PACK INSERT FOR MALAYSIA

HERCEPTIN ®

Information as set forth in this label only applies to HERCEPTIN

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Antineoplastic agent
ATC code: L01 XC03

1.2 TYPE OF DOSAGE FORM

Subcutaneous (SC) formulation (Herceptin SC): Solution for injection.

1.3 ROUTE OF ADMINISTRATION

Herceptin SC: Subcutaneous injection.

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile product.

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: trastuzumab.

Herceptin SC formulation in vial (Herceptin SC Vial):
600 mg/5 ml fixed dose vial containing solution for injection (do not reconstitute or dilute).

Excipients: Herceptin SC contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.
Other Excipients: L-Histidine, L-Histidine hydrochloride monohydrate, α,α-Trehalose dehydrate, L-Methionine, Polysorbate 20, Water

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Breast Cancer
Metastatic Breast Cancer (MBC)
Herceptin is indicated for the treatment of patients with metastatic breast cancer who have tumours that overexpress HER2:

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

Early Breast Cancer (EBC)
Herceptin is indicated for the treatment of patients with HER2-positive early breast cancer

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin, for locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter.

2.2 DOSAGE AND ADMINISTRATION

General
HER2 testing is mandatory prior to initiation of Herceptin therapy.

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 should be administered by a qualified health care professional.

It is important to check the product labels to ensure that the correct formulation (Herceptin IV or Herceptin SC) is being administered to the patient as prescribed.

Switching treatment between Herceptin IV and Herceptin SC and vice versa, using a three-weekly (q3w) dosing regimen, was investigated in study MO22982 (see section 2.6.1 Undesirable Effects / Clinical Trials).

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

Herceptin SC is not to be used for intravenous administration and must be administered as a subcutaneous injection only.

No loading dose is required.

The recommended fixed dose of Herceptin SC is 600 mg irrespective of the patient's body weight.

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 previous site on 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.

When administering Herceptin SC Vial, this dose should be administered over 2-5 minutes every three weeks.

Duration of treatment

- Patients with MBC should be treated with Herceptin until progression of disease or unmanageable toxicity.
- Patients with EBC should be treated for 1 year or until disease recurrence or unmanageable toxicity, whichever occurs first. Extending treatment in EBC beyond one year is not recommended (see section 3.1.2 Clinical / Efficacy Studies).

Missed doses

If one dose of Herceptin SC is missed, it is recommended to administer the next 600 mg dose (i.e. the missed dose) as soon as possible. The interval between subsequent Herceptin SC doses should not be less than three weeks.

Dose modification

If the patient develops an infusion-related reaction (IRR), the infusion rate of Herceptin IV may be slowed or interrupted (see section 2.4 Warnings and Precautions).

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.

2.2.1 Special Dosage Instructions

Geriatric use

Data suggest that the disposition of Herceptin is not altered based on age (see section 3.2.5 Pharmacokinetics in Special Populations). In clinical trials, patients ≥ 65 years of age did not receive reduced doses of Herceptin.

Paediatric use

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

2.3 CONTRAINDICATIONS

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

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

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

Infusion/Administration-related reactions (IRRs/ARRs)

IRRs/ARRs are known to occur with the administration of Herceptin (see section 2.6. Undesirable Effects).

IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions.

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

Serious IRRs/ARRs to Herceptin including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, supraventricular tachyarrhythmia and urticaria have been reported (see section 2.6. Undesirable Effects). Patients should be observed for IRRs/ARRs. Interruption of an IV infusion may help control such symptoms and the infusion may be resumed when symptoms abate. These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients who are experiencing dyspnoea at rest due to complications of advanced malignancy or co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Herceptin.

Pulmonary reactions

Severe pulmonary events have been reported with the use of Herceptin IV in the post-marketing setting. These events have occasionally resulted in fatal outcome and may occur as part of an IRR 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 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 taxane following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. This may be moderate to severe and has been associated with death (see section 2.6 Undesirable Effects). In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age.

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 3.2 Pharmacokinetic Properties). Patients who receive anthracycline after stopping Herceptin may also be at increased risk of cardiac dysfunction.

