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Herceptin®

Trastuzumab

WARNING: Do not substitute Herceptin for or with trastuzumab emtansine (Kadcyla). In order to prevent medication errors, check the vial labels to ensure that the medicine being prepared and administered is Herceptin (trastuzumab) and not trastuzumab emtansine (Kadcyla).

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent.
ATC code: L01 XC03

1.2 Type of Dosage Form

Intravenous (IV) formulation (Herceptin IV): powder for concentrate for solution for infusion.
Subcutaneous (SC) formulation (Herceptin SC): solution for injection.

1.3 Route of Administration

Herceptin IV: Intravenous infusion.
Herceptin SC: Subcutaneous injection.

1.4 Sterile / Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

Active ingredient: trastuzumab.

Herceptin IV
Dosage Preparations: 440 mg multidose vial containing powder for concentrate for solution for infusion. Reconstituted Herceptin concentrate contains 21 mg/ml of trastuzumab.
Excipients: see 4.4 List of Excipients.

Herceptin SC:
Dosage Preparations: 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 (see 4.4 List of Excipients).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indications

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

a) as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease
b) in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease
c) in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with Herceptin. This indication is based on data from one Phase III trial which studied the use of Herceptin in combination with anastrozole (see 3.1.2 Clinical/ Efficacy Studies). Experience with other aromatase inhibitors is limited.

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) (see section 3.1).
- 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 therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 2.4 and 3.1).

Herceptin should only be used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

Herceptin IV only
Metastatic Gastric Cancer (MGC)
Herceptin in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herceptin should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, or IHC 3+, as determined by an accurate and validated assay.

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.

The safety and efficacy of alternating or switching between Herceptin and products that are biosimilar but not deemed interchangeable to Herceptin has not been established. Therefore, the benefit/risk of alternating or switching need to be carefully considered.

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 IV (see section 4. Pharmaceutical Particulars):
Herceptin IV is not to be used for subcutaneous administration and should be administered as intravenous infusion.

Do not administer as an intravenous push or bolus.

Metastatic breast cancer
Weekly schedule:
Loading dose: The recommended initial loading dose is 4 mg/kg body weight Herceptin IV administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see 2.6 Undesirable effects). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses: The recommended weekly dose of Herceptin IV is 2 mg/kg body weight. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see 2.6 Undesirable effects).

Administration in combination with an aromatase inhibitor
In the pivotal trial Herceptin IV and anastrozole were administered from day 1. There were no restrictions on the relative timing of Herceptin IV and anastrozole at administration (for dose, see the Product Information for anastrozole or other aromatase inhibitors).

3-weekly schedule:
Alternatively the following loading and subsequent doses are recommended for monotherapy and in combination with paclitaxel or an aromatase inhibitor.

Initial Herceptin IV loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

Early breast cancer
3-weekly schedule:
As a three-weekly regimen the recommended initial loading dose of Herceptin IV is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Alternative weekly schedule:
As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

Metastatic Gastric Cancer
3-weekly schedule:
Herceptin IV is administered at an initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the initial loading dose is well tolerated, the subsequent doses can be administered as a 30-minute infusion (See section 3.1 for chemotherapy combination dosing).

Herceptin SC (see section 4. Pharmaceutical Particulars):
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 every three weeks 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, the dose should be administered over 2-5 minutes every three weeks. In the pivotal trial (BO22227) Herceptin subcutaneous formulation was administered in the neoadjuvant-adjuvant setting in patients with early breast cancer. The preoperative chemotherapy regimen consisted of docetaxel (75mg/m^2) followed by FEC (5-FU, epirubicin and cyclophosphamide) at standard doses. See section 3.1.2 Clinical/ Efficacy Studies for chemotherapy combination dosing.

Duration of treatment
In clinical studies, patients with metastatic breast cancer or metastatic gastric cancer were treated with Herceptin until progression of disease or unmanageable toxicity. Patients with early breast cancer 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).

For instructions for use and handling refer to Section 4.2.

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.

Missed doses
If the patient has missed a dose of Herceptin IV by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent Herceptin IV maintenance doses be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.
If the patient has missed a dose of Herceptin IV by more than one week, a re-loading dose of Herceptin IV should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; 3-weekly regimen: 8 mg/kg) as soon as possible. Subsequent Herceptin IV maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively.
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.

