiles) for Herceptin SC dosing regimen in EBC patients are shown in Table 11 below.

Table 11 Population Predicted PK Exposure Values (with 5th - 95th Percentiles) for the Herceptin SC 600 mg Q3W Dosing Regimen in EBC patients

Primary tumour type and Regimen	**Cycle**	**N**	**C_{min} (µg/mL)**	**C_{max} (µg/mL)**	**$AUC_{0\text{-}21days}$ (µg.day/mL)**
EBC 600 mg Herceptin SC q3w	Cycle 1	297	28.2 (14.8 - 40.9)	79.3 (56.1 – 109.1)	1064.9 (717.6 – 1503.8)
	Cycle 7 (steady state)	297	75.0 (35.1 – 123.4)	148.8 (86.1 – 213.6)	2337.3 (1257.7 – 3478.1)

Intravenous (IV) formulation
Information in this section reports data from the Herceptin Product Information for the intravenous formulation.

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 patients from 18 Phase I, II and III trials receiving Herceptin IV to treat a range of cancers, but mostly breast and gastric cancer. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to the non-linear elimination, total clearance increased with decreasing concentrations. Linear clearance was 0.127 L/day for breast cancer (metastatic and early). The nonlinear elimination parameter values were 8.81 mg/day for the maximum elimination rate (V_{max}) and 8.92 mg/L for the Michaelis-Menten constant (Km). The central compartment volume was 2.62 L for patients with breast cancer.

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 patients treated with the approved q1w and q3w dosing regimens are shown in Table 12 (Cycle 1) and Table 13 (steady-state) below.

Table 12: Population Predicted Cycle 1 PK Exposure Values (with 5th - 95th Percentiles) for Herceptin IV Regimens in Breast Cancer Patients

Regimen	Primary tumour type	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC (µg.day/mL)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	29.4 (5.8 - 59.5)	178.0 (116.5 – 290.5)	1372.5 (735.8 – 2245.0)
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 13: Population Predicted Steady State PK Exposure Values (with 5th - 95th Percentiles) for Herceptin IV Dosing Regimens in Breast Cancer Patients

Regimen	Primary tumour type	N	Cmin,ss (µg/mL)	Cmax,ss (µg/mL)	AUCss (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	47.4 (5.0 - 114.7)	179.4 (107.3 – 308.8)	1794.2 (673.0 – 3618.4)	12	0.173 - 0.283
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 of the IV formulation showed that the estimated creatinine clearance (Cockcroft and Gault) does not correlate with the pharmacokinetics of trastuzumab.

5.3 PRECLINICAL SAFETY DATA

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Vorhyaluronidase alfa (an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously)
Histidine hydrochloride monohydrate
Histidine
Trehalose dehydrate
Polysorbate 20
Methionine
Water for Injections.

6.2 INCOMPATIBILITIES
No incompatibilities between Herceptin and the following materials have been observed:

- propylene or polycarbonate syringe
- stainless steel transfer
- injection needles
- polyethylene luer cones stoppers

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store Herceptin SC vials at 2°C to 8°C. Refrigerate. Do not freeze. Store in the original package in order to protect from light. Do not use beyond the expiration date stamped on the vial.

From a microbiological point of view, Herceptin SC solution should be used immediately. Once transferred from the vial to the syringe, the product is physically and chemically stable at 2 to 8°C for 24 hours.

Once removed from the refrigerator, Herceptin SC solution in the vial or transferred to syringe should not be kept for more than 6 hours in total at ambient temperature (do not store above 30°C).

6.5 NATURE AND CONTENTS OF CONTAINER
Herceptin SC solution for injection is a ready-to-use solution (600 mg/5 mL) supplied as one single use vial.

Herceptin is also available as a sterile single-dose vial, white to pale yellow, preservative-free lyophilised powder for IV infusion containing 60 mg or 150 mg of trastuzumab (See separate Herceptin Powder for Intravenous (IV) Infusion Product Information).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.
The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Herceptin (trastuzumab) is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG_1 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 humanised 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.

CAS number

180288-69-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA
Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

19 March 2015

10. DATE OF REVISION OF THE TEXT

27 May 2020

Summary table of changes

Section Changed	Summary of new information
4.4	Addition of warning for Tumour Lysis Syndrome
4.6	Clarification in Use in Lactation
4.7	Updated to align with the company Core Data Sheet
4.8	Updated to align with the company Core Data Sheet