If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

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

If 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 has declined further, or if 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 standard medications for heart failure (HF). In the pivotal trials, most patients who developed HF or asymptomatic cardiac dysfunction improved with standard HF treatment consisting of an 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 with Herceptin without additional clinical cardiac events.

Metastatic breast cancer (MBC)

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

Early breast cancer (EBC)
For patients with EBC, 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 hemodynamic effective pericardial effusion were excluded from adjuvant breast cancer clinical trials with Herceptin.

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

In patients with EBC 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).

Neoadjuvant-adjuvant treatment
In patients with EBC eligible for neoadjuvant-adjuvant treatment, Herceptin concurrently 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.

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

2.4.2 Drug Abuse and Dependence
No data to report.

2.4.3 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 2.6 Undesirable Effects). Patients experiencing infusion-related symptoms (see section 2.4 Warnings and Precautions) should be advised not to drive or use machines until symptoms resolve completely.

2.5 USE IN SPECIAL POPULATIONS
2.5.1 Females and Males of Reproductive Potential
Fertility
It is not known whether Herceptin can affect reproductive capacity. Animal reproduction studies revealed no evidence of impaired fertility or harm to the foetus (see section 3.3.4 Reproductive Toxicity).

Contraception
Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin IV or Herceptin SC formulation and for 7 months after treatment has concluded (see section 3.2 Pharmacokinetic Properties).

2.5.2 Pregnancy
Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some of which resulted in fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin.

Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herceptin, or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable.

Labour and Delivery
No data to report.

2.5.3 Lactation
It is not known whether trastuzumab is secreted 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 [see section 3.3.5 Other (Preclinical Safety)].

2.5.4 Paediatric Use
The safety and efficacy of Herceptin in paediatric patients below the age of 18 have not been established.

2.5.5 Geriatric Use
Data suggest that the disposition of Herceptin is not altered based on age (see section 3.2.5 Pharmacokinetics in Special Populations).

2.5.6 Renal Impairment
In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition.

2.5.7 Hepatic Impairment
No data to report.

2.6 UNDESIRABLE EFFECTS
2.6.1 Clinical Trials
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 pivotal clinical trials. All the terms included are based on the highest percentage seen in pivotal clinical trials.

As Herceptin is commonly used with other chemotherapeutic agents and radiotherapy it is often difficult to ascertain the causal relationship of an adverse event to a particular drug/radiotherapy.

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 should be presented in order of decreasing seriousness.

Table 1: Summary of adverse drug reactions occurring in patients treated with Herceptin in clinical trials

System organ class	Adverse reaction*	Frequency
Infections and infestations	Nasopharyngitis	Very common
	Infection	Very common
	Influenza	Common
	Neutropenic sepsis	Common
	Pharyngitis	Common
	Sinusitis	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
Blood and lymphatic system disorders	Anaemia	Very common
	Thrombocytopenia	Very common
	Febrile neutropenia	Very common
	White blood cell count decreased/leukopenia	Very common
	Neutropenia	Very common
Immune system disorders	Hypersensitivity	Common
	Anaphylactic shock	Rare
Metabolism and nutrition disorders	Weight decreased	Very common
	Weight increased	Very common
	Decreased appetite	Very common
Psychiatric disorders	Insomnia	Very common
	Depression	Common
	Anxiety	Common
Nervous system disorders	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Dysgeusia	Very common

System organ class	Adverse reaction*	Frequency
	Hypertonia	Common
	Peripheral neuropathy	Common
	Somnolence	Common
Eye disorders	Lacrimation increased	Very common
	Conjunctivitis	Very common
Ear and labyrinth disorder	Deafness	Uncommon
Cardiac disorders	Ejection fraction decreased	Very common
	[+1]Supraventricular tachyarrhythmia	Common
	[+]Cardiac failure (congestive)	Common
	Cardiomyopathy	Common
	[1]Palpitation	Common
	Pericardial effusion	Uncommon
Vascular disorders	Lymphoedema	Very common
	Hot flush	Very common
	[+1] Hypotension	Common
	Hypertension	Common
	Vasodilation	Common
Respiratory, thoracic and mediastinal disorders	[+]Dyspnoea	Very common
	Epistaxis	Very common
	Oropharyngeal pain	Very common
	Cough	Very common
	Rhinorrhoea	Very common
	Asthma	Common
	Lung disorder	Common
	[+]Pleural effusion	Common
	Pneumonia	Common
	Pneumonitis	Uncommon
	Wheezing	Uncommon
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
Hepatobiliary disorder	Hepatocellular injury	Common
	Jaundice	Rare
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	Alopecia	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Nail disorder	Very common
	Acne	Common
	Dermatitis	Common
	Dry skin	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck pain	Common
	Pain in extremity	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common

