Herceptin®

Trastuzumab

Composition

Active ingredient

Trastuzumab (manufactured by recombinant DNA technology using CHO [Chinese hamster ovary] cells).

Excipients

L-histidine hydrochloride, l-histidine, trehalose, polysorbate, water for injection

Pharmaceutical form and quantity of active substance per unit

1 single-injection vial of Herceptin contains:

a white lyophilized powder for preparation of a concentrated solution for infusion with 150 mg trastuzumab.

Reconstituted Herceptin concentrated solution for infusion (water for injections not supplied) contains 21 mg/ml trastuzumab.

1 multiple-injection vial of Herceptin contains:

a white lyophilized powder for preparation of a concentrated solution for infusion with 440 mg trastuzumab.

1 vial of solvent contains:

water for injections containing 1.1% benzyl alcohol preservative (bacteriostatic water for injections).

Reconstituted Herceptin concentrated solution contains 21 mg/ml trastuzumab.

Indications and potential uses

Breast cancer

Before the start of Herceptin therapy, overexpression of HER2 in the tumor tissue of the patient must have been demonstrated either by immunohistochemistry at a 3+ level or by molecular biology (detection of HER2 gene amplification using fluorescence *in situ* hybridization [FISH] or chromogenic *in situ* hybridization [CISH]).

Metastatic breast cancer

Herceptin is indicated for the treatment of HER2-overexpressing metastatic breast cancer:

a) as single-agent therapy in patients who have previously received one or more chemotherapy regimens for their metastatic disease,

b) in combination with paclitaxel or docetaxel in patients who have not yet received chemotherapy for their metastatic disease,

c) in combination with an aromatase inhibitor for the treatment of post-menopausal patients with hormone-receptor-positive metastatic breast cancer and who have not yet received chemotherapy for their metastatic disease.

No data are available on patients given Herceptin as adjuvant therapy in early breast cancer.

Early breast cancer

Herceptin is indicated for the treatment of patients with HER2-positive early breast cancer:

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

Metastatic gastric cancer or cancer of the gastroesophageal junction
Herceptin in combination with capecitabine or intravenous 5-fluorouracil and cisplatin is indicated for the treatment of patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received chemotherapy for their metastatic disease.

Herceptin should only be used in patients with metastatic gastric cancer whose tumors overexpress HER2 defined by IHC2+ and confirmed by a positive FISH+ or silver *in situ* hybridization (SISH) result, or by IHC3+ determined in a validated test.

Dosage and administration

It is mandatory for Herceptin therapy only to be initiated under the supervision of a physician experienced in the treatment of cancer patients.

A validated HER2 test is mandatory before initiating therapy (see *Properties and effects*).

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).

Metastatic breast cancer – weekly schedule

Herceptin should be administered by intravenous infusion. Do not administer as an intravenous bolus injection.

The following loading and maintenance doses are recommended both for monotherapy and for combination with chemotherapy:

Monotherapy

Initial dose

The recommended initial dose is 4 mg Herceptin/kg body weight administered as a 90-minute intravenous infusion.

Subsequent doses

The recommended weekly maintenance dose is 2 mg Herceptin/kg body weight. If the loading dose was well tolerated, this can be administered as a 30-minute infusion.

Combination therapy with paclitaxel or docetaxel

The dosage of Herceptin in combination therapy is the same as that in monotherapy. Paclitaxel or docetaxel is administered on the day following the first dose of Herceptin treatment. Thereafter, they can be administered at 3-weekly intervals immediately after the subsequent Herceptin doses, provided that preceding Herceptin administration was well tolerated. For the dosage of paclitaxel or docetaxel, see the relevant prescribing information.

Administration in combination with an aromatase inhibitor

The dosage of Herceptin in therapy based on this combination is the same as that in monotherapy. Herceptin and anastrozole were administered on day 1 in the pivotal study concerned. No restriction has been set on the relative durations of administration of these two therapeutic products when used in combination (see the relevant prescribing information for the dosage of anastrozole). In patients receiving tamoxifen, treatment with tamoxifen must be discontinued at least one day before starting combination therapy.

Metastatic breast cancer – 3-weekly schedule

As an alternative to weekly administration, the following 3-weekly schedule is recommended in monotherapy as well as in combination with paclitaxel, docetaxel or an aromatase inhibitor.

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

Early breast cancer

For the following treatment regimens, Herceptin is given until recurrence or for a total of 52 weeks.

Weekly dosing

With weekly administration the initial dose is 4 mg/kg body weight, followed by 2 mg/kg body weight every week.

Three-weekly dosing

With 3-weekly administration the recommended initial dose of Herceptin is 8 mg/kg body weight. The recommended maintenance dose of Herceptin at 3-weekly intervals is 6 mg/kg body weight, beginning 3 weeks after the initial dose.

When Herceptin is continued alone following combination with chemotherapy, 6 mg/kg is given at 3-weekly intervals.

How Herceptin was investigated in the studies in combination with chemotherapy can be seen from the section on clinical studies in early breast cancer under *Properties and effects*.

Advanced gastric cancer or cancer of the gastroesophageal junction – 3-weekly schedule

The initial dose is 8 mg/kg body weight, followed 3 weeks later by 6 mg/kg body weight. The subsequent 6 mg/kg Herceptin doses are repeated at 3-weekly intervals. Treatment is administered by infusion over approximately 90 minutes. If the initial dose was well tolerated, the maintenance dose can be administered as a 30-minute infusion.

Breast cancer (early or metastatic), metastatic gastric cancer or cancer of the gastroesophageal junction

Duration of use

Patients with metastatic breast cancer, metastatic gastric cancer or cancer of the gastroesophageal junction should be treated with Herceptin until disease progression. Patients with early breast cancer should be treated for 1 year or until disease recurrence, whichever occurs first. Treatment of early breast cancer beyond 1 year is not recommended (see *Properties and effects, Clinical data*).

Missed doses

If the patient has missed a dose of Herceptin by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg body weight; 3-weekly regimen: 6 mg/kg body weight) should be given as soon as possible. Do not wait until the next planned cycle. Subsequent Herceptin maintenance doses should be given 7 to 21 days later according to the weekly or 3-weekly schedule, respectively.

If the patient has missed a dose of Herceptin by more than one week, a reloading dose of Herceptin should be given over approximately 90 minutes (weekly regimen: 4 mg/kg body weight; 3-weekly regimen: 8 mg/kg body weight) as soon as possible. Subsequent Herceptin maintenance doses (weekly regimen: 2 mg/kg; 3-weekly regimen 6 mg/kg) should be given 7 or 21 days later according to the weekly schedule, respectively.

Dose reduction

No reductions in the dose of Herceptin were made in 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 special instructions for dose reductions or prolongation of intervals in chemotherapy are to be followed.

Elderly patients

Given the available data, it is probable that the availability of Herceptin is not age-dependent (see *Pharmacokinetics, Pharmacokinetics in special patient groups*).

In clinical trials, elderly patients did not receive reduced doses of Herceptin.

Use in children and adolescents

The use and safety of Herceptin in children and adolescents have not yet been investigated.

Contraindications

Herceptin is contraindicated in patients with known hypersensitivity to trastuzumab, hamster (CHO) cell protein or any other product or solvent excipient.

Herceptin and anthracycline should not be given concurrently in the metastatic breast cancer or adjuvant treatment setting. In the neoadjuvant treatment setting concurrent administration of Herceptin and anthracyclines should be used with caution and only in chemotherapy-naïve patients. Herceptin is also contraindicated in patients who suffer from dyspnea at rest due to advanced malignancy or comorbidities.

