NEW ZEALAND DATA SHEET
Herceptin SC (trastuzumab)

1. PRODUCT NAME

Herceptin SC 600mg/5mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Herceptin SC vial contains 600mg/5mL of trastuzumab.

For the full list of excipients, see section 6.1.

Herceptin is also available as a powder for concentrate solution, for intravenous infusion containing 150 mg (single-dose vial) or 440mg (multi-dose vial) of trastuzumab (See separate Herceptin Powder for Intravenous (IV) Infusion Data Sheet).

3. PHARMACEUTICAL FORM

Solution for subcutaneous (SC) injection

Colourless to yellowish, clear to opalescent liquid solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

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

Early breast cancer
Herceptin SC is indicated for the treatment of patients with:

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

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose
HER2 testing is mandatory prior to initiation of Herceptin SC therapy (see Dosage and Administration, Detection of HER2 Overexpression or Gene Amplification).

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.

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded in the patient's medical record. Substitution by any other biological medicinal product requires the consent of the prescribing physician. Caution should be taken when no switching data are available to support interchangeability of Herceptin and a given biosimilar.

Herceptin SC 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.

Switching treatment between Herceptin IV and SC formulation and vice versa, using the three-weekly dosing regimens, was investigated in the study MO22982 (see section 4.8).

Herceptin SC is not to be used for intravenous (IV) administration and must be administered via the subcutaneous route only.

The recommended dose of Herceptin SC is 600 mg, irrespective of patient body weight (fixed dose) given once every 3 weeks (q3w). No loading dose is required. The injection 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 1 inch/2.5 cm from the old 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.

Duration of treatment
In clinical studies, patients with metastatic breast cancer were treated with Herceptin until progression of disease. Patients with early breast cancer should be treated for a maximum of 12 months or until disease recurrence, whichever occurs first. Extending treatment in early breast cancer beyond one year is not recommended. Treatment should be discontinued for any patient experiencing unmanageable toxicity.

Missed doses
If a dose is missed, it is recommended to administer the next 600 mg dose as soon as possible. The interval between subsequent Herceptin SC injections should not be less than three weeks.

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

Special Dosage Instructions
Elderly
Data suggest that the disposition of Herceptin is not altered based on age (see section 5.2). In clinical trials, patients ≥ 65 years of age did not receive reduced doses of Herceptin.

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

Detection of HER2 Overexpression or Gene Amplification
Herceptin should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification. 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 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 assay performance and interpretation please refer to the package inserts of validated FISH, CISH and SISH assays. Official recommendations on HER2 testing may also apply.

Method of Administration
For instructions on reconstitution of the medicine before administration, see section 6.6.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
General
Herceptin therapy should only be initiated under supervision of a physician experienced in the treatment of cancer patients.

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

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

Administration-related reactions (ARRs
ARRs are known to occur with Herceptin SC (see section 4.8).

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

Serious ARRs including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress and supraventricular tachyarrhythmia have been reported (see section 4.8).

Patients should be observed for ARRs. Symptoms can be treated with an analgesic/antipyretic such as pethidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions have been treated successfully with supportive therapy such as oxygen, intravenous fluids, beta-agonists and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome.

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

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

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

Cardiac dysfunction

General considerations

Patients treated with Herceptin 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 paclitaxel following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. This may be moderate to severe and has been associated with death (see section 4.8). In addition, caution should be exercised in treating patients with increased cardiac risk (e.g. hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age)

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

Candidates for treatment with Herceptin, especially those with prior exposure to 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 treatments until 24 months from the last administration of Herceptin.

If Left Ventricular Ejection Fraction (LVEF) percentage drops 10 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 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 breast cancer

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

Patients with history of myocardial infarction (MI), angina pectoris requiring medication, history of or present CHF (NYHA 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 breast cancer clinical trials with Herceptin.

Neoadjuvant-adjuvant treatment

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

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

Clinical experience in the neoadjuvant-adjuvant setting is limited in patients above 65 years of age.