2.2.1 Special Dosage Instructions

Geriatric use
Data suggest that the disposition of Herceptin is not altered based on age or serum creatinine (see Pharmacokinetics in special populations). In clinical trials, patients ≥ 65 years of age did not receive reduced doses of Herceptin. Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. However in a population pharmacokinetic analysis, age and renal impairment were not shown to affect Herceptin disposition.

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

2.3 Contraindications

Patients with known hypersensitivity to Herceptin, murine proteins, hyaluronidase or to any other component of the product. Patients with severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

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.

Currently no data from clinical trials are available on Herceptin re-treatment of patients with previous exposure to Herceptin in the adjuvant setting.

Infusion/Administration related reactions (IRRs/ARRs)
IRRs/ARRs are known to occur with the administration of Herceptin. IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions. Pre-medication may be used to reduce risk of occurrence of IRRs/ARRs.
Although serious IRRs/ARRs, including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, supraventricular tachyarrhythmia and urticaria were not reported in the clinical trial with the Herceptin subcutaneous formulation, caution should be exercised as these have been associated with the intravenous formulation. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms (see section 4.2). The majority of patients experienced resolution of symptoms and subsequently received further infusions of Herceptin. 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. They can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions to intravenous Herceptin have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions were associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Herceptin (see section 2.3).
Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms or pulmonary symptoms more than six hours after the start of the Herceptin infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

Pulmonary events
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 infusion related reaction (IRR) or with a delayed onset. In addition, cases of lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with Herceptin. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.
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.

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 Herceptin may persist in the circulation for up to 7 months after stopping Herceptin IV or Herceptin SC treatment (see 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, electrocardiogram (ECG) and echocardiogramor multigated acquisition scanning (MUGA) scan. In EBC, the following patients were excluded from the HERA trial, there are no data about the benefit-risk balance, and therefore treatment cannot be recommended in such patients:

- History of documented congestive heart failure
- High-risk uncontrolled arrhythmias
- Angina pectoris requiring a medicinal product
- Clinically significant valvular disease
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. Cardiac function should be further monitored during treatment (e.g. every 12 weeks). 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 diuretics, cardiac glycosides, 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 was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence was more marked when Herceptin was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months.
Risk factors for a cardiac event identified in 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/m2 (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.

Benzyl alcohol
Benzyl alcohol, used as a preservative in bacteriostatic water for injection in the 440 mg multidose vial, has been associated with toxicity in neonates and children up to 3 years old. When administering Herceptin to a patient with a known hypersensitivity to benzyl alcohol, Herceptin should be reconstituted with water for injection, and only one dose per Herceptin vial should be used. Any unused portion must be discarded.

2.4.2 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 administration-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 at least 7 months after treatment has concluded (see 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 fetus. In the postmarketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, 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 is available.

2.5.3 Lactation
It is not known whether Herceptin is secreted in human milk. As human 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, *Lactation*).

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 Herceptin disposition.

2.5.7 Hepatic Impairment
No data is available.

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.

Amongst the most serious and/or common adverse reactions reported in Herceptin usage (intravenous and subcutaneous formulations) to date are cardiac dysfunction, administration-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.
The safety profile of Herceptin subcutaneous formulation (evaluated in 298 and 297 patients treated with the intravenous and subcutaneous formulations respectively) from the pivotal trial in EBC was overall similar to the known safety profile of the intravenous formulation.

Severe adverse events (defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE grade ≥3) version 3.0) were equally distributed between both Herceptin formulations (52.3 % versus 53.5 % in the intravenous formulation versus subcutaneous formulation respectively).

Some adverse events / reactions were reported with a higher frequency for the subcutaneous formulation:
- Serious adverse events (most of which were identified because of in-patient hospitalisation or prolongation of existing hospitalisation): 14.1 % for the intravenous formulation versus 21.5 % for the subcutaneous formulation. The difference in SAE rates between formulations was mainly due to infections with or without neutropenia (4.4 % versus 8.1 %) and cardiac disorders (0.7 % versus 1.7 %);
- Post-operative wound infections (severe and/or serious): 1.7 % versus 3.0 % for the intravenous formulation versus subcutaneous formulation, respectively;
- Administration-related reactions: 37.2 % versus 47.8 % for the intravenous formulation versus subcutaneous formulation, respectively;
- Hypertension: 4.7 % versus 9.8 % for the intravenous formulation versus subcutaneous formulation respectively.