Warnings and precautions

In order to improve the traceability of biologicals, the trade name Herceptin must be clearly entered in the patient's record. Replacement by another biological requires the consent of the prescribing physician. Data in this prescribing information relate only to Herceptin.

Herceptin for multiple injections (benzyl alcohol)

Benzyl alcohol, the preservative used in the supplied bacteriostatic water for injections, has caused toxic reactions in neonates and children up to 3 years of age. When administering Herceptin to patients with known hypersensitivity to benzyl alcohol, the lyophilized powder for the concentrate for solution for infusion should be reconstituted exclusively with water for injection and only a single dose of Herceptin should be withdrawn from the vial, any unused portion being discarded.

The sterile water for injections used for reconstitution of a concentrated solution for infusion for single-dose administration of 150 mg trastuzumab contains no benzyl alcohol.

Infusion-related reactions

Sometimes serious infusion-related reactions (typical symptoms e.g. dyspnea, hypotension, nausea, fever, bronchospasm, tachycardia, reduced oxygen saturation, urticaria and rash) have been observed in patients during treatment with Herceptin. These adverse effects can occur as part of an infusion-related reaction or as a delayed reaction. Premedication may be given to reduce the risk of occurrence of infusion-related reactions.

Patients should be observed for infusion-related reactions. Interruption of the infusion may help to control such symptoms. The infusion can be resumed when symptoms abate. These symptoms can be treated with an analgesic/antipyretic such as pethidine or paracetamol, or an antihistamine such as diphenhydramine. Severe reactions have been managed successfully with symptomatic therapy such as the administration of oxygen, beta-agonists and corticosteroids. In rare cases, these reactions are associated with a potentially fatal clinical course. Patients who suffer dyspnea at rest due to advanced malignancy or comorbidities may be at increased risk for a fatal infusion reaction. Therefore, these patients should not be treated with Herceptin (see *Contraindications*). Infusion-related reactions may sometimes be clinically difficult to distinguish from hypersensitivity reactions.

Cardiotoxicity

General information

Patients treated with Herceptin are at increased risk of developing NYHA class II–IV congestive heart failure or asymptomatic cardiac dysfunction. This has been observed during treatment with Herceptin alone or in combination with taxanes following anthracycline (doxorubicin or epirubicin) therapy. Heart failure may be moderate to severe and lead to death (see *Undesirable effects*). Caution should be exercised in treating patients with increased cardiac risk (e.g. hypertension, documented coronary artery disease, congestive heart failure, diastolic dysfunction, older age).

Herceptin and anthracyclines should not be given concurrently in the metastatic breast cancer or adjuvant treatment setting. In the neoadjuvant treatment setting concurrent administration of Herceptin and anthracyclines should be used with caution and only in chemotherapy-naïve patients (see *Contraindications*). The maximum cumulative dose of low-dose anthracycline therapy should not exceed 180 mg/m^2 (doxorubicin) or 360 mg/m^2 (epirubicin). If patients have been treated concurrently with low-dose

anthracyclines and Herceptin in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. Clinical experience in the neoadjuvant-adjuvant setting is limited in patients above 65 years of age.

Most symptomatic cardiac side effects occurred within the first 18 months, regardless of the regimen employed. The cumulative incidence did not increase after 3 years. Most cases of left ventricular dysfunction improved on discontinuation of Herceptin therapy and/or initiation of cardiac medication.

Population pharmacokinetic- model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping treatment with intravenously or subcutaneously administered Herceptin (see Pharmacokinetics). Patients who receive anthracyclines after stopping Herceptin are probably also at increased risk of cardiotoxicity.

If possible, anthracycline-based therapy should be avoided for up to 7 months after stopping Herceptin.

Before treatment with Herceptin, especially if preceded by anthracycline therapy, patients should undergo cardiac assessment including history and physical examination, ECG, echocardiogram and/or MUGA scan. Monitoring for early detection of patients developing cardiac dysfunction should be undertaken by cardiac assessment, as performed at baseline, 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 be repeated yearly up to 5 years from the last administration of Herceptin, or longer if a continuous decrease of left ventricular ejection fraction (LVEF) is observed.

If LVEF decreases by 10 or more points from baseline or falls below 50%, Herceptin should be suspended and LVEF reassessed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if clinically significant heart failure developed, discontinuation of Herceptin should be considered as a matter of urgency, unless the benefits for the patient are deemed to outweigh the risks. Patients who develop asymptomatic cardiac dysfunction should be monitored more frequently (e.g. every 6–8 weeks). If patients show a sustained decrease in left ventricular function but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Herceptin therapy is apparent.

The safety of resumption or continuation of Herceptin in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic heart failure develops during Herceptin therapy, it should be treated with the standard medications for heart failure. Most patients in the pivotal trials developing heart failure or asymptomatic cardiac dysfunction improved on treatment with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and beta-blockers.

Adjuvant and neoadjuvant treatment

Patients with a history of myocardial infarction, angina pectoris requiring medication, history of or present congestive heart failure (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.

In patients with early breast cancer an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin was administered after anthracycline-containing chemotherapy compared to treatment with a non-anthracycline regimen such as docetaxel or carboplatin. The incidence was greater when Herceptin was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the treatment regimen used, most symptomatic cardiac events occurred within the first 18 months.

The risk factors for cardiac events were 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 antihypertensive 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).

Pulmonary reactions

Severe pulmonary adverse effects have been reported on Herceptin therapy in the post-marketing phase (see *Undesirable effects*). These events have occasionally been fatal and may occur as part of an infusion-related reaction or with a delayed onset. In addition, the following reactions have also been reported: interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema and respiratory failure.

Risk factors associated with interstitial lung disease include prior or concomitant administration of other anti-neoplastic therapies known to be associated with interstitial lung disease such as taxanes, gemcitabine, vinorelbine and radiotherapy. Patients experiencing dyspnea 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.

Interactions

Pharmacokinetic/pharmacodynamic interactions

There have been no formal 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 in which Herceptin was administered at therapeutic doses in combination with docetaxel, carboplatin or anastrozole, there was no change in the pharmacokinetics of either these drugs or trastuzumab.

Concentrations of paclitaxel and doxorubicin (and of their major metabolites 6-α-hydroxyl-paclitaxel [POH] and doxorubicinol [DOL]) were unchanged in the presence of trastuzumab.

However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, 7-deoxy-13-dihydrooxorubicinone (D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite are 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 suggest that exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggest that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or of capecitabine plus trastuzumab.

Pregnancy and lactation

Pregnancy

Herceptin should not be administered during pregnancy unless the potential benefit to the mother outweighs the risk incurred by the fetus.

In the post-marketing setting, cases of fetal renal growth (e.g. renal hypoplasia) and/or functional impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin. Women of childbearing age should use effective contraception during treatment with Herceptin and for 7 months after treatment has concluded (see *Pharmacokinetics*). Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Herceptin, or if a patient becomes pregnant while receiving Herceptin or within 7 months following the last dose of Herceptin, close monitoring by a multidisciplinary team is indicated.

Whether Herceptin can impair reproductive capacity when administered to pregnant women is unknown.

Reproduction studies were conducted in cynomolgus monkeys at doses up to 25 times the weekly maintenance dose of 2 mg/kg body weight recommended in humans. Placental transfer of trastuzumab was observed during the early (days 20–50 of gestation) and late (days 120–150 of gestation) fetal development period. However, these studies revealed no evidence of fetotoxicity or impaired fertility.

