Herceptin®

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Herceptin 440mg powder for concentrate for solution for infusion.

2. Qualitative and quantitative composition

Single-dose vials containing 150 mg trastuzumab. Multidose vials containing 440 mg trastuzumab (produced by recombinant DNA technology using CHO [Chinese hamster ovary] cells).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

White powder for concentrate for solution for infusion.

White powder

4. Clinical particulars

4.1 Therapeutic indications

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

Metastatic breast cancer
Herceptin is indicated for the treatment of patients with metastatic breast cancer whose tumours overexpress HER2:
a) as a single agent for the treatment of patients who have received one or more chemotherapy regimens for their metastatic disease,

b) in combination with paclitaxel or docetaxel for the treatment of 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 who have not received chemotherapy for their metastatic disease.
No data are available on breast cancer patients who received adjuvant treatment with Herceptin in the early stage.

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.
in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin for locally advanced (including inflammatory) breast cancer or tumours >2 cm in diameter.

Metastatic gastric cancer or cancer of the gastro-oesophageal 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 gastro-oesophageal junction who have not received chemotherapy for their metastatic disease. Herceptin should only be used in patients with metastatic gastric cancer whose tumours overexpress HER2, as defined by IHC2+ and confirmed by a positive FISH+ or silver *in situ* hybridisation (SISH) result, or by IHC3+ determined in a validated test.

4.2 Posology and method of administration

It is essential that treatment with Herceptin be initiated under the supervision of a physician who is experienced in the treatment of cancer patients.
A validated HER2 test is mandatory before initiating therapy (see "Properties/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).
To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Metastatic breast cancer – weekly schedule
Herceptin should be administered as an intravenous infusion. Do not administer as an intravenous bolus.
The following initial and subsequent doses are recommended both for monotherapy and for combination with chemotherapy:

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

Subsequent doses
The recommended weekly maintenance dose is Herceptin 2 mg/kg body weight, which can be administered as a 30-minute infusion if the initial dose was well tolerated.

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 paclitaxel or docetaxel can be administered at 3-weekly intervals immediately after the subsequent Herceptin doses, if preceding Herceptin administration has been well tolerated. For the dosage of paclitaxel or docetaxel, see the relevant prescribing information.

Combination therapy with an aromatase inhibitor
The dosage of Herceptin in combination therapy is the same as that in monotherapy. In the pivotal trial, Herceptin and anastrozole were administered on day 1. There were no restrictions on the relative timing for coadministration. For the dosage of anastrozole, see the relevant prescribing information. If the patient has been receiving tamoxifen, it should be discontinued at least a day before starting combination therapy.

Metastatic breast cancer – 3-weekly schedule
Monotherapy and combination therapy
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 initial dose is Herceptin 8 mg/kg body weight, followed 3 weeks later by 6 mg/kg body weight. 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/Effects”.

Advanced gastric cancer or cancer of the gastro-oesophageal 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 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.

Duration of treatment
Patients with metastatic breast cancer, advanced gastric cancer or cancer of the gastro- oesophageal junction should be treated with Herceptin until disease progression or unmanageable toxicity. Patients with early breast cancer should be treated for 1 year or until disease recurrence or unmanageable toxicity, whichever occurs first. Treatment of early breast cancer beyond one year is not recommended (see "Properties/Effects: Clinical efficacy").

Dose adjustment following undesirable effects
If the patient develops an infusion-related reaction (IRR), the infusion rate of Herceptin IV should be slowed or the infusion interrupted, and the patient should be monitored until resolution of all observed symptoms (see "Warnings and precautions").
No dose reduction of Herceptin was undertaken in clinical studies.
Treatment with Herceptin can be continued during phases of reversible, chemotherapy-induced myelosuppression, but patients should be carefully monitored during this time for complications of neutropenia. The special instructions on dose reduction or prolongation of intervals for the chemotherapy must be observed.
If the left ventricular ejection fraction (LVEF) falls by ≥10 percentage points from baseline or to below 50%, treatment should be suspended and a repeat LVEF measurement performed within approximately 3 weeks. If LVEF does not improve or declines further, or if symptomatic congestive heart failure (CHF) develops, discontinuation of Herceptin treatment should be seriously considered unless the benefits for the individual patient are assumed to outweigh the risks. These patients should be referred to a cardiologist for investigation and kept under observation.