Adjuvant treatment

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

In patients with early breast cancer an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin 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 four large adjuvant studies included advanced age (> 50 years), low level of baseline and declining LVEF (< 55%), low LVEF prior to or following the initiation of paclitaxel treatment, Herceptin treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving Herceptin after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Herceptin and a high body mass index (BMI) (>25 kg/m^2).

Metastatic breast cancer

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

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No formal interaction studies have been performed with Herceptin in humans. Clinically significant interactions between Herceptin and the 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 in 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 IV. Similarly, docetaxel pharmacokinetics determined during the first dose of Herceptin IV in the standard weekly regimen (n = 10) were not altered appreciably relative to those determined 2 weeks earlier for docetaxel alone.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Pregnancy Category: D

Herceptin should be avoided during pregnancy and as 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, becomes pregnant while receiving Herceptin or within 7 months following the last dose of Herceptin, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

It is not known whether trastuzumab is secreted in human breast milk. As human IgG is secreted into human breast milk, and the potential for harm to the infant is unknown, breast-feeding should be avoided during Herceptin therapy and for 7 months after the last dose of Herceptin (see section 5.3).

Fertility

Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg trastuzumab and revealed no evidence of impaired fertility or harm to the foetus. However, when assessing the risk of reproductive toxicity to humans, it is also important to consider the significance of the rodent form of the HER2 receptor in normal

embryonic development and the embryonic death in mutant mice lacking this receptor. Placental transfer of trastuzumab during the early (days 20 - 50 of gestation) and late (days 120 - 150 of gestation) foetal development period was observed.

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 Undesirable Effects). Patients experiencing administration-related symptoms should be advised not to drive or use machines until symptoms resolve completely.

4.8 UNDESIRABLE EFFECTS

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

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Early Breast Cancer

- **BO16348 (HERA)**: Herceptin arm (n = 1678). Control arm (n = 1708)
- **B-31/N9831 Joint Analysis**: Herceptin arms (n = 2345). Control arm (n = 1673)
- **BCIRG 006**: Herceptin arm (n = 2133). Control arm (n = 1041)
- **BO16216 (TanDEM)**: Herceptin arm (n = 161). Control arm (n = 161)
- **MO16432 (NOAH)**: Herceptin arm (n = 115). Control arm (n = 116)
- **BO22227 (HANNAH)**: Herceptin SC arm (n = 297). Herceptin IV arm (n = 298).

Metastatic Breast Cancer

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

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

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

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

Table 1: Summary of adverse drug reactions occurring in patients treated with Herceptin in Clinical Trials and in the Post-Market setting

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

System organ class	Adverse reaction	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
	Neutropenia	Very common
	Thrombocytopenia	Very common
	White blood cell count decreased / leukopenia	Very common
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Immune system disorders	Hypersensitivity	Common
	[+]Anaphylactic reaction	Not known
	[+]Anaphylactic shock	Rare
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
	Anxiety	Common
	Depression	Common
	Thinking abnormal	Common
Nervous system disorders	Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Dysgeusia	Very common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Peripheral neuropathy	Common

System organ class	Adverse reaction	Frequency
	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	[1]Blood pressure decreased	Very common
	[1]Blood pressure increased	Very common
	[1]Heart beat irregular	Very common
	[1]Palpitation	Very common
	[1]Cardiac flutter	Very common
	Ejection fraction decreased^	Very Common
	[+]Cardiac failure (congestive)	Common
	[+1]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	Hot flush	Very common
	Lymphoedema	Very common
	[+1]Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	[+1]Wheezing	Very common
	[+]Dyspnoea	Very common
	Cough	Very common
	Epistaxis	Very common
	Rhinorrhoea	Very common
	Oropharyngeal pain	Very common
	Asthma	Common
	Lung disorder	Common
	[+]Pneumonia	Common
	[+]Pleural effusion	Common
	Pneumonitis	Rare
	[+]Pulmonary fibrosis	Not known
	[+]Respiratory distress	Not known
	[+]Respiratory failure	Not known
	[+]Lung infiltration	Not known
	[+]Acute pulmonary oedema	Not known