Lactation

A study conducted in lactating cynomolgus monkeys at doses 25 times the weekly maintenance dose of 2 mg/kg body weight recommended in humans demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development

from birth to one month of age. It is not known whether trastuzumab is secreted in human milk. Nevertheless, as human IgG is secreted in human milk and the toxicological potential for the infant is unknown, breastfeeding should be avoided during Herceptin therapy.

Effects on ability to drive and use machines

No relevant study has been performed.

It is not known whether Herceptin administration affects the ability to drive or operate machinery. There is no evidence of such effects on the basis of the drug's pharmacological activity or of its adverse effects reported to date.

Patients experiencing infusion-related symptoms should be advised not to drive or use machines until their symptoms have fully resolved.

Undesirable effects

The most serious and/or frequently reported undesirable effects during treatment with Herceptin are cardiotoxicity, infusion reactions, hematotoxicity (especially neutropenia) infections and pulmonary adverse events.

NYHA class II–IV cardiotoxicity (heart failure) is a common undesirable effect during treatment with Herceptin and may be fatal in some cases (see *Warnings and precautions*).

An estimated 49%–54% (MBC) and 18%–54% (EBC) of patients treated with Herceptin will experience infusion-related reactions of any kind. However, most of these infusion-related undesirable effects are of mild to moderate severity (based on NCI-CTC criteria) and occur mainly in the first treatments, particularly during the first three infusions and with decreasing frequency in subsequent infusions. Reactions include chills, fever, nausea, urticaria, rash, dyspnea, bronchospasm, tachycardia and hypotension (see *Warnings and precautions*).

Serious anaphylactic reactions necessitating immediate additional intervention occur very rarely and normally during the first or second infusion of Herceptin (see *Warnings and precautions*).

Leukopenia, febrile neutropenia, anemia and thrombocytopenia are very common. Frequently occurring adverse events include neutropenia. The frequency of hypoprothrombinemia is unknown.

Serious pulmonary undesirable effects occur rarely during treatment with Herceptin, but have occasionally been associated with fatal outcome. They include pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema and respiratory failure (see *Warnings and precautions*).

List of undesirable effects

The frequency categories are listed using MedDRA terminology: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to

<1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and infestations

Very common: Nasopharyngitis (>10%), infection.

Common: Cystitis, *Herpes zoster*, infection, influenza, sinusitis, skin infection, rhinitis, upper respiratory tract infection, urinary tract infection, pharyngitis.

Frequency not known: Cellulitis, erysipelas, neutropenic sepsis, sepsis, meningitis, bronchitis.

Benign and malignant and unspecific neoplasms (including cysts and polyps)

Frequency not known: Progressive malignant neoplasia, progressive neoplasia.

Blood and lymphatic system disorders

Very common: Anemia (>10%), thrombocytopenia (>10%), febrile neutropenia (>10%), leukopenia.

Common: Neutropenia.

Frequency not known: Hypoprothrombinemia, leukemia, immune thrombocytopenia.

Rare cases of severe immune thrombocytopenia with hemorrhage, which may occur within a few hours of infusion, have been observed in the post-marketing setting.

Immune system disorders

Common: Hypersensitivity.

Frequency not known: Anaphylactic reaction, anaphylactic shock.

Metabolic and nutritional disorders

Very common: Weight gain (>10%), weight loss (>10%), decreased appetite (>10%).

Common: Anorexia.

Frequency not known: Hyperkalemia.

Psychiatric disorders

Very common: Insomnia (>10%).

Common: Anxiety, depression, thought disorders.

Frequency not known: Lethargy, paraneoplastic cerebellar degeneration.

Nervous system disorders

Very common: Tremor (>10%), dizziness (11%), headache (21%), paresthesia (>10%), hypoesthesia (>10%), dysgeusia (>10%).

Common: Taste disturbance, hypertonia, peripheral neuropathy, light-headedness, somnolence.

Frequency not known: Paresis, ataxia, brain edema, lethargy, coma, cerebrovascular disorders.

Eye disorders

Very common: Increased lacrimation (>10%), conjunctivitis (>10%).

Common: Dry eye.

Frequency not known: Papilledema, retinal hemorrhage, madarosis.

Ear and labyrinth ear disorders

Uncommon: Deafness.

Cardiac disorders*

Very common: Atrial flutter (>10%), irregular heartbeat (>10%), ejection fraction decreased.

Common: Congestive heart failure, supraventricular tachyarrhythmia, cardiomyopathy, palpitations.

Frequency not known: Cardiogenic shock, pericardial effusion, pericarditis, bradycardia, gallop rhythm, tachycardia.

Vascular disorders

Very common: Lymphedema (>10%), hot flushes (>10%).

Common: Hypotension, hypertension, vasodilatation.

Respiratory, thoracic and mediastinal disorders

Very common: Wheezing (>10%), dyspnea (14%), cough (>10%), rhinorrhea (>10%), epistaxis (>10%), oropharyngeal pain (>10%).

Common: Asthma, lung disorder, pleural effusion, pneumonia.

Uncommon: Pneumonitis.

Frequency not known (post-marketing report): Interstitial lung disease including pulmonary infiltration, pulmonary fibrosis, respiratory insufficiency, respiratory arrest, acute pulmonary edema, acute respiratory distress, bronchospasm, hypoxia, laryngeal edema, orthopnea, exertional dyspnea, hiccups, acute respiratory distress syndrome, respiratory distress syndrome, decreased oxygen saturation, Cheyne-Stokes respiration.

Gastrointestinal disorders

Very common: Abdominal pain (16%), diarrhea (43%), labial edema (>10%), nausea (67%), vomiting (50%), dyspepsia (>10%), stomatitis (>10%), constipation (>10%)

Common: Dry mouth, hemorrhoids.

Uncommon: Pancreatitis.

Frequency not known: Gastritis.

Hepatobiliary disorders

Common: Hepatitis, liver tenderness, hepatocellular injury.

Rare: Jaundice.

Frequency not known: Liver failure.

Skin and subcutaneous tissue disorders

Very common: Erythema (23%), rash (24%), facial edema (>10%), alopecia (>10%), palmoplantar dysesthesia (>10%), nail toxicity (>10%), nail disorder.

Common: Acne, dry skin, subcutaneous bleeding, hyperhidrosis, maculopapular rash, pruritus, onychoclasis, dermatitis.

Uncommon: Urticaria.

Frequency not known: Angioedema, onychorrhexis, Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders

Very common: Arthralgia (27%), muscle stiffness (>10%), myalgia (27%).

Common: Arthritis, back pain, bone pain, muscle cramps, neck pain, pain in the extremities, musculoskeletal pain.

Renal and urinary tract disorders

Common: Renal disorder.

Frequency not known: Membranous glomerulonephritis, glomerulonephropathy, renal failure, dysuria.

Reproductive system and breast disorders

Common: Mastitis, mastodynia.

General disorders and administration site reactions

Very common: Asthenia (45%), chest pain (11%), chills (15%), fatigue (35%), influenza symptoms (12%), infusion-related reactions (40%), pain (12%), fever (12%), peripheral edema (>10%), mucosal inflammation (>10%).

Common: Malaise, edema.

Immunogenicity

In the neoadjuvant-adjuvant setting, anti-trastuzumab antibodies were detected in 8.1% (24/296) of patients (regardless of baseline anti-trastuzumab antibody levels). Neutralizing antibodies were found in post-baseline samples in 2 of 24 Herceptin patients. The clinical relevance of these antibodies is not known. Nevertheless, the pharmacokinetics, efficacy (determined by pathological complete response [pCR]) and safety (determined by frequency of infusion-related reactions) of trastuzumab did not appear to be adversely affected by these anti-trastuzumab antibodies.