Tabulated list of adverse reactions with the intravenous formulation
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
	[+]Pneumonia	Common (<1 %)
	Cystitis	Common
	Herpes zoster	Common
	Skin infection	Common
	Erysipelas	Common
	Cellulitis	Common
	Sepsis	Uncommon
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
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Immune system disorders	Hypersensitivity	Common
	[+]Anaphylactic reaction	Not known
	[+]Anaphylactic shock	Rare
Metabolism and nutrition disorders	Weight Increased	Very common
	Weight Decreased/Weight Loss	Very common
	Decreased appetite	Very common
	Anorexia	Common
	Hyperkalaemia	Not known
Psychiatric disorders	Anxiety	Common
	Depression	Common
	Insomnia	Very common
	Thinking abnormal	Common
Nervous system disorders	[1]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Peripheral neuropathy	Common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Hypertonia	Very common
	Somnolence	Common
	Dysgeusia	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	Common
	[1]Cardiac flutter	Very common
	[+1]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	Ejection fraction decreased*	Very Common
	[+]Cardiac failure (congestive)	Common (2 %)
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Pericarditis	Not known
	Bradycardia	Not known
	Gallop rhythm present	Not known
Vascular disorders	Lymphoedema	Very common
	Hot flush	Very Common
	[+1] Hypotension	Common
	Hypertension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	[+1]Wheezing	Very common
	[+]Dyspnoea	Very common (14 %)
	Cough	Very Common
	Epistaxis	Very Common
	Oropharyngeal pain	Very Common
	Rhinorrhoea	Very Common
	Asthma	Common
	Lung disorder	Common
	Pneumonia	Common
	[+]Pleural effusion	common
	Pneumonitis	Uncommon
	[+]Pulmonary fibrosis	Not known
	[+]Respiratory distress	Not known
	[+]Respiratory failure	Not known
	[+]Lung infiltration	Not known
	[+]Acute pulmonary oedema	Not known
	[+]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
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Haemorrhoids	Common
	Constipation	Very common
	Stomatitis	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
	[1] Swelling face	Very common
	Nail disorder	Very common
	Acne	Common
	Alopecia	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	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
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Pain in extremity	Common
	Neck pain	Common
Renal and urinary conditions	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known
	Renal failure	Not known
Pregnancy, puerperium and perinatal disorders	Oligohydramnios	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza like illness	Very common
	Infusion/Administration related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Mucosal inflammation	Very common
	Oedema	Common
	Injection site pain**	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common
	Contusion	Common

[+] 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.
* Observed with combination therapy following anthracyclines and combined with taxanes
** 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.
Note: Specific percentage frequencies have been provided in brackets for terms that have been reported in association with a fatal outcome with the frequency designation 'common' or 'very common'. The specific percentage frequencies relate to total number of these events, both fatal and non-fatal.

The following adverse reactions were reported in pivotal clinical trials with a frequency of ≥ 1/10 in either treatment arm (in HERA, BO16348 ≥ 1% at 1 year) and with no significant difference between the Herceptin-containing arm and the comparator arm: lethargy, hypoaesthesia, pain in extremity, oropharyngeal pain, conjunctivitis, lymphoedema, weight increased, nail toxicity, musculoskeletal pain, pharyngitis, bronchitis, chest discomfort, abdominal pain upper, gastritis, stomatitis, vertigo, hot flush, hypertension, hiccups, palmar-plantar erythrodysaesthesia syndrome, breast pain, onychorrhexis, dyspnoea exertional and dysuria.

Additional information for selected adverse drug reactions
Infusion/Administration-related reactions (IRRs) 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 Herceptin clinical trials (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 Herceptin 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 Herceptin 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 Herceptin containing arm compared to 5 to 6% in the comparator arm.

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

In the neoadjuvant-adjuvant EBC treatment setting (BO22227), the rates of IRRs/ARRs were in line with the above and was 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 arm, respectively during the treatment phase. There were no grade 4 or 5 IRRs/ARRs.

Anaphylactoid reactions were observed in isolated cases.

Serious Pulmonary Events
Single cases of pulmonary infiltrates, pneumonia, pulmonary fibrosis, pleural effusion, respiratory distress, acute pulmonary oedema, acute respiratory distress syndrome (ARDS) and respiratory insufficiency have been reported rarely. These events have been reported rarely with fatal outcome (see Section 2.4).

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 Herceptin given in combination with chemotherapy the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in patients who were administered Herceptin sequentially 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 (Herceptin) was estimated at 3.2%, compared with 0.8% in AC→P treated patients. No increase in the cumulative incidence of cardiac events was seen with further follow-up at 5 years.