System organ class	Adverse reaction*	Frequency
	Influenza-like symptoms	Very common
	Infusion/Administration related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Mucosal inflammation	Very common
	Oedema	Common
	Injection site pain**	Common
	Malaise	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common

* 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.
** Injection site pain was identified as an ADR in the SC arm in the BO22227 study. 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.
+ Denotes adverse reactions that have been reported in association with a fatal outcome.
1 Denotes adverse reactions that are reported largely in association with Infusion-related reactions. Specific percentages for these are not available.

Additional information for selected adverse drug reactions

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 all trastuzumab clinical trials and for the IV and the SC formulation (see section 2.4 Warnings and Precautions).

IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions.

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

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

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

In the neoadjuvant-adjuvant EBC treatment setting (BO22227), the rates of IRRs/ARRs were in line with the above and were 37.2% in the Herceptin IV arm to 47.8% in the Herceptin SC arm. Severe (grade 3) IRRs/ARRs were 2.0% and 1.7% in the Herceptin IV and Herceptin SC arms, respectively during the treatment phase. There were no grade 4 or 5 IRRs/ARRs.

Anaphylactoid reactions were observed in isolated cases.

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 cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S_3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin (see section 2.4 Warnings and Precautions).

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 group, compared with 1% - 4% in the paclitaxel alone group. For Herceptin monotherapy, the rate was 6% - 9%. The highest rate of cardiac dysfunction was seen in patients receiving concurrent Herceptin + anthracycline/cyclophosphamide (27%), and was significantly higher than in the anthracycline/cyclophosphamide alone group (7% - 10%). In a subsequent trial 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 CHF.

Early Breast Cancer (adjuvant setting)
In three pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in

patients who were administered Herceptin sequentially 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 (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 the AC→D and DCarbH arms; relative to both the AC→D and DCarbH arms there was an increased risk of developing a symptomatic cardiac event for patients in the AC→DH arm, being discernable by a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events up to 2.3% compared to approximately 1% in the two comparator arms (AC→D and DCarbH).

When Herceptin was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6% of patients in the 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 $\geq$ 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 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 an 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.

Early Breast Cancer (neoadjuvant-adjuvant setting)
In the pivotal trial MO16432 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 1.7% in the Herceptin arm.

In the pivotal trial BO22227, Herceptin was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/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.

Haematological toxicity
Breast Cancer
Haematological toxicity is infrequent following the administration of Herceptin IV monotherapy in the metastatic setting, WHO Grade 3 leukopenia, thrombocytopenia and anaemia occurring in < 1% of patients. No WHO Grade 4 toxicities were observed. 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% versus 21%). Haematological toxicity was also increased in patients receiving Herceptin and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using NCI-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin plus docetaxel (23% versus 17% for patients treated with docetaxel alone).

Using NCI-CTC criteria, in the BO16348 study, 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

Breast Cancer

WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of Herceptin IV 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 IV and paclitaxel than among patients receiving paclitaxel alone (7% compared with 15%). No WHO Grade 3 or 4 renal toxicity was observed.

Diarrhoea

Breast Cancer

Of patients treated with Herceptin IV monotherapy in the metastatic setting 27% experienced diarrhoea. An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has also been observed in patients receiving Herceptin in combination with paclitaxel compared with patients receiving paclitaxel alone.

In the BO16348 study, 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 in patients treated with Herceptin.

Switching treatment from Herceptin IV to Herceptin SC 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 Herceptin IV infusion or Herceptin SC injection. In this trial, 2 cohorts (one using Herceptin SC vial and one using Herceptin SC SID) were 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 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 3.1.2 Clinical / Efficacy Studies) were also consistent with the known safety profile for Herceptin IV and Herceptin SC, and no new safety signals were observed.