** Long-term cardiological follow-up in early breast cancer*

After a median follow-up of 8 years the incidence of severe chronic heart failure (NYHA class III and IV) following 1 year of Herceptin therapy in study BO16348 was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Reversibility of severe chronic heart failure (defined as a sequence of at least two consecutive LVEF values ≥50% after the event) was evident for 71.4% of affected patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of affected patients. Approximately 17% of

cardiac dysfunction-related events occurred after completion of Herceptin treatment.

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

Overdosage

No case of overdosage has been observed in human clinical trials. Single doses higher than 10 mg/kg body weight have not been tested.

Properties and effects

ATC code: L01XC03

Mechanism of action/Pharmacodynamics

Trastuzumab is a recombinant humanized monoclonal IgG1 kappa antibody produced in CHO (Chinese hamster ovary) cells that has murine hypervariable regions of the variable region. The antibody selectively binds to the extracellular domain of human epidermal growth factor receptor 2 (HER2).

The HER2 proto-oncogene (or c-erbB2) codes for a transmembrane-spanning, receptor-like, single-chain protein of 185 kDa which is structurally related to the human epidermal growth factor receptor 2 (HER2). HER2 overexpression is observed in 15%–20% of primary breast cancers. The overall rate of HER2 positivity in advanced gastric cancer observed during screening for study BO18255 is 15% based on IHC3+ or IHC2+/FISH+, or 22.1% when applying the broader definition in which IHC3+ or FISH+ suffices for HER2 positivity. HER2 gene amplification results in an increase in HER2 protein expression on the surface of these tumor cells and consequently in potent HER2 activation.

Studies have shown that breast cancer patients with tumors that overexpress HER2 have shorter disease-free survival than patients with tumors that do not overexpress HER2.

Trastuzumab has been shown, both in in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. Trastuzumab is a mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro data show that trastuzumab-mediated antibody-dependent cell-mediated cytotoxicity is exerted preferentially on HER2-overexpressing cancer cells.

Detection of HER2 overexpression or HER2 gene amplification in breast cancer

Herceptin should only be used to treat patients whose tumors exhibit HER2 overexpression or HER2 gene amplification. HER2 overexpression should be diagnosed using an immunohistochemistry(IHC)-based assessment of fixed tumor blocks (see *Dosage and administration*). HER2 gene amplification should be detected using fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) of fixed tumor blocks. Patients are eligible for Herceptin treatment if they show strong HER2 overexpression as described by a 3+ score by IHC or a positive FISH or CISH result.

To achieve accurate and reproducible results, testing must be performed in specialized laboratories able to ensure validation of the test methods.

The recommended scoring system to evaluate the IHC staining patterns is as follows:

Staining intensity score	**Staining pattern**	**HER2 overexpression assessment**
0	No staining is observed or membrane staining is observed in <10% of the tumor cells.	Negative
1+	A faint/barely perceptible membrane staining is detected in >10% of the tumor cells. The cells are only stained in part of their membrane.	Negative
2+	A weak to moderate complete membrane staining is detected in >10% of the tumor cells.	Mild to moderate overexpression Equivocal
3+	Moderate to strong complete membrane staining is detected in >10% of the tumor cells.	Positive

In general, FISH is considered positive if the ratio of the HER2 gene copy number per tumor cell to the chromosome 17 copy number is greater than or equal to 2, or if there are more than 4 copies of the HER2 gene per tumor cell if no chromosome 17 control is used.

In general, the CISH test result is considered positive if there are more than 5 copies of the HER2 gene per nucleus in more than 50% of tumor cells.

For full instructions on assay performance and interpretation please refer to the package inserts of validated FISH and CISH assays.

Detection of HER2 overexpression or HER2 gene amplification in gastric cancer or cancer of the gastroesophageal junction

Only a reliable and validated assay should be used to detect HER2 overexpression or HER2 gene amplification. IHC is recommended as the first testing modality. In cases where HER2 gene amplification status is also required, either silver-enhanced *in situ* hybridization (SISH) or a FISH technique must be used. To achieve accurate and

reproducible results, testing must be performed in specialized laboratories able to ensure validation of the test methods. Full details on the performance and interpretation of these tests can be found in the product information leaflets of validated FISH and SISH assays.

In the ToGA study patients whose tumors were either IHC3+ or FISH positive were defined as HER2 positive and thus included in the trial. Based on the clinical study results, the beneficial effects were limited to patients with the highest level of HER2 protein overexpression, defined by a 3+ score by IHC, or a 2+ score by IHC and a positive FISH result.

In a method comparison study (study D008548) a high degree of concordance (>95%) was observed between SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

Herceptin should only be used in patients whose tumors exhibit strong HER2 overexpression, i.e. IHC3+ or IHC2+ plus a positive FISH or SISH result.

HER2 gene amplification should be detected using *in situ* hybridization, e.g. by either SISH or FISH, on fixed tumor blocks.

The recommended scoring system to evaluate the IHC staining patterns is as follows:

Score	**Surgical specimen – staining pattern**	**Biopsy specimen – staining pattern**	**HER2 overexpression assessment**
0	No staining, reactivity or membranous reactivity in <10% of tumor cells	No reactivity or membranous reactivity in any tumor cell	Negative
1+	Faint/barely perceptible membranous reactivity in ≥10% of tumor cells; cells are reactive only in part of their membrane	Tumor cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumor cells stained	Negative
2+	Weak to moderate complete basolateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of tumor cells	Tumor cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained	Positive

In general, the SISH or FISH test result is considered positive if the ratio of the HER2 gene copy number per tumor cell to the chromosome 17 copy number is greater than or equal to 2.

HER2 expression occurs mainly in the intestinal histological subtype. In contrast to breast cancer immunohistochemistry staining in gastric cancer is mostly incomplete.

HER2 can be detected as a free molecule in plasma (shedding). However, the level of HER2 expression in plasma does not correlate with the clinical course. No data on shedding are available in gastric cancer.

Clinical data

Metastatic breast cancer

Herceptin was used in the clinical trials as monotherapy for patients with metastatic breast cancer who had tumors that overexpressed HER2 and who had failed to respond to one or more chemotherapy regimens for their metastatic disease (Herceptin alone).

Herceptin has also been used in combination with paclitaxel or docetaxel to treat patients who have never received chemotherapy for their metastatic breast cancer. Patients who had previously received anthracycline-based adjuvant chemotherapy received paclitaxel (175 mg/m^2 infused over 3 hours) with or without Herceptin. In the pivotal study of docetaxel (100 mg/m^2 infused over 1 hour) with or without Herceptin, 60% of patients had received adjuvant anthracycline-based chemotherapy beforehand. Patients were treated with Herceptin until disease progression.

The efficacy of Herceptin combined with paclitaxel in patients who have received no adjuvant anthracycline chemotherapy has not been studied. Nevertheless, Herceptin plus docetaxel was effective in all patients – whether they had received adjuvant anthracycline or not.

The HER2 overexpression assay used to determine patient eligibility in the pivotal study (Herceptin monotherapy and Herceptin plus paclitaxel) was based on the immunohistochemical staining of HER2 in fixed material from breast cancer tumors using monoclonal murine antibodies CB11 and 4D5. These tissues were fixed in formalin or Bouin's fluid. In the clinical trials this technique was performed in a central laboratory using a scale of 0 to 3+. Patients scoring 2+ or 3+ were included while those scoring 0 or 1+ were excluded. More than 70% of included patients exhibited 3+ overexpression. The data suggest that positive effects were greater in patients with more marked overexpression of HER2 (3+).