At 5.5 years, the rates of symptomatic cardiac or LVEF events were 1.0%, 2.3%, and 1.1% in the AC→D (doxorubicin plus cyclophosphamide, followed by docetaxel), AC→DH (doxorubicin plus cyclophosphamide, followed by docetaxel plus Herceptin), and DCarbH (docetaxel, carboplatin and Herceptin) treatment arms, respectively. For symptomatic CHF (NCI-CTC Grade 3 - 4), the 5-year rates were 0.6%, 1.9%, and 0.4% in the AC→D, AC→DH, and DCarbH treatment arms, respectively. The overall risk of developing symptomatic cardiac events was low and similar for patients in 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 ≥ 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 Herceptin), 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 decrease 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.

Metastatic Gastric Cancer
In BO18255 study, at screening, the median LVEF value was 64% (range 48 %-90 %) in the Fluoropyrimidine/Cisplatin arm (FP) and 65 % (range 50 %-86 %) in the Herceptin IV plus Fluoropyrimidine/Cisplatin arm (FP+H).

The majority of the LVEF decreases noted in BO18255 study were asymptomatic, with the exception of one patient in the Herceptin-containing arm whose LVEF decrease coincided with cardiac failure.

Table 2 Summary of LVEF Change from baseline (BO18255 study)

LVEF Decrease: Lowest Post-screening Value	Herceptin/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)
*LVEF decrease of ≥ 10% to a value of < 50%	4.6%	1.1%
Absolute Value < 50%	5.9%	1.1%
*LVEF decrease of ≥ 10% to a value of ≥ 50%	16.5%	11.8%

*Only includes patients whose method of assessment at that visit is the same as at their initial assessments (FP, n = 187 and FP+H, n = 237)

Table 3 Cardiac Adverse Events (BO18255 study)

	Fluoropyrimidine/Cisplatin (N = 290) (% of patients in each treatment arm)	Herceptin/Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)
Total Cardiac Events	6%	6%
≥ Grade 3 NCI CTCAE v3.0	*3%	**1%

* 9 patients experienced 9 Events
** 4 patients experienced 5 Events

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

Haematological toxicity
Breast Cancer
Haematological toxicity was infrequent following the administration of Herceptin as a single agent in the metastatic setting, WHO Grade 3 leucopenia, 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). Note that this is likely to be an underestimate since docetaxel alone at a dose of 100mg/m^2 is known to result in neutropenia in 97 % of patients, 76% grade 4, based on nadir blood counts. 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 trial, 0.4% of Herceptin-treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

Advanced Gastric Cancer
The most frequently reported AEs, of Grade ≥ 3 occurring with an incidence rate of at least 1% by trial treatment, that were categorised under the Blood and Lymphatic System Disorders SOC are shown below:

Table 4 Frequently reported AEs grade ≥ 3 in blood and lymphatic system disorders SOC

	Fluoropyrimidine/ Cisplatin (N = 290) (% of patients in each treatment arm)	Herceptin/ Fluoropyrimidine/ Cisplatin (N = 294) (% of patients in each treatment arm)
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile neutropenia	3%	5%
Thrombocytopenia	3%	5%

The total percentage of patients who experienced an AE of ≥ grade 3 NCI-CTCAE v3.0 that has been categorised under this SOC were 38% in the FP arm and 40% in the FP + H arm.

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

Hepatic and renal toxicity
Breast Cancer
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 (7 % compared with 15 %). No WHO Grade 3 or 4 renal toxicity was observed.

Metastatic Gastric Cancer
In BO18255 study no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

NCI-CTCAE (version 3.0) grade ≥3 renal toxicity was not significantly higher in patients receiving Herceptin IV + FP than those in the FP arm (3% and 2% respectively).

NCI-CTCAE (version 3.0) grade ≥3 adverse event in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported AE and was not significantly higher in patients receiving Herceptin IV + FP than those in the FP arm (1% and < 1% respectively).

Diarrhoea
Breast Cancer
Of patients treated with Herceptin IV as a single agent 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 trial, 8 % of Herceptin-treated patients experienced diarrhea during the first year of treatment.

Metastatic Gastric Cancer
In BO18255 study, 109 patients (37 %) participating in the Herceptin-containing treatment arm versus 80 patients (28 %) in the comparator arm experienced any grade diarrhoea. Using NCI CTCAE severity criteria, the percentage of patients experiencing grade ≥ 3 diarrhoea was 4 % in the FP arm vs 9 % in the FP+H arm.