2.6.2 Postmarketing Experience

The following adverse drug reactions have been identified from postmarketing experience with Herceptin (Table 2).

Table 2: Adverse Reactions reported in the postmarketing setting

System organ class	Adverse reaction
Blood and lymphatic system disorders	Hypoprothrombinemia Immune thrombocytopenia
Immune system disorders	Anaphylactoid reaction
	Anaphylactic reaction
Metabolism and nutrition disorders	Tumour lysis syndrome
Eye disorders	Madarosis
Cardiac disorders	Cardiogenic shock
	Tachycardia
Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Oxygen saturation decreased
	Respiratory failure
	Interstitial lung disease
	Lung infiltration
	Acute respiratory distress syndrome
	Respiratory distress
	Pulmonary fibrosis
	Hypoxia

System organ class	Adverse reaction
	Laryngeal oedema
Renal and urinary disorders	Glomerulonephropathy
	Renal failure
Pregnancy, puerperium and perinatal conditions	Pulmonary hypoplasia
	Renal hypoplasia
	Oligohydramnios

2.6.3 Adverse Events

Table 3 below indicates adverse events that historically have been reported in patients who have received Herceptin. As no evidence of a causal association has been found between Herceptin and these events, these events are not considered expected for the purposes of regulatory reporting.

Table 3: Adverse Events

.System organ class	Adverse Event
Infections and infestations	Meningitis
	Bronchitis
Blood and lymphatic system disorders	Leukaemia
Nervous system disorders	Cerebrovascular disorder
	Lethargy
	Coma
Ear and labyrinth disorders	Vertigo
Respiratory, Thoracic and Mediastinal system disorders	Hiccups
	Dyspnoea exertional
Gastrointestinal system disorders	Gastritis
	Pancreatitis
Musculoskeletal and connective tissue disorders	Musculoskeletal pain
Renal and urinary system disorders	Dysuria
Reproductive system and breast disorders	Breast pain
General disorders and administration site conditions	Chest discomfort

2.7 OVERDOSE

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

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

There have been no formal drug interaction studies performed with Herceptin in humans. Clinically significant interactions between Herceptin and the concomitant medications used in clinical trials have not been observed (see section 3.2 Pharmacokinetic Properties).

In studies where Herceptin was administered in combination with docetaxel, carboplatin, or anastrozole, the pharmacokinetics of these medications was not altered nor was the pharmacokinetics of Herceptin altered.

Concentrations of paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) were not altered in the presence of trastuzumab. However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite is unclear. No changes were observed in trastuzumab concentrations in the presence of paclitaxel and doxorubicin.

The results of a small drug interaction substudy evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 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 human 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 cancer. The overall rate of HER2 positivity in advanced gastric cancers 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 breast cancer 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.

3.1.2 Clinical / Efficacy Studies

Metastatic Breast Cancer

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 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. 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 Herceptin and paclitaxel is 3.9 months (6.9 months versus. 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% versus 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 versus 22.7 months).

Combination treatment with Herceptin and anastrozole

Herceptin has been studied in combination with anastrozole for first line treatment of metastatic breast cancer in HER2 overexpressing, hormone-receptor [i.e. oestrogen-receptor (ER) and/or progesterone-receptor (PR)] positive patients. Progression free survival was doubled in the Herceptin plus anastrozole arm compared to anastrozole (4.8 months versus 2.4 months). For the other parameters the improvements seen for the combination were; for overall response (16.5% versus 6.7%); clinical benefit rate (42.7% versus 27.9%); time to progression (4.8 months versus 2.4 months). For time to response and duration of response no difference could be recorded between the arms. The median overall survival was extended by 4.6 months for patients in the combination arm. The difference was not statistically significant, however more than half of the patients in the anastrozole alone arm crossed over to a Herceptin containing regimen after progression of disease. Fifty two percent of the patients taking Herceptin plus anastrozole survived for at least 2 years compared to 45% taking anastrozole alone.