In the pivotal study of docetaxel with or without Herceptin, immunohistochemistry was the main method of testing for HER2 overexpression. FISH was used in a minority of patients. In this study 87% of included patients displayed IHC3+ overexpression and 95% were IHC3+ and/or FISH positive.

Combination therapy with Herceptin plus paclitaxel or docetaxel

The following table presents the efficacy data from the studies of monotherapy and combination therapy (with paclitaxel or docetaxel):

Parameter	**Combination therapy**				**Monotherapy**
	Herceptin plus Paclitaxel[1]	**Paclitaxel[1]**	**Herceptin plus Docetaxel[2]**	**Docetaxel[2]**	**Herceptin[1]**
	n=68	**n=77**	**n=92**	**n=94**	**n=172**

Median duration of response (months) (95% confidence interval)	8.3 (7.3–8.8)	4.6 (3.7–7.4)	11.7 (9.3–15.0)	5.7 (4.6–7.6)	9.1 (5.6–10.3)
Median TTP (months) (95% confidence interval)	7.1 (6.2–12.0)	3.0 (2.0–4.4)	11.7 (9.2–13.5)	6.1 (5.4–7.2)	3.2 (2.6–3.5)
Median survival time (months) (95% confidence interval)	24.8 (18.6–33.7)	17.9 (11.2–23.8)	31.2 (27.3–40.8)	22.7 (19.1–30.8)	16.4 (12.3–ND)
Response rate (%) (95% confidence interval)	49% (36–61)	17% (9–27)	61% (50–71)	34% (25–45)	18% (13–25)

TTP, time to progression; ND, not determinable or not yet reached
[1] Patient subgroup with IHC3+ overexpression
[2] Full analysis (intent-to-treat) population

Combination therapy with Herceptin plus anastrozole

Herceptin has been studied in combination with anastrozole for first-line treatment of metastatic breast cancer in HER2-overexpressing, hormone-receptor-positive (e.g. estrogen-receptor [ER] and/or progesterone-receptor [PR]) post-menopausal patients who have not previously had chemotherapy for their metastatic disease. Patients with brain metastases were also excluded. Progression-free survival was significantly enhanced in the Herceptin plus anastrozole group compared to the group on anastrozole alone

(4.8 months versus 2.4 months, p=0.0016). Herceptin administration also significantly improved the following parameters: overall response rate (16.5% versus 6.7%), clinical benefit rate (42.7% versus 27.9%) and time to disease progression (4.8 months versus 2.4 months). No difference was detected between the two groups in either time to response or duration of response. Mean overall survival was 4.6 months longer in the group of patients receiving combination therapy. The difference was not statistically significant. In this regard, it should nevertheless be borne in mind that over half the patients in the anastrozole monotherapy group crossed over to a Herceptin containing regimen after disease progression. 52% of the patients receiving Herceptin plus anastrozole survived for at least 2 years compared to 45% of patients who had received anastrozole alone on starting therapy (statistically non-significant difference).

Early breast cancer

In the adjuvant setting, Herceptin was investigated in four multicenter, randomized phase III studies:

The BO16348 (HERA) study was designed to compare one and two years of 3-weekly Herceptin treatment with a period of observation in patients with HER2-positive early breast cancer. Patients had previously undergone surgery, validated chemotherapy and (if appropriate) radiotherapy. In addition, two-year and one-year Herceptin treatments were compared. Patients assigned to Herceptin treatment received a loading dose of 8 mg/kg body weight, followed by a dose of 6 mg/kg body weight every 3 weeks for one or two years.

HER2-positive early breast cancer in the BO16348 (HERA) study was limited to operable primary invasive adenocarcinoma of the breast with positive axillary lymph nodes or negative axillary lymph nodes with tumors at least 1 cm in diameter.

The following table summarises the efficacy results from the BO16348 (HERA) study:

Efficacy results (BO16348/HERA) for Herceptin (treatment for 1 year) versus non-treatment: results after median follow-up for 12 months* and 8 years**

Parameter	Median follow-up 12 months		Median follow-up 8 years	
	No Herceptin, observation only n=1693	**Herceptin 1 year n=1693**	**No Herceptin, observation only n=1697*** **	**Herceptin 1 year n=1702*** **
Disease-free survival				
- Number of patients with event	219 (12.9%)	127 (7.5%)	570 (33.6%)	471 (27.7%)
- Number of patients without event	1474 (87.1%)	1566 (92.5%)	1127 (66.4%)	1231 (72.3%)
p vs observation	<0.0001		<0.0001	
Hazard ratio vs observation	0.54		0.76	
Recurrence-free survival				
- Number of patients with event	208 (12.3%)	113 (6.7%)	506 (29.8%)	399 (23.4%)
- Number of patients without event	1485 (87.7%)	1580 (93.3%)	1191 (70.2%)	1303 (76.6%)
p vs observation	<0.0001		<0.0001	
Hazard ratio vs observation	0.51		0.73	
Distant disease-free survival				
- Number of patients with event	184 (10.9%)	99 (5.8%)	488 (28.8%)	399 (23.4%)
- Number of patients without event	1508 (89.1%)	1594 (94.6%)	1209 (71.2%)	1303 (76.6%)
p vs observation	<0.0001		<0.0001	
Hazard ratio vs observation	0.50		0.76	
Overall survival (death)				
- Number of patients with event	40 (2.4%)	31 (1.8%)	350 (20.6%)	278 (16.3%)
- Number of patients without event	1653 (97.65%)	1662 (98.2%)	1347 (79.4%)	1424 (83.7%)
p vs observation	0.24		0.0005	
Hazard ratio vs observation	0.75		0.76	

* The co-primary endpoint of disease-free survival after 1 year versus observation was within the predefined statistical limits.

** 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 group of patients who were randomized after the cut-off date for the 12-month median follow-up.

The efficacy results in the interim analysis exceeded the statistical limits predefined in the protocol for comparing 1-year Herceptin treatment with observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease-free survival was 0.54 (95% CI 0.44, 0.67), which translates into an absolute benefit in disease-free survival of 7.6 percentage points (85.8% vs 78.2%) in favor of the Herceptin arm after two years.

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

In this final analysis, extending Herceptin treatment to 2 years did not show additional benefit over treatment for 1 year (disease-free survival HR in the intent to treat [ITT] population of 2 years versus 1 year = 0.99 [95% CI: 0.87, 1.13], p=0.90 and overall survival HR=0.98 [0.83, 1.15]; p=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%) than in the 1-year treatment arm (16.3%).

The jointly analyzed NCCTG N9831 and NSABP B-31 studies were designed to investigate the clinical utility of combining Herceptin (H) treatment with paclitaxel (P) following AC (doxorubicin plus cyclophosphamide) chemotherapy. The NCCTG N9831 study additionally investigated administration of Herceptin sequentially to AC/paclitaxel chemotherapy in patients with HER2-positive early breast cancer following surgery.

In the joint analysis of the NCCTG N9831 and NSABP B-31 studies, early breast cancer was limited to women with operable high-risk tumors, defined as HER2 positive and positive axillary lymph nodes or HER2 positive and negative axillary lymph nodes with high-risk features (tumor size >1 cm and ER negative or tumor size >2 cm regardless of hormonal status).

Herceptin was administered in combination with paclitaxel after AC chemotherapy. Paclitaxel was administered as follows:

– intravenous paclitaxel 80 mg/m^2 as a continuous i.v. infusion, given every week for 12 weeks

or

– intravenous paclitaxel 175 mg/m^2 as a continuous i.v. infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

In studies NCCTG N9831 and NSABP B-31, Herceptin i.v. was administered weekly together with chemotherapy: a loading dose of 4 mg/kg body weight as a 90-minute infusion, followed by 2 mg/kg body weight as a 30-minute infusion. Treatment with Herceptin was continued for a period of 1 year from the time of first administration.