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.

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

2.6.2 Postmarketing Experience
The following adverse drug reactions have been identified from postmarketing experience with Herceptin (Table 5).

Table 5 Adverse Reactions reported in the post marketing setting

System organ class	Adverse reaction
Blood and lymphatic system disorders	Hypoprothrombinaemia 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
	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 6 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 6 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 disorders	Gastritis
	Pancreatitis
Musculoskeletal and connective tissue disorders	Musculoskeletal pain
Renal and urinary disorders	Dysuria
Reproductive system and breast disorders	Breast pain
General disorders and administration site conditions	Chest discomfort

2.7 Overdose
Herceptin IV
There is no experience with overdose in human clinical trials. Single doses higher than 10 mg/kg have not been tested.

Herceptin SC
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.

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 trastuzumab 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 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

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

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

Herceptin has been shown, both in *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. *In vitro*, Herceptin-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

Efficacy

MBC

Herceptin monotherapy has been used in clinical trials for patients with metastatic breast cancer who have tumors 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 tumors that overexpress HER2.

Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m² 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 HER-2, results in an overall tumor 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 HER-2 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 vs. 3.0 months). Tumor response and one year survival rate are also increased for Herceptin in combination with paclitaxel versus paclitaxel alone.

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. estrogen-receptor (ER) and/or progesterone-receptor (PR)) positive postmenopausal 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.

3-weekly dosing in MBC

The efficacy results from the non-comparative monotherapy and combination therapy studies are summarised in the following table:

Table 7

Parameter	Monotherapy		Combination Therapy
	Herceptin[1] N=105	**Herceptin[2] N=72**	**Herceptin plus paclitaxel[3] N=32**
Response rate (95%CI)	24% (15 - 35)	27% (14 - 43)	59% (41-76)
Median duration of response (months) (range)	10.1 (2.8-35.6)	7.9 (2.1-18.8)	10.5 (1.8-21)
Median TTP (months) (95%CI)	3.4 (2.8-4.1)	7.7 (4.2-8.3)	12.2 (6.2-ne)
Median Survival (months) (95%CI)	ne	ne	ne

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.
1. Study WO16229: loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule
2. Study MO16982: loading dose 6mg/kg weekly x 3; followed by 6mg/kg 3-weekly schedule
3. BO15935

EBC

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

- Study BO16348 study was designed to compare one year 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 B-31 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 study 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 Study BO16348 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 8 Efficacy Results BO16348 study: Results at 12months* 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 randomized 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/m² as a continuous IV infusion, given every week for 12 weeks, or
- intravenous paclitaxel - 175 mg/m² as a continuous IV infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

Table 9 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: Herceptin
* 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→P H group). Treatment with AC→P H 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→P H arm and 79.4% in the AC→P arm, an absolute benefit of 7.4% (95% CI 4.9%, 10.0%).

The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in the following table:

Table 10 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: Herceptin

In the BCIRG 006 study, HER-2 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, estrogen 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/m² 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/m² 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 11 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 Herceptin; CI = confidence interval

Table 12 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 Herceptin; 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 randomized 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, a multicenter randomised trial, was designed to 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. The clinical utility of concurrent administration of Herceptin with neoadjuvant chemotherapy including both an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H, followed by adjuvant Herceptin, up to a total treatment duration of 1 year) as follow:

- Doxorubicin 60mg/m^2 and paclitaxel 150 mg/m^2, administered 3-weekly for 3 cycles, which was followed by
- Paclitaxel 175 mg/m^2 administered 3-weekly for 4 cycles, which was followed by
- CMF on day 1 and 8 every 4 weeks for 3 cycles which was followed after surgery by
- additional cycles of adjuvant Herceptin (to complete 1 year of treatment)

The study 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, or neoadjuvant chemotherapy alone.

Table 13 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
Overall survival No. patients with event	22	33	Hazard Ratio (95% CI) 0.59 (0.35, 1.02) p=0.0555

* 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 % vs 52 %) in favour of the Herceptin arm.

Study BO22227 was designed to demonstrate non-inferiority of treatment with Herceptin SC versus Herceptin IV based on co-primary PK and efficacy endpoints (Herceptin 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.

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 14 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 Herceptin 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]).