Early Breast Cancer

In the adjuvant treatment setting, Herceptin was investigated in 4 large multicentre, randomised, phase 3 trials:

- Study BO16348 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2-positive early breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of two years of Herceptin treatment versus one year of 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 three weeks for either one or two years.
- Studies NSABP-B31 and NCCTG N9831 that comprise the joint analysis were designed to investigate the clinical utility of combining Herceptin IV treatment with paclitaxel following AC chemotherapy; additionally the NCCTG N9831 study investigated adding Herceptin sequentially to AC-paclitaxel chemotherapy in patients with HER2-positive early breast cancer following surgery.

- Study BCIRG 006 was designed to investigate combining Herceptin IV treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2-positive early breast cancer following surgery.

Early breast cancer in the BO16348 study was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes-positive or axillary nodes-negative tumours of at least 1 cm in diameter.
The efficacy results from the BO16348 study are summarized in the following table:

Table 4: Efficacy Results (BO16348 study): Results at 12 months* and 8 years of median follow-up**

	Median follow-up 12 months		Median follow-up 8 years	
Parameter	Observation N=1693	Herceptin 1 Year N = 1693	Observation N= 1697***	Herceptin 1 Year N = 1702***
Disease-free survival				
- No. patients with event	219 (12.9%)	127 (7.5%)	570 (33.6%)	471 (27.7%)
- No. patients without event	1474 (87.1%)	1566 (92.5%)	1127 (66.4%)	1231 (72.3%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.54		0.76	
Recurrence-free survival				
- No. patients with event	208 (12.3%)	113 (6.7%)	506 (29.8%)	399 (23.4%)
- No. patients without event	1485 (87.7%)	1580 (93.3%)	1191 (70.2%)	1303 (76.6%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease-free survival				
- No. patients with event	184 (10.9%)	99 (5.8%)	488 (28.8%)	399 (23.4%)
- No. patients without event	1508 (89.1%)	1594 (94.6%)	1209 (71.2%)	1303 (76.6%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death)				
- No. patients with event	40 (2.4%)	31 (1.8%)	350 (20.6%)	278 (16.3%)
- No. patients without event	1653 (97.6%)	1662 (98.2%)	1347 (79.4%)	1424 (83.7%)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

* Co-primary endpoint of DFS of 1 year vs observation met the pre-defined statistical boundary
** Final analysis (including crossover of 52% of patients from the observation arm to Herceptin)
*** There is a discrepancy in the overall sample size due to a small number of patients who were randomised after the cut-off date for the 12-month median follow-up analysis

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary for the comparison of 1-year of Herceptin vs. observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (95% CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8% versus 78.2%) in favour of the Herceptin arm.

A final analysis was performed after a median follow-up of 8 years, which showed that 1 year Herceptin treatment is associated with a 24% risk reduction compared to observation only (HR=0.76, 95% CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8 year disease free survival rate of 6.4 percentage points in favour of 1 year Herceptin treatment.

In this final analysis, extending Herceptin treatment for a duration of two 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% versus 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%).

In the joint analysis of the NSABP B-31 and NCCTG N9831 studies, early breast cancer was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node-positive or HER2-positive and lymph node-negative with high risk features (tumour size > 1 cm and ER negative or tumour size > 2 cm, regardless of hormonal status). Herceptin was administered in combination with paclitaxel, following AC chemotherapy. Paclitaxel was administered as follows:

- intravenous paclitaxel - 80 mg/m^2 as a continuous IV infusion, given every week for 12 weeks, or
- intravenous paclitaxel - 175 mg/m^2 as a continuous IV infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

Table 5: 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 (N=1679)	AC→PH (N=1672)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Disease-free survival No. patients with event (%)	261 (15.5)	133 (8.0)	< 0.0001	0.48 (0.39, 0.59)
Distant Recurrence No. patients with event (%)	193 (11.5)	96 (5.7)	< 0.0001	0.47 (0.37, 0.60)
Death (OS event): No. patients with event (%)	92 (5.5)	62 (3.7)	0.014**	0.67 (0.48, 0.92)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab
* 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
Source: Table 15 Clinical Study Report: Joint Analysis of B-31 and N9831, 04 February 2006, Genentech, Inc.