At the time of the interim analysis, the median duration of follow-up was 1.8 years for the AC→P arm and 2.0 years for the AC→PH arm.

Summary of efficacy results from the joint analysis of studies NCCTG 9831 and NSABP B31 at the time of the definite DFS analysis*:

Parameter	**AC→P n=1679**	**AC→PH n=1672**	**p value**	**Hazard ratio**
Disease-free survival				

- Patients with event	261 (15.5%)	133 (8.0%)	<0.0001	0.48 (0.39–0.59)
- Patients without event	1418 (84.5%)	1539 (92.0%)		
Recurrence				
- Patients with event	235 (14.0%)	117 (7.0%)	<0.0001	0.47 (0.37–0.58)
- Patients without event	1444 (86.0%)	1555 (93.0%)		
Distant recurrence (metastasis)				
- Patients with event	193 (11.5%)	96 (5.7%)	<0.0001	0.47 (0.37–0.60)
- Patients without event	1486 (88.5%)	1576 (94.3%)		
Overall survival				
- Patients with event	92 (5.5%)	62 (3.7%)	0.014**	0.67 (0.48–0.92)
- Patients without event	1587 (94.5%)	1610 (96.3%)		

* With median follow-up of 1.8 years for patients in the AC→P arm and 2.0 years for patients in the AC→PH arm.

** p value for overall survival did not cross the prespecified statistical boundary for comparison of AC→PH vs AC→P.

For the primary endpoint, disease-free survival, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence. In terms of the 3-year disease-free survival rate, the hazard ratio reflects an absolute benefit of 11.8 percentage points (87.2% vs 75.4%) in favor of the AC→PH (Herceptin) arm.

The preplanned final analysis of overall survival from the joint analysis of studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC→PH group). Treatment with AC→PH resulted in a statistically significant improvement in overall survival compared with AC→P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p value <0.0001). At 8 years, the survival rate was estimated to be 86.9% in the AC→PH arm and 79.4% in the AC→P arm, corresponding to an absolute benefit of 7.4% (95% CI: 4.9%, 10.0%).

Study BCIRG 006 investigated the combination of Herceptin and docetaxel either following AC chemotherapy or the combination of Herceptin with docetaxel and carboplatin in patients with HER2-positive early breast cancer following surgery.

In study BCIRG 006 HER2-positive early breast cancer was restricted to either lymph-node-positive patients or lymph-node-negative patients at high risk, defined as negative (pN0) lymph node involvement and at least 1 of the following factors: tumor size >2 cm, estrogen receptor and progesterone receptor negative, histological and/or nuclear grade 2–3 or age <35 years.

In study BCIRG 006 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:

– 100 mg/m^2 as an i.v. infusion over 1 hour, given every 3 weeks for 4 cycles (day 2 of docetaxel cycle 1, then day 1 of each subsequent cycle)

or

– 75 mg/m^2 as an i.v. infusion over 1 hour, given every 3 weeks for 6 cycles (day 2 of docetaxel cycle 1, then day 1 of each subsequent cycle)

followed by

– carboplatin at a target AUC of 6 mg/ml/min as an i.v. infusion over 30–60 minutes, administered every 3 weeks for a total of 6 cycles.

Herceptin i.v. was administered weekly with chemotherapy: a loading dose of 4 mg/kg body weight as a 90-minute infusion, followed by 2 mg/kg body weight as a 30-minute infusion. After the end of chemotherapy, Herceptin was administered every 3 weeks (loading dose 8 mg/kg body weight as a 90-minute infusion, followed by 6 mg/kg body weight as a 30-minute infusion). Treatment with Herceptin was continued for a period of 1 year from the time of first administration.

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.

The following tables summarize the efficacy results from the BCIRG 006 study:

Overview of AC→D versus AC→DH efficacy analyses (study BCIRG 006)

Parameter	**AC→D (n=1073)**	**AC→DH (n=1074)**	**p value vs AC→D (log-rank)**	**Hazard ratio vs AC→D (95% CI)**
Disease-free survival - No. of patients with event - No. of patients without event	195 (18.2%) 878 (81.8%)	134 (12.5%) 940 (87.5%)	<0.0001	0.61 (0.49–0.77)
Distant metastases - No. of patients with event - No. of patients without event	144 (13.4%) 929 (86.6%)	95 (8.8%) 979 (91.2%)	<0.0001	0.59 (0.46–0.77)
Death (overall survival event) - No. of patients with event - No. of patients without event	80 (7.5%) 993 (92.5%)	49 (4.6%) 1025 (95.4%)	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

Overview of AC→D versus DCarbH efficacy analyses (study BCIRG 006)

Parameter	AC→D (n=1073)	DCarbH (n=1075)	p value vs AC→D (log-rank)	Hazard ratio vs AC→D (95% CI)
Disease-free survival - No. of patients with event - No. of patients without event	195 (18.2%) 878 (81.8%)	145 (13.5%) 930 (86.5%)	0.0008	0.67 (0.54–0.83)
Distant metastases - No. of patients with event - No. of patients without event	144 (13.4%) 929 (86.6%)	103 (9.6%) 972 (90.4%)	0.0008	0.65 (0.50–0.84)
Death (overall survival event) - No. of patients with event - No. of patients without event	80 (7.5%) 993 (92.5%)	56 (5.2%) 1019 (94.8%)	0.0182	0.66 (0.47–0.93)

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

For the primary endpoint, disease-free survival, the hazard ratio in study BCIRG 006 reflects an absolute benefit in 3-year disease-free survival of 5.8 percentage points (86.7% vs 80.9%) in favor of the AC→DH (Herceptin) arm and 4.6 percentage points (85.5% vs 80.9%) in favor 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% compared to AC→D; in patients treated with DCarbH the risk of death was reduced by 34% compared to AC→D.

In study BCIRG 006, 213/1075 patients in the DCarbH arm, 221/1074 patients in the AC→DH arm and 217/1073 in the AC→D arm had a Karnofsky performance status ≤90 (either 80 or 90). No disease-free survival benefit was noted in this patient subgroup (hazard ratio = 1.16, 95% CI [0.73, 1.83] for DCarbH vs AC→D; hazard ratio 0.97, 95% CI [0.60, 1.55] for AC→DH vs AC→D).

Neoadjuvant/adjuvant treatment

Study MO16432 (NOAH) investigated the administration of Herceptin together with a total of 10 cycles of neoadjuvant chemotherapy comprising both an anthracycline and a taxane (doxorubicin [A] and paclitaxel [P] plus Herceptin [H], followed by P+H, followed by cyclophosphamide/methotrexate/fluorouracil [CMF] plus H, followed by adjuvant Herceptin to an overall treatment duration of 1 year) in patients with newly diagnosed locally advanced (stage III) or inflammatory HER2-positive breast cancer.

Median duration of follow-up in the Herceptin arm was 3.8 years. Pathological complete remission is defined as the absence of invasive tumor in both breast and axillary lymph nodes.

Parameter	Chemotherapy + Herceptin (n=115)	Chemotherapy alone (n=116)	
Event-free survival Number of patients with event	46	59	Hazard ratio (95% CI) 0.65 (0.44–0.96) p=0.0275
Total pathological complete remission (95% CI)	40% (31.0, 49.6)	20.7% (13.7, 29.2)	p=0.0014

With respect to the primary endpoint, event-free survival, the addition of Herceptin to 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 (hazard ratio: 0.65 [95% CI: 0.44–0.96]; p<0.0275). After 3 years 65% of patients in the Herceptin arm and 52% in the control arm were event-free. This translates into a 13% improvement in favor of the Herceptin arm.