System organ class	Adverse reaction	Frequency
	[+]Acute respiratory distress syndrome	Not known
	[+]Bronchospasm	Not known
	[+]Hypoxia	Not known
	[+]Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	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
	Constipation	Very common
	Pancreatitis	Very common
	Haemorrhoids	Common
	Dyspepsia	Very 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
	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
	[1]Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common

System organ class	Adverse reaction	Frequency
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
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
	Administration 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
	Confusion	Common

1 Adverse drug rections (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

[#] Injection site pain was identified as an ADR in the Herceptin SC formulation arm in study BO22227 (HANNAH). ADRs were added to the appropriate system organ class (SOC) category and are presented in a single table according to the highest incidence seen in any of the major clinical trials.

Administration-related reactions (ARRs), Allergic reactions and Hypersensitivity

ARRs/hypersensitivity reactions such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress were seen in Herceptin clinical trials (see section 4.4).

ARRs may be clinically difficult to distinguish from hypersensitivity reactions.
The rate of IRRs of all grades varied between studies depending on the indication, whether Herceptin was given concurrently with chemotherapy or as monotherapy and data collection methodology.

In the neoadjuvant-adjuvant study BO22227 (HANNAH), the rate of infusion related reactions (IRRs) were 37.2% in the IV arm, compared to the rate of ARRs of 47.8% in the SC arm. Severe grade 3 IRR/ARR events were 2.0% and 1.7% in the IV and SC arms, respectively. There were no grade 4 or 5 IRRs/ARRs.

Anaphylactoid reactions were observed in isolated cases.

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

Early breast cancer
Neoadjuvant-adjuvant setting
In the pivotal trial MO16432 (NOAH), when Herceptin was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2), the incidence of symptomatic cardiac dysfunction was up to 1.7 % in the Herceptin arm.

In Study BO22227 (HANNAH), 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 cardiac 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.

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

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

continuous increase in the cumulative rate of symptomatic cardiac or LVEF events up to 2.3% compared to approximately 1% in the two comparator arms (AC→D and DCarbH).

When Herceptin was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6% of patients in the one-year arm after a median follow-up of 12 months. After a median follow-up of 3.6 years the incidence of severe CHF and left ventricular dysfunction after 1 year Herceptin therapy remained low at 0.8% and 9.8%, respectively. In study BO16348, after a median follow-up of 8 years, the incidence of severe CHF (NYHA Class III & IV) in the Herceptin 1 year treatment arm was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

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

In the joint analysis of studies NSABP B-31 and NCCTG N9831, with a median follow-up of 8.1 years for the AC→PH group (doxorubicin plus cyclophosphamide, followed by paclitaxel plus trastuzumab), the per patient incidence of new onset cardiac dysfunction, as determined by LVEF, remained unchanged compared to the analysis performed at a median follow up of 2.0 years in the AC→PH group: 18.5% of AC→PH patients with LVEF decreased of ≥10% to below 50%. Reversibility of left ventricular dysfunction was reported in 64.5% of patients who experienced a symptomatic CHF in the AC→PH group being asymptomatic at latest follow up, and 90.3% having full or partial LVEF recovery.

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% in the paclitaxel alone subgroup. For Herceptin monotherapy, the rate was 6% - 9%. The highest rate of cardiac dysfunction was seen in patients receiving Herceptin + anthracycline/cyclophosphamide (27%), and was 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 monotherapy in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in < 1% of patients. No WHO Grade 4 toxicities were observed.

Combination Therapy – Studies H0648g and M77001
WHO Grade 3 or 4 haematological toxicity was observed in 63% of patients treated with Herceptin and an anthracycline/cyclophosphamide compared to an incidence of 62% in patients treated with the anthracycline/cyclophosphamide combination without Herceptin.