Metastatic Gastric Cancer
Herceptin has been investigated in one randomised, open-label phase III trial BO18255 in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:
- capecitabine - 1000 mg/m^2 orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle)

or
- intravenous 5-fluorouracil - 800 mg/m^2/day as a continuous i.v. infusion over 5 days, given every 3 weeks for 6 cycles (days 1 to 5 of each cycle)

Either of which was administered with:
- cisplatin - 80 mg/m^2 every 3 weeks for 6 cycles on day 1 of each cycle.

The efficacy results from study BO18225 are summarized in the following table:

Table 15 Summary of Efficacy (from study BO18255 study)

Parameter	FP N = 290	FP +H N = 294	HR (95% CI)	p-value
Overall Survival, Median months	11.1	13.8	0.74 (0.60-0.91)	0.0046
Progression-Free Survival, Median months	5.5	6.7	0.71 (0.59-0.85)	0.0002
Time to Disease Progression, Median months	5.6	7.1	0.70 (0.58-0.85)	0.0003
Overall Response Rate, %	34.5%	47.3%	1.70[a] (1.22, 2.38)	0.0017
Duration of Response, Median months	4.8	6.9	0.54 (0.40-0.73)	< 0.0001

FP + H: Fluoropyrimidine/cisplatin + Herceptin
FP: Fluoropyrimidine/cisplatin
[a] Odds ratio

Patients were recruited to the trial who were previously untreated for HER2-positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction not amenable to curative therapy. The primary endpoint was overall survival which was defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis a total of 349 randomized patients had died: 182 patients (62.8 %) in the control arm and 167 patients (56.8 %) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

Post-hoc subgroup analyses indicate that positive treatment effects are limited to targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ or IHC 3+). The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR 0.65 (95 % CI 0.51-0.83) and the median progression free survival was 5.5 months versus 7.6 months, HR 0.64 (95 % CI 0.51-0.79) for FP versus FP + H, respectively. For overall survival, the HR was 0.75 (95% CI 0.51-1.11) in the IHC 2+/FISH+ group and the HR was 0.58 (95% CI 0.41-0.81) in the IHC 3+/FISH+ group.

In a method comparison study a high degree of concordance (>95%) was observed for SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

In an exploratory subgroup analysis performed in the BO18255 trial there was no apparent benefit on overall survival with the addition of Herceptin in patients with ECOG PS 2 at baseline [HR 0.96 (95% CI 0.51-1.79)], non-measurable [HR 1.78 (95% CI 0.87-3.66)] and locally advanced disease [HR 1.20 (95% CI 0.29-4.97)].

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

The population predicted PK exposures (with 5th - 95th Percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for breast cancer and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 16 (Cycle 1) and Table 17 (steady-state) below.

Table 16 Population Predicted Cycle 1 PK Exposure Values (with 5th - 95th Percentiles) for IV Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumor type	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC (µg.day/mL)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	29.4 (5.8 - 59.5)	178 (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 17 Population Predicted Steady State PK Exposure Values (with 5th - 95th Percentiles) for Herceptin IV Dosing Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumor type	N	Cmin,ss (µg/mL)	Cmax,ss (µg/mL)	AUCss (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	47.4 (5 - 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

Herceptin SC
The pharmacokinetics of Herceptin 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, Herceptin trough concentration at pre-dose Cycle 8, showed non-inferior Herceptin 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 Herceptin 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 Herceptin 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 Herceptin 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 Herceptin trough concentrations with Herceptin SC tended to increase slightly up to Cycle 13. The mean observed Herceptin trough concentration at 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_{0-21} 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 Herceptin trough concentration and AUC_{0-21} days values. In patients with body weight (BW), below 51 kg (10th percentile), the mean steady state AUC value of Herceptin 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) 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 Herceptin concentration and AUC_{0-21} days values that were comparable to or higher than those observed in patients who received Herceptin IV. Multiple logistic regression analyses showed no correlation of Herceptin 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 Herceptin 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 Herceptin 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 5th - 95th Percentiles) for the Herceptin SC 600 mg q3w regimen in EBC patients is shown in table 18 below.

Table 18 Population Predicted PK Exposure Values (with 5th - 95th Percentiles) for Herceptin SC 600 mg SC q3w Regimen in EBC patients

Primary tumor 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)

Herceptin washout
Herceptin 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 Herceptin 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 geriatric population 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 Herceptin disposition.