CNS metastases

In the HERA study, an analysis of the site of first recurrence showed a difference of 0.3% in terms of CNS metastases in the Herceptin group (1.2% of patients versus 0.9% of patients in the control group). The overall incidence of CNS metastases (first and subsequent recurrences) was similar in the two treatment groups (23 patients in the observation group versus 25 in the Herceptin group). This indicates that at the end of the adjuvant chemotherapy the incidence of micrometastases in the CNS was in all probability approximately equal in the two treatment groups.

According to the joint analysis of studies NCCTG N9831 and NSAPB B-31, the occurrence of isolated brain metastases as a first event was more common in the Herceptin group than in the control group (21 versus 11 in study B-31, 12 versus 4 in study N9831). The patients in study B-31 were followed up for further recurrences after the occurrence of their first distant metastases. In this study the overall occurrence of brain metastases as a first or subsequent event was diagnosed in 28 patients in the Herceptin group and in 35 patients in the control group (hazard ratio 0.79, p=0.35).

Thus, the incidence of brain metastases in the Herceptin group was not higher than that in the control group. The different incidence of brain metastases as a first event in patients in the control group is probably attributable to earlier relapse in another organ system.

Metastatic adenocarcinoma of the stomach or gastroesophageal junction

The efficacy results from study BO18255 are summarized in the following table. Patients taking part in the study had not previously been treated for metastatic gastric or gastroesophageal junction adenocarcinoma. The primary endpoint was overall survival. At the time of analysis a total of 349 of the 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.

In the Herceptin + capecitabine/5-FU and cisplatin arm overall survival was significantly better than in the capecitabine/5-FU and cisplatin arm (p=0.0046, log-rank test). Mean

survival was 11.1 months if treated with capecitabine/5-FU and cisplatin, and 13.8 months on Herceptin + capecitabine/5-FU and cisplatin. The risk of death for patients in the Herceptin arm was 26% lower than for patients in the capecitabine/5-FU arm (hazard ratio [HR] 0.74 [95% CI 0.60–0.91]).

Post-hoc subgroup analyses showed that treatment was more effective in tumors with higher concentrations of HER2 protein (IHC2+/FISH+ and IHC3+/irrespective of FISH status). Mean overall survival in the high HER2-expressing group was 11.8 months versus 16 months (HR 0.65 [95% CI 0.51–0.83]) and mean progression-free survival was 5.5 months versus 7.6 months (HR 0.64 [95% CI 0.51–0.79]) for capecitabine/5-FU and cisplatin and Herceptin + capecitabine/5-FU and cisplatin respectively.

Summary efficacy data (Study BO18255)

Population/Parameter	FP n=290	FP+H n=294	HR (95% CI)	p value
Overall population				
Median overall survival (months)	11.1	13.8	0.74 (0.60–0.91)	0.0046
Median progression-free survival (months)	5.5	6.7	0.71 (0.59–0.85)	0.0002
Overall response rate, %	34.5%	47.3%	1.70[a] (1.22, 2.38)	0.0017
IHC3+ (n=287)				
Median overall survival (months)	12.5	17.9	0.59 (0.43–0.81)	n.a.[b]
Median progression-free survival (months)	5.7%	8.4%	0.59 (0.45–0.78)	n.a.[b]
IHC2+ and FISH+ (n=159)				
Median overall survival (months)	10.8	12.3	0.75 (0.51–1.11)	n.a.[b]
Median progression-free survival (months)	5.0	5.7	0.73 (0.53–1.03)	n.a.[b]
Gastric cancer				
Median overall survival (months)	11.1	14.6	0.76 (0.60–0.96)	n.a.[b]
Median progression-free survival (months)	5.4	6.3	0.73 (0.60–0.90)	n.a.[b]
Gastroesophageal junction cancer				
Median overall survival (months)	8.6	10.9	0.67 (0.42–1.08)	n.a.[b]
Median progression-free survival (months)	5.6	7.6	0.61 (0.40–0.93)	n.a.[b]

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

[b] Subgroup p values not given as power was insufficient to demonstrate differences between study arms.

Pharmacokinetics

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1582 subjects from 18 phase I, II and III studies receiving intravenous Herceptin. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to the non-linear elimination, total clearance increased with decreasing concentrations. Linear clearance was 0.127 l/day for breast cancer (MBC/EBC) and 0.176 l/day for AGC). The maximum elimination rate (V_{max}) for non-linear elimination was 8.81 mg/day and the Michaelis-Menten constant (K_M) was 8.92 mg/l. The central

compartment volume was 2.62 l for patients with breast cancer and 3.63 l for patients with AGC.
The following tables show 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 regimens.

Population-predicted cycle 1 PK exposure values (with the median 5th–95th percentiles) for intravenous regimens in breast cancer and AGC patients

Dosage	Primary tumor type	N	C_{min} (µg/ml)	C_{max} (µg/ml)	AUC (µg.day/ml)
8 mg/kg + 6 mg/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)
4 mg/kg + 2 mg/kg qw	MBC/EBC	1195	37.7 (12.3–70.9)	88.3 (58–144)	1066 (586–1754)

Population-predicted steady-state PK exposure values (with 5th–95th percentiles) for intravenous regimens in breast cancer and AGC patients

Dosage	Primary tumour type	N	$C_{min,ss}$ (µg/ml)	$C_{max,ss}$ (µg/ml)	AUC_{ss} (µg.day/ml)	Time to steady state (week)	Total CL range at steady state (l/day)
8 mg/kg + 6 mg/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
4 mg/kg + 2 mg/kg qw	MBC/EBC	1195	66.1 (14.9–142)	109 (51.0–209)	1765 (647–3578)	12	0.201–0.244

Trastuzumab washout

The trastuzumab washout period was assessed following intravenous and subcutaneous administration using the respective population PK models. The results of these simulations indicate that at least 95% of patients have reached serum trastuzumab concentrations <1 µg/ml (approximately 3% of the population-predicted $C_{min,ss}$, or about 97% washout) 7 months after the last dose.

Elimination
Trastuzumab is degraded in the liver and other tissues such as skin and muscle. The elimination half-life of trastuzumab in breast cancer is 28–38 days. Mean elimination half-life in gastric cancer is 26 days.

Circulating shed antigen
Breast cancer: Measurable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the serum of 64% of the patients with HER2-overexpressing breast cancers (up to 1880 ng/ml; median 11 ng/ml). Patients with higher

baseline shed-antigen levels were more likely to have lower serum trough concentrations of trastuzumab. With weekly dosing, most patients with elevated shed-antigen levels achieved target serum concentrations of trastuzumab by week 6. No significant relationship has been observed between baseline shed antigen and clinical response.

There are no data on shed-antigen levels in patients with gastric or gastroesophageal junction cancer.

Pharmacokinetics in special patient groups

Detailed pharmacokinetic studies have not been carried out in the elderly or in patients with renal or hepatic impairment. A population pharmacokinetic analysis showed that renal impairment does not affect trastuzumab disposition.

Factors such as patient age and serum creatinine have not been shown to influence the pharmacological disposition of trastuzumab.

Preclinical data

Trastuzumab was well tolerated by mice (non-binding species) and cynomolgus monkeys (binding species) in single-dose and repeat-dose toxicity studies of up to 6 months' duration, respectively. No evidence of acute or chronic toxicity was identified.