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

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→PH 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 summarized in the following table:

Table 6: 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

In the BCIRG 006 study, HER2-positive, early breast cancer was limited to either lymph node-positive or high risk node-negative patients, defined as negative (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, oestrogen receptor and progesterone receptor negative, histologic and/or nuclear grade 2 - 3, or age < 35 years. Herceptin was administered either in combination with docetaxel, following AC chemotherapy (AC-DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenously (100 mg/m^2 as an IV infusion over 1 hour) given every 3 weeks for 4 cycles (day 2 of first docetaxel cycle, then day 1 of each subsequent cycle), or
- intravenously (75 mg/m^2 as an IV infusion over 1 hour) given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each cycle).

Docetaxel therapy was followed by carboplatin (at target AUC = 6 mg/ml/min) administered by IV infusion over 30-60 minutes repeated every 3 weeks for a total of 6 cycles.

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

Table 7: Overview of Efficacy Analyses AC→D versus AC→DH (BCIRG 006 study)

Parameter	AC→D (N=1073)	AC→DH (N=1074)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival No. patients with event	195	134	< 0.0001	0.61 (0.49, 0.77)
Distant recurrence No. patients with event	144	95	< 0.0001	0.59 (0.46, 0.77)
Overall Survival (Death) 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 8: Overview of Efficacy Analyses AC→D versus DCarbH (BCIRG 006 study)

Parameter	AC→D (N=1073)	DCarbH (N=1075)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
Distant recurrence No. patients with event	144	103	0.0008	0.65 (0.50, 0.84)
Death (OS event) No. patients with event	80	56	0.0182	0.66 (0.47, 0.93)

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

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of a 3-year disease-free survival rate, of 5.8 percentage points (86.7% versus 80.9%) in favour of the AC→DH (Herceptin) arm and 4.6 percentage points (85.5% versus 80.9%) in favour of the DCarbH (Herceptin) arm compared to AC→D.

For the secondary endpoint overall survival, treatment with AC→DH reduced the risk of death by 42% when compared to AC→D (hazard ratio 0.58 [95% CI: 0.40, 0.83] p = 0.0024, log-rank test) and the risk of death was reduced by 34% for patients treated with DCarbH compared to patients treated with AC→D (hazard ratio 0.66 [95% CI: 0.47, 0.93], p = 0.0182). In the BCIRG 006 study at the second interim analysis, 185 randomised patients had died: 80 patients (7.5%) in the AC→D arm, 49 patients (4.6%) in the AC→DH arm, and 56 patients (5.2%) in the DCarbH arm. The median duration of follow-up was 2.9 years in the AC→D arm and 3.0 years in both the AC→DH and DCarbH arms.

In the neoadjuvant-adjuvant treatment setting, Herceptin was evaluated in two phase 3 trials.

- Study MO16432 investigated a total of 10 cycles of neoadjuvant chemotherapy [an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H] concurrently with neoadjuvant-adjuvant Herceptin, or neoadjuvant chemotherapy alone, followed by adjuvant Herceptin for up to a total treatment duration of 1 year) in newly diagnosed locally advanced (Stage III) or inflammatory HER2-positive breast cancer patients.
- Study BO22227 was designed to demonstrate non-inferiority of treatment with Herceptin SC versus Herceptin IV based on co-primary PK 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 IV or Herceptin SC concurrently with chemotherapy (docetaxel followed by FEC), followed by surgery, and continued therapy with Herceptin SC or Herceptin IV as originally randomised for an additional 10 cycles for a total of one year of treatment .

The efficacy results from Study MO16432 are summarized in the table below. The median duration of follow-up in the Herceptin arm was 3.8 years.

Table 9: Overview of Efficacy Analyses (MO16432 study)

Parameter	Chemo + Herceptin (n=115)	Chemo only (n=116)	
Event-free survival No. patients with event	46	59	Hazard Ratio (95% CI) 0.65 (0.44, 0.96) p=0.0275
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

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

In Study BO22227 the analysis of the efficacy co-primary endpoint, 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 Herceptin 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 for the co-primary endpoint.

Table 10: Summary of pathological Complete Response (pCR) (BO22227 HannaH Study)

	Herceptin IV (N = 263)	Herceptin SC (N=260)
pCR (absence ofinvasive 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, refer to section 3.2 Pharmacokinetic Properties.