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

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

Hepatic and renal toxicity
WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of Herceptin as single agent, in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60% of these patients.

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

Diarrhoea
Monotherapy – Study H0649G
Of patients treated with Herceptin monotherapy in the metastatic setting, 27% experienced diarrhoea.

In the HERA trial (median follow-up 1 year), 7% of Herceptin-treated patients had diarrhoea.

Combination Therapy – Studies H0648g and M77001
An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has been observed in patients receiving Herceptin in combination with chemotherapy compared with patients receiving chemotherapy-alone or Herceptin-alone.

Early breast cancer setting – HERA Study
In the HERA trial, 8% of Herceptin treated patients experienced diarrhoea during the first year of treatment.

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

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

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

Switching treatment between Herceptin IV and Herceptin SC formulation and vice versa
Study MO22982 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 the Herceptin IV infusion or Herceptin SC injection. In this trial, 2 cohorts (one using Herceptin SC vial and one using Herceptin SC single use injection device) were investigated using a 2-arm, cross-over design with patients being randomised 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 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.

Herceptin SC safety and tolerability in EBC patients
Study MO28048 investigating the safety and tolerability of Herceptin SC as adjuvant therapy enrolled HER2 positive EBC patients in either a Herceptin SC Vial cohort (n=1868 patients, including 20 patients receiving neoadjuvant therapy) or a Herceptin SC SID cohort (n=710 patients, including 21 patients receiving neoadjuvant therapy). The primary analysis included patients with a median follow-up of up to 23.7 months. No new safety signals were observed and 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 patients. The final results of study BO22227 at a median follow-up exceeding 70 months (see section 5.1 Clinical Trials) were also consistent with the known safety profile for Herceptin IV and Herceptin SC, and no new safety signals were observed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 OVERDOSE

Single doses up to 960 mg of Herceptin SC have been administered with no reported adverse effect.

Treatment of overdose should consist of general supportive measures.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

Mechanism of Action

Trastuzumab is a recombinant humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG_1 isotype that contains human framework regions with the complementarity-determining regions of a murine anti-p185 HER2 antibody that binds to HER2.

The HER2 proto-oncogene or c-erbB2 encodes for a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 15% - 20% of primary breast cancers. The overall rate of HER2 positivity in advanced gastric cancer as observed during screening for study BO18255 is 15% for IHC3+ and IHC2+/FISH+ or 22.1% when applying the broader definition of IHC3+ or FISH+. A consequence of HER2 gene amplification is an increase in HER2 protein expression on the surface of these tumour cells, which results in a constitutively activated HER2 protein.

Studies indicate that patients whose tumours have amplification or overexpression of HER2 have a shortened disease-free survival compared to patients whose tumours do not have amplification or overexpression of HER2.

Trastuzumab has been shown, both in *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. *In vitro*, trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Clinical trials

Early Breast Cancer

Herceptin in combination with neoadjuvant-adjuvant chemotherapy

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

- Study BO22227 (HANNAH) was designed to demonstrate non-inferiority of treatment with Herceptin SC versus Herceptin IV based on co-primary pharmacokinetic and efficacy endpoints (trastuzumab C_{trough} at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively). Patients with HER2-positive, operable or locally advanced breast cancer (LABC) including inflammatory breast cancer received eight cycles of either Herceptin SC or Herceptin IV concurrently with chemotherapy [docetaxel followed by FEC 5-fluorouracil, epirubicin and cyclophosphamide)],

followed by surgery, and continued therapy with Herceptin SC or IV as originally randomised for an 10 additional cycles for a total of one year of treatment.

- *Study MO16432 (NOAH)*, 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 IV

Study BO22227 (HANNAH)

The analysis of the efficacy co-primary endpoints, pCR, defined as 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 SC arm. The lower boundary of the one-sided 97.5% confidence interval for the difference in pCR rates was -4.0, whereas the pre-defined non-inferiority margin was -12.5%, establishing the non-inferiority of Herceptin SC compared to Herceptin IV based on this endpoint.