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

3.3 Nonclinical Safety
Herceptin IV
Herceptin was well tolerated in mice (non-binding species) and cynomolgus monkeys (binding species) in single- and repeat-dose toxicity studies of up to 6 months duration, respectively. There was no evidence of acute or chronic toxicity identified.

Herceptin SC
Herceptin was well tolerated in rabbits (non-binding species) and cynomolgus monkeys (binding species) in single-dose 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 IV 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 fetus. 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 Herceptin during the early (days 20-50 of gestation) and late (days 120-150 of gestation) fetal 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 Herceptin is secreted in the milk postpartum. The exposure to trastuzumab in utero and the presence of Herceptin 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. It is not known whether Herceptin is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during Herceptin therapy and for 6 months after the last dose of Herceptin.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Herceptin IV

Store vials at 2°C–8°C.

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

440 mg vials (multidose vials)

Shelf-life of the reconstituted solution

Reconstituted solutions made with bacteriostatic water for injection for the 440 mg vial of Herceptin, as supplied, are stable for 28 days when stored refrigerated at 2°C-8°C. The reconstituted solution contains preservative and is therefore suitable for multiple use. Any remaining reconstituted solution should be discarded after 28 days.

When administering Herceptin to a patient with a known hypersensitivity to benzyl alcohol (see section 2.4 Warnings and Precautions), Herceptin should be reconstituted with sterile water for injection. In case Herceptin is reconstituted with sterile water for injection, only one dose per Herceptin vial should be used. The reconstituted solution should be used immediately. Any unused portion must be discarded.

Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product

The infusion solution (0.9% sodium chloride infusion solution) containing the reconstituted product is physically and chemically stable for 24 hours at 2°C - 8°C.

From a microbiological point of view, the Herceptin infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use is the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Herceptin SC Vial

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

The vials should **not be kept for 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.

Herceptin IV

Reconstitution

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

Instructions for Reconstitution - 440 mg vial:

Reconstitution is to be performed with bacteriostatic water for injection, containing 1.1% benzyl alcohol, as supplied. This yields a solution for multiple use, containing 21 mg/mL Herceptin, at a pH of approximately 6.0. Use of other reconstitution solvents should be avoided except for sterile water for injection in case of a patient with a known hypersensitivity to benzyl alcohol.

1. Using a sterile syringe, slowly inject 20 ml of Bacteriostatic Water for Injection into the vial containing the lyophilized Herceptin, directing the stream into the lyophilized cake.
2. Swirl vial gently to aid reconstitution. DO NOT SHAKE!

Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Herceptin results in a colorless to pale yellow transparent solution and should be essentially free of visible particles.

Dilution of the reconstituted solution

Determine the volume of the solution required:

- *based on a loading dose of 4 mg Herceptin/kg body weight, or a subsequent weekly dose of 2 mg Herceptin/kg body weight:*

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

- *based on a loading dose of 8 mg Herceptin/kg body weight, or a subsequent 3 weekly dose of 6 mg Herceptin/kg body weight:*

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

The appropriate amount of solution should be withdrawn from the vial using a sterile needle and syringe and added to an infusion bag containing 250 ml of 0.9% sodium chloride. Dextrose (5%) solution should not be used (see Incompatibilities). The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral drug products should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately (see section 4.1 Storage).

Incompatibilities

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

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

Herceptin should not be mixed or diluted with other drugs.

Herceptin SC

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 28 days at 2°C - 8°C and for 6 hours (cumulative time in the vial and the syringe) at ambient temperature (do not store above 30°C) in diffused daylight (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 procedures 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).

Local requirements should be followed for the disposal process of unused/expired medicines or waste material.

4.3 Packs

Herceptin IV

440 mg vial

1 pack containing 1 vial with 440 mg trastuzumab
+ 1 vial with 20 ml bacteriostatic water for injection containing benzyl alcohol

Herceptin SC

1 pack containing 1 vial of Herceptin with 600 mg trastuzumab

4.4 List of Excipients

Herceptin IV

L-histidine
L-histidine hydrochloride
α, α-trehalose dihydrate
Polysorbate 20
Water for injection

Herceptin SC

Recombinant human hyaluronidase (rHuPH20)
L-histidine
L-histidine hydrochloride monohydrate
α, α-trehalose dihydrate
L-methionine
Polysorbate 20
Water for injection

Medicine: keep out of reach of children

Current at February 2021

Product Owner: F. Hoffmann-La Roche Ltd, Basel, Switzerland