Reproduction studies conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg Herceptin revealed no evidence of impaired female fertility. The effect on the fertility of male animals was not investigated. Teratogenicity, late gestational toxicity and placental-transfer studies produced no evidence of reproductive toxicity.

Two non-clinical toxicity studies to assess the cardiotoxic effects of Herceptin were carried out in cynomolgus monkeys (Java).

The effects of Herceptin were investigated in animals suffering from manifest cardiac damage due to previous treatment with doxorubicin. After treatment with Herceptin there were no changes in parameters that indicate myocardial cell necrosis. The results revealed changes in one parameter – E-point to septal separation (EPSS) distance – but not in two other parameters – left ventricular fractional shortening (FS) and velocity of circumferential fibre shortening (Vcf) – that might have indicated impairment of cardiac function.

A study compared the adverse effects of combination therapy with doxorubicin and Herceptin on cardiac function and on erythrocytes and leukocytes with the corresponding adverse effects of monotherapy with each of these drugs. The adverse effects of the combination therapy were somewhat more severe and were more prolonged than those of monotherapy with doxorubicin. Monotherapy with Herceptin resulted in no adverse effects.

Additional information

Incompatibilities

No incompatibility between Herceptin and polyvinylchloride, polyethylene or polypropylene bags has been observed.

Glucose solutions (5%) should not be used as they cause protein aggregation.

Herceptin should not be mixed or diluted with other drugs.

Stability

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Special precautions for storage

Store the rubber-stoppered vials of lyophilized powder for the preparation of a concentrated solution for infusion in a refrigerator (2°C–8°C).

Instructions for use and handling

Instructions for the handling of Herceptin 150 mg single-injection vials

Preparation for use

Each vial of Herceptin is reconstituted with 7.2 ml of sterile water for injections (not supplied). Other reconstitution agents should not be used. This yields a 7.4 ml solution for single-dose use containing approximately 21 mg/ml trastuzumab at a pH of approximately 6.0.

In order to prevent any precipitation and consequent reduction in the amount of dissolved Herceptin, shaking and excessive foaming should be avoided during reconstitution of Herceptin and preparation of diluted solutions for infusion. Too rapid expulsion from a syringe should likewise be avoided.

Instructions for reconstitution

1. Using a sterile syringe, slowly inject 7.2 ml of sterile water for injections onto the Herceptin lyophilized powder for the preparation of a concentrated solution for infusion contained in the vial.
2. Rock the vial gently to and fro. DO NOT SHAKE!

The occurrence of slight foaming during the reconstitution process is not unusual. The vial should therefore be left to stand for about 5 minutes after reconstitution. After this the solution should contain essentially no visible particles.

The reconstituted preparation is a colorless to pale yellow transparent solution.

Instructions for the handling of Herceptin 440 mg multiple-injection vials

Preparation for use

An appropriate aseptic technique should be used. The contents of each vial of Herceptin should be reconstituted with 20 ml of the enclosed bacteriostatic water for injections containing 1.1% benzyl alcohol. This yields a multi-injection solution containing

21 mg/ml trastuzumab with a pH of approximately 6.0. Use of other solvents for reconstitution should be avoided.

For the preparation of a single dose, water for injections (not supplied) can also be used. Such preparations should be used immediately and any unused portion discarded. Use of other solvents should be avoided.

In order to prevent any precipitation and consequent reduction in the amount of dissolved Herceptin, shaking and excessive foaming should be avoided during reconstitution of Herceptin and preparation of diluted solutions for infusion. Too rapid expulsion from a syringe should likewise be avoided.

Instructions for reconstitution

1. Using a sterile syringe, slowly inject 20 ml of sterile water for injections onto the Herceptin lyophilized powder for the preparation of a concentrated solution for infusion contained in the vial.

2. Rock the vial gently to and fro. DO NOT SHAKE!

The occurrence of mild foaming during the reconstitution process is not unusual. After reconstitution, allow the vial to stand for about 5 minutes. After this the solution should contain essentially no visible particles.

The reconstituted preparation is a colorless to pale yellow transparent solution.

Instructions for the handling of Herceptin single-dose and multidose vials

Dilution of the reconstituted solution

The volume of reconstituted solution needed for the treatment of a given patient is calculated as follows:

- based on a loading dose of 4 mg trastuzumab/kg body weight or weekly doses of 2 mg trastuzumab/kg body weight:

$$\textbf{Volume}\ (\text{ml}) = \frac{\textbf{body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{4}\ \text{mg/kg initial or}\ \textbf{2}\ \text{mg/kg subsequent doses})}{\textbf{21}\ (\text{mg/ml, concentration of reconstituted solution})}$$

- based on a loading dose of 8 mg trastuzumab/kg body weight and subsequent 3-weekly doses of 6 mg trastuzumab/kg body weight:

$$\textbf{Volume}\ (\text{ml}) = \frac{\textbf{body weight}\ (\text{kg}) \times \textbf{dose}\ (\textbf{8}\ \text{mg/kg initial or}\ \textbf{6}\ \text{mg/kg subsequent doses})}{\textbf{21}\ (\text{mg/ml, concentration of reconstituted solution})}$$

The appropriate volume of reconstituted solution should be withdrawn from the vial (either a 150 mg single-injection vial or a 440 mg multiple-injection vial) and added to an

infusion bag containing 250 ml of 0.9% sodium chloride. Glucose (5%) solutions should not be used (see *Incompatibilities*). The bag should be gently rotated to mix the solution without causing foaming. Parenteral drug products should be inspected visually for particulates or discoloration prior to administration.

The infusion should be used immediately after preparation. If diluted under aseptic conditions, it can be stored for 24 hours refrigerated at 2°C–8ºC.

Stability of reconstituted solution and solution for infusion

Any remaining reconstituted solution or solution for infusion not prepared under controlled and validated aseptic conditions should be discarded.

Herceptin 150 mg for single-injection use

After reconstitution with sterile water for injections the solution is physically and chemically stable for 48 hours at 2°C–8ºC (do not freeze). For microbiological reasons, the reconstituted Herceptin solution should be used immediately unless it was prepared under controlled and validated aseptic conditions.

Herceptin 440 mg for multiple-injection use

The contents of a vial of Herceptin reconstituted with bacteriostatic water for injections, as supplied, are stable for 28 days when stored at a temperature of 2°C–8ºC. The reconstituted solution contains a 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 known hypersensitivity to benzyl alcohol (see *Warnings and precautions, Herceptin for multidose use [benzyl alcohol]*), Herceptin should be reconstituted with water for injections, with only one dose of Herceptin taken from each vial. The reconstituted solution should be used immediately. Leftover solution should be discarded.

Do not freeze reconstituted solution.

Herceptin solution for infusion

Herceptin solution for infusion in polyvinylchloride, polyethylene or polypropylene bags containing 0.9% sodium chloride is physically and chemically stable for 24 hours at temperatures up to 30°C. For microbiological reasons, Herceptin solution for infusion should be used immediately, since it contains no preservative. If prepared under aseptic conditions, it can be stored in a refrigerator for 24 hours at 2°C–8°C.

Disposal instructions
Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Packs

150 mg single-dose vials:

1 vial containing Herceptin (trastuzumab)

440 mg multiple-dose vials:

Pack containing 1 vial of Herceptin (trastuzumab) and 1 vial of solvent

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at February 2016

150 mg vials:

Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel

Made for F. Hoffmann-La Roche Ltd, Basel by
- Roche Diagnostics GmbH, Mannheim, Germany

440 mg vials:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland by
- Genentech Inc., South San Francisco, California, USA
- Genentech Inc., Hillsboro, Oregon, USA