Table 2: Summary of pathological Complete Response (pCR) (BO22227 HannaH Study)

	Herceptin IV (N = 263)	Herceptin SC (N=260)
pCR (absence of invasive neoplastic cells in breast	107 (40.7%)	118 (45.4%)
Non-responders	156 (59.3%)	142 (54.6%)
Exact 95% CI for pCR Rate[1]	(34.7; 46.9)	(39.2; 51.7)
Difference in pCR (SC minus IV arm)	4.70	
Lower bound one-sided 97.5% CI for the difference in pCR[2]	-4.0	

1 Confidence interval for one sample binomial using Pearson-Clopper method

2 Continuity correction of Anderson and Hauck (1986) has been used in this calculation

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).

For non-inferiority of the PK co-primary endpoint, steady-state trastuzumab C_{trough} value at the end of treatment Cycle 7, see section 5.2.

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 rate 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)
The primary endpoint for the study, 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 study 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 3: 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^ (95% CI)	40% (31.0, 49.6)	20.7% (13.7, 29.2)	p = 0.0014	

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

The addition of Herceptin 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 IV arm.

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

The design of these studies is summarised in Table 4 below and efficacy results are presented in Tables 5 - 8.

Table 4: Clinical Trials in Early Breast Cancer

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

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

The HERA trial was designed to compare 1 and 2 years of 3-weekly Herceptin treatment vs. observation in patients with HER2 positive breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of 2 years Herceptin treatment vs. 1 year Herceptin treatment was performed. Patients assigned to receive Herceptin were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks for either 1 or 2 years. The efficacy results from the HERA trial are summarised in the following table:

Table 5: Efficacy Results from the HERA Trial at 12 months[1] and 8 years[2] of median follow up

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

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

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

In the final analysis (8-year median follow up) extending Herceptin treatment for a duration of 2 years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years vs. 1 year = 0.99 (95% CI: 0.87, 1.13); p-value = 0.90 and OS HR = 0.98 (0.83, 1.15); p-value = 0.78]. The rate of asymptomatic cardiac dysfunction was increased in the 2-year treatment arm (8.1% vs. 4.6% in the 1-year treatment arm). More patients experienced at least one grade 3 or 4 adverse event in the 2-year treatment arm (20.4%) compared with the 1-year treatment arm (16.3%).

The efficacy results from the joint analysis of the NCCTG 9831 and NSABP B-31 trials at the time of definitive analysis of DFS* are summarised in the following table:

Table 6: Summary of Efficacy Results from the joint analysis studies NSABP B-31 and NCCTG N9831 at the time of the definitive DFS analysis*

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

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

* At median duration of follow up was 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

For the primary endpoint, DFS, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit,

in terms of 3-year disease-free survival rate estimates of 11.8 percentage points (87.2 % versus 75.4 %) in favour of the AC→PH (Herceptin IV) arm.

At the time of a safety update, after a median of 3.5-3.8 years follow up, an analysis of DFS reconfirms the magnitude of the benefit shown in the definitive analysis of DFS. Despite the cross-over to Herceptin IV in the control arm, the addition of Herceptin IV to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The addition of Herceptin IV to paclitaxel chemotherapy also resulted in a 37 % decrease in the risk of death.

The pre-planned final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→P H group). Treatment with AC→PH resulted in a statistically significant improvement in OS compared with AC→P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p-value < 0.0001). At 8 years, the survival rate was estimated to be 86.9% in the AC→PH 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 summarised in the table below:

Table 7: 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**	**HR (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: Herceptin

DFS analysis was also performed at the final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831. The updated DFS analysis results (stratified HR = 0.61; 95% CI [0.54, 0.69]) showed a similar DFS benefit compared to the definitive primary DFS analysis, despite 24.8% patients in the AC→P arm who crossed over to receive Herceptin IV. At 8 years, the disease-free survival rate was estimated to be 77.2% (95% CI: 75.4, 79.1) in the AC→PH arm, an absolute benefit of 11.8% compared with the AC→P arm.