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]).

3.1.3 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) of patients receiving Herceptin SC Vial developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the Herceptin IV arm and 3 of 47 patients in the Herceptin SC arm.

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

3.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of trastuzumab given as a fixed 600 mg dose of Herceptin SC Vial administered q3w were compared to those of Herceptin IV given as a weight-based 8 mg/kg loading dose followed by 6 mg/kg maintenance doses administered q3w in the phase III study BO22227. The pharmacokinetic results for the co-primary PK endpoint, trastuzumab trough concentration at pre-dose Cycle 8, showed non-inferior trastuzumab exposure for the Herceptin SC arm with fixed 600 mg 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 600 mg 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: 43.9 µg/ml) as compared to 57.8 µg/ml standard deviation: 30.3 µg/ml). During the adjuvant treatment phase, at the pre-dose Cycle 13 time point, the mean observed trastuzumab trough 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 or Herceptin SC 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 a 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 3 days, with high variability (range 1-14 days). The mean C_{max} was, as expected 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 $AUC_{0\text{-}21\ days}$ 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 Herceptin IV and Herceptin SC, body weight had an influence on the pre-dose trastuzumab trough concentration and $AUC_{0\text{-}21days}$ values. In patients with body weight (BW), below 51 kg (10^{th} 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 (90^{th} percentile) the mean steady state AUC value 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 trastuzumab 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 nonlinear 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 or Herceptin SC administration in 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 (V_c) was 2.91 L. The nonlinear elimination Michaelis-Menten parameters were 11.9 mg/day and 33.9 mg/L for V_{max} and Km, respectively. The population predicted PK exposure parameter values (with 5^{th} - 95^{th} Percentiles) for the Herceptin SC 600mg q3w regimen in EBC patients is shown in Table 11 below.

Table 11: Population Predicted PK Exposure Value (with 5^{th} - 95^{th} Percentiles) for Herceptin SC 600 mg q3w Regimen in EBC patients

Primary tumor type and Regimen	Cycle	N	C_{min} (µg/mL)	C_{max} (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)

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.

3.2.1 Pharmacokinetics in Special Populations
Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out.

Renal Impairment
Detailed pharmacokinetic studies in patients with renal impairment have not been carried out. In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition

Geriatric Population
Age has been shown to have no effect on the disposition of trastuzumab (see section 2.2 Dosage and Administration).

3.3 NONCLINICAL SAFETY
Trastuzumab was well tolerated in rabbits (non-binding species) and cynomolgus monkeys (binding species) in single- and repeat-dose toxicity studies, respectively.

3.3.1 Carcinogenicity
No carcinogenicity studies have been performed to establish the carcinogenic potential of Herceptin.

3.3.2 Genotoxicity
No data to report.

3.3.3 Impairment of 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 Herceptin and have revealed no evidence of impaired fertility.

3.3.4 Reproductive Toxicity
Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin IV and have revealed no evidence of 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.

3.3.5 Other

Lactation

A study conducted in Cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin IV from days 120 to 150 of pregnancy demonstrated that trastuzumab is secreted in the milk postpartum. 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.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

This medicine should not be used after the expiry date (EXP) shown on the label.

Store vials at 2°C - 8°C (WHO Climatic Zones I – IV). Do not freeze. Store in the original package in order to protect from light.

The vials should not be kept more than 6 hours at ambient temperature (do not store above 30°C).

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Appropriate aseptic technique should be used.

The 600 mg/5 ml solution is a ready to use solution for injection which does not need to be diluted.

Herceptin should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Herceptin solution for injection is for single-use only.

Once transferred from the vial to the syringe, the medicine should be used immediately, from a microbiological point of view, since the medicine does not contain any antimicrobial-preservative. If not used immediately, preparation should take place in controlled and validated aseptic conditions. 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 diffused 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 (see section 4.1 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 5 ml.

Incompatibilities

No incompatibilities between Herceptin and polypropylene syringes have been observed.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

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.

4.3 PACKS

Vials 600 mg/5 ml…… 1

Medicine: keep out of reach of children

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