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

Table 8: Overview of Efficacy Analyses BCIRG 006 AC→D versus AC→DH

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

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

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

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

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

Metastatic Breast Cancer

Herceptin monotherapy or in combination with chemotherapy

Herceptin monotherapy has been used in clinical trials for patients with metastatic breast cancer who have tumours that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease.

Herceptin has also been used in clinical trials in combination with paclitaxel or an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC) as first line therapy for patients with metastatic breast cancer who have tumours that overexpress HER2.

Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m^2 infused over 3 hours) with or without Herceptin IV. Patients could be treated with Herceptin until progression of disease.

Herceptin monotherapy, when used as second- or third-line treatment of women with metastatic breast cancer which overexpresses HER2, results in an overall tumour response rate of 15% and a median survival of 13 months.

The use of Herceptin in combination with paclitaxel as first-line treatment of women with metastatic breast cancer that overexpresses HER2 significantly prolongs the median time to disease progression, compared with patients treated with paclitaxel alone. The increase in median time to disease progression for patients treated with paclitaxel is 3.9 months (6.9 months vs. 3.0 months). Tumour response and one-year survival rate are also increased for Herceptin in combination with paclitaxel versus paclitaxel alone.

Herceptin has also been studied in a randomised, controlled trial, in combination with docetaxel, as first-line treatment of women with metastatic breast cancer. The combination of Herceptin and docetaxel significantly increased response rate (61% vs. 34%) and prolonged the median time to disease progression, (by 5.6 months) compared with patients treated with docetaxel alone. Median survival was also significantly increased in patients receiving the combination, compared with those receiving docetaxel alone (31.2 months vs. 22.7 months).

Herceptin in combination with anastrozole

The TAnDEM trial was a multi-centre, randomised, open-label, phase III study comparing Herceptin + anastrozole with anastrozole alone for the first-line treatment of metastatic breast cancer in HER2 overexpressing, hormone-receptor (i.e. oestrogen-receptor (ER) and/or progesterone-receptor (PR))

positive post-menopausal patients. Two hundred and seven patients were randomised to receive oral anastrozole (1 mg/day) with or without Herceptin IV (4 mg/kg loading dose, followed by 2 mg/kg weekly). Patients who had previously received Herceptin were excluded from this trial.

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

5.2 PHARMACOKINETIC PROPERTIES

SC formulation

The pharmacokinetics of trastuzumab given as a fixed 600 mg dose of Herceptin SC vial administered 3-weekly; was compared to those of Herceptin IV given as a weight based 8 mg/kg loading dose followed by 6 mg/kg maintenance doses administered every 3 weeks) in the phase III Study BO22227. The pharmacokinetic results for the co-primary endpoint, trastuzumab trough concentration at pre-dose Cycle 8, showed non-inferior trastuzumab exposure for the Herceptin SC arm with fixed 600mg q3w dosing compared to the Herceptin IV arm with body weight adjusted q3w dosing. Analysis of cycle 1 serum trastuzumab trough values confirmed that no loading dose is needed when using the Herceptin SC 600mg fixed dose, in contrast to when using Herceptin IV weight based dosing.

The mean observed trastuzumab concentration during the neoadjuvant treatment phase, at the pre-dose Cycle 8-time point, was higher in the Herceptin SC arm than in the Herceptin IV arm of the study, 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 of the study. While approximate steady state concentrations with Herceptin IV and Herceptin SC formulations are reached at approximately Cycle 8, observed trastuzumab trough concentrations with Herceptin SC tended to increase slightly up to Cycle 13. The mean observed trastuzumab trough concentration at the SC pre-dose Cycle 18 was 90.7 µg/mL, similar to that of Cycle 13, suggesting no further increase after Cycle 13.

The median T_{max} following Herceptin SC Cycle 7 administration was approximately 43 days, with high variability (range 1 – 14 days). The mean C_{max} was expectedly lower in Herceptin SC arm (149 µg/mL) than in the Herceptin IV arm (end of infusion value: 221 µg/mL).

The mean observed $AUC_{0\text{-}21\ days}$ value following the Cycle 7 dose was approximately 10% higher with Herceptin SC as compared to Herceptin IV, with mean AUC values of 2268 µg/mL•day and 2056 µg/mL•day, respectively. With the Herceptin IV and Herceptin SC, body weight (BW) had an influence on the pre-dose trastuzumab concentration and $AUC_{0\text{-}21days}$ values. In patients with BW below 51 kg (10th percentile), the mean steady state AUC value 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 body weight subsets patients who received Herceptin SC had pre-dose trastuzumab concentration and $AUC_{0\text{-}21days}$ values that were comparable to or higher than those observed in patients who received Herceptin IV. Multiple logistic regression analyses showed no correlation of PK to efficacy (pCR) or safety (AE) outcomes, and dose adjustment for body weight is not needed.

A population PK model, with parallel linear and non-linear elimination from the central compartment, was constructed using pooled trastuzumab PK data from the phase III study BO22227 of Herceptin SC vs. Herceptin IV, to describe the observed PK concentrations following Herceptin IV and Herceptin SC administration in early breast cancer (EBC) patients. Bioavailability of trastuzumab given as Herceptin SC was estimated to be 77.1%, and the first order absorption rate constant was estimated to be 0.4 day^{-1}. Linear elimination clearance was 0.111 L/day and the central compartment volume (Vc) was 2.91 L. The nonlinear elimination Michealis-Menten parameters were 11.9 mg/day and 33.9 mg/L for Vmax and Km, respectively. Body weight and serum alanine aminotransferase showed a statistically significant influence on PK, however, simulations demonstrated no dose adjustments are required in the early breast cancer setting. The population predicted PK exposure parameter values (with 5^{th} - 95^{th} Percentiles) for the Herceptin SC 600 mg q3w regimen in EBC patients is shown in Table 10 below.

Table 10: Population Predicted PK Exposure Values (with 5^{th} - 95^{th} Percentiles) for Herceptin SC 600 mg SC q3w Regimen in EBC patients

Primary tumour type and Regimen	Cycle	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC (µg.day/mL)
EBC Herceptin SC 600 mg q3w	Cycle 1	297	28.2 (14.8 - 40.9)	79.3 (56.1 - 109)	1065 (718 - 1504)
	Cycle 7 (steady state)	297	75.0 (35.1 - 123)	149 (86.1 - 214)	2337 (1258 - 3478)

IV formulation

The pharmacokinetics of trastuzumab was evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects from 18 Phase I, II and III trials receiving intravenous Herceptin. A two-compartment model with parallel linear and non-linear elimination pathways from the central compartment was used to describe trastuzumab concentration-time profile. Due to the non-linear elimination pathway, total clearance increases with decreasing concentrations. Linear elimination clearance was 0.127 L/day for breast cancer (MBC/EBC) and 0.176 L/day for AGC. The nonlinear elimination parameter values were 8.81 mg/day for the maximum elimination rate (Vmax) and 8.92 mg/L for the Michaelis-Menten constant (Km). The central compartment volume was 2.62 L for patients with breast cancer and 3.63 L for patients with AGC.

The population predicted PK exposures (with 5th - 95th Percentiles) and PK parameters at clinically relevant concentrations (C_{max} and C_{min}) for breast cancer and AGC patients following the approved Q1W and Q3W regimens are shown in Table 11 (Cycle 1) and Table 12(steady-state) below.

Table 11: Population Predicted Cycle 1 PK Exposures (with 5th - 95th Percentiles) for IV Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumour type	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC (µg.day/mL)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	29.4 (5.8 - 59.5)	178 (117 - 291)	1373 (736 - 2245)
	AGC	274	23.1 (6.1 - 50.3)	132 (84.2 - 225)	1109 (588 - 1938)
4mg/kg + 2mg/kg qw	MBC/EBC	1195	37.7 (12.3 - 70.9)	88.3 (58 - 144)	1066 (586 - 1754)

Table 12: Population Predicted Steady State PK Exposures (with 5th - 95th Percentiles) for IV Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumour type	N	Cmin,ss (µg/mL)	Cmax,ss (µg/mL)	AUCss (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	47.4 (5 - 115)	179 (107 - 309)	1794 (673 - 3618)	12	0.173 - 0.283
	AGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875)	9	0.189 - 0.337
4mg/kg + 2mg/kg qw	MBC/EBC	1195	66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 - 0.244

Trastuzumab washout

Trastuzumab washout time period was assessed following Herceptin IV and Herceptin SC administration using the respective population PK models. The results of these simulations indicate that at least 95% of patients will reach serum trastuzumab concentrations that are <1 µg/mL (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) by 7 months after the last dose.

Special Populations

Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. The data from Study H0649g suggest that the disposition of trastuzumab is not altered by patient characteristics such as age or serum creatinine. The population pharmacokinetic

analysis also shows that the estimated creatinine clearance (Cockcroft and Gault) does not correlate with the pharmacokinetics of trastuzumab.

Elderly
Age has been shown to have no effect on the disposition of trastuzumab (see section 4.2).

5.3 PRECLINICAL SAFETY DATA

There was no evidence of acute or multiple dose-related toxicity in studies of up to 6 months, or reproductive toxicity in teratology, female fertility or late gestational toxicity/placental transfer studies. Herceptin is not genotoxic. A study of trehalose, a major formulation excipient did not reveal any toxicities.

No long-term animal studies have been performed to establish the carcinogenic potential of Herceptin, or to determine its effects on fertility in males.

Lactation
A study conducted in lactating cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin demonstrated that trastuzumab is secreted in the milk. The exposure to trastuzumab in utero and the presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age.

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)
L-histidine hydrochloride monohydrate
L-histidine
α,α-trehalose dehydrate
polysorbate 20
L-methionine
water for injections.

6.2 INCOMPATIBILITIES

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

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

6.3 SHELF LIFE

21 months

Once transferred from the vial to the syringe, the medicinal product is physically and chemically stable for 48 hours at 2 °C – 8 °C and subsequently 6 hours at ambient temperature (do not store

above 30 °C) in diffuse daylight. This exposure time at ambient temperature should not be cumulated to any previous exposure time at room temperature of the medicinal product in the vial.

From a microbiological point of view, since the medicine does not contain any antimicrobial preservative, once it is transferred from the vial to the syringe, the medicine should be used immediately. If it is not being used immediately, preparation should take place in controlled and validated aseptic conditions.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vials at 2 °C – 8 °C.
Do not freeze.
Store in the original package in order to protect from light.

Once removed from the refrigerator, Herceptin SC must be administered within 6 hours and should not be kept above 30 °C.

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

6.5 NATURE AND CONTENTS OF CONTAINER

One 6 mL clear glass type I vial containing 5 mL of solution (600 mg of trastuzumab).

Each carton contains one vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Appropriate aseptic technique should be used.

Herceptin SC 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.

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 5 mL.

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).
- Dispose of the full container according to local requirements.

7. MEDICINE SCHEDULE
Prescription medicine

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

Medical enquiries: 0800 276 243

9. DATE OF FIRST APPROVAL
2 October 2014

10. DATE OF REVISION OF THE TEXT
31 January 2020

Summary of Changes Table

Section Changed	Summary of new information
4.7	Updated information on EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
4.8	Updated information on UNDESIRABLE EFFECTS
5.3	Updated information on PRECLINICAL SAFETY DATA