Special dosage instructions
Elderly patients
Data indicate that the availability of Herceptin is not age-dependent (see "Kinetics in specific
patient groups").
In clinical trials, patients ≥65 years of age did not receive reduced doses of Herceptin.

Children and adolescents
The use and safety of Herceptin in children and adolescents <18 years of age have not yet been tested.

Delayed administration

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 or 21 days later according to the weekly or 3-weekly schedule, respectively.
If the patient has missed a Herceptin dose by more than one week, an initial dose of Herceptin should be readministered 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 or 3-weekly schedule, respectively.

4.3 Contraindications

Herceptin is contraindicated in patients with known hypersensitivity to trastuzumab, Chinese hamster ovary (CHO) cell proteins, or any product or solvent excipient.
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.
Herceptin is contraindicated in patients suffering dyspnoea at rest due to advanced malignancy or comorbidities.

4.4 Special warnings and precautions for use

Herceptin for multidose use (benzyl alcohol)
The solvent for Herceptin 440 mg (bacteriostatic water for injection) contains 220 mg benzyl alcohol/20 ml as a preservative. Benzyl alcohol may cause allergic reactions. Benzyl alcohol has been linked to the risk of serious adverse reactions including breathing problems (called “gasping syndrome”) in young children. The product must not be used in neonates or young children. For patients with known hypersensitivity to benzyl alcohol, the Herceptin powder 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 injection used for reconstitution of the Herceptin 150 mg single-dose vials contains no benzyl alcohol.

Infusion-related reactions
Sometimes serious infusion-related reactions (typical symptoms e.g. dyspnoea, hypotension, nausea, fever, bronchospasm, tachycardia, reduced oxygen saturation, urticaria and rash) have been observed in patients during treatment with Herceptin. These undesirable 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 dyspnoea at rest due to advanced malignancy or comorbidities may be at increased risk of 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/m2 (doxorubicin) or 360 mg/m2 (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 10 or more percentage points from baseline or falls below 50%, Herceptin should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has meanwhile not improved or has declined further, or if clinically significant heart failure has developed, discontinuation of Herceptin should be strongly considered, unless the individual benefit is 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, unless the benefit to the individual patient is deemed to outweigh the risks. These patients should be referred to a cardiologist for investigation and kept under observation.
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 haemodynamically 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. Most symptomatic cardiac side effects occurred within the first 18 months, regardless of the regimen employed.
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/m2).

Pulmonary reactions
Severe pulmonary undesirable effects have been reported with the use of Herceptin 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, cases of interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory failure have been reported.
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 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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Pharmacokinetic interactions
In vivo data
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-dihydro-doxorubicinone (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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Women of childbearing potential should use effective contraception during treatment with
Herceptin and for 7 months after treatment has concluded (see "Pharmacokinetics").
The medicinal product has adverse pharmacological effects on pregnancy and/or the foetus and/or newborn.
Herceptin should not be administered during pregnancy unless clearly necessary, i.e. the potential benefit to the mother outweighs the potential risk to the fetus.
In the post-marketing setting, cases of impaired fetal renal growth (e.g. renal hypoplasia) and/or function 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 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.

Lactation
A study in which cynomolgus monkeys received doses 25 times the weekly human maintenance dose of 2 mg/kg Herceptin i.v. from day 120 to 150 of gestation demonstrated that trastuzumab is secreted in the milk post-partum. Trastuzumab exposure in utero and the presence of trastuzumab in the serum of infant monkeys were not associated with adverse effects on their growth or development from birth to 1 month of age.
It is not known whether trastuzumab is secreted in human milk. Nevertheless, as human IgG passes from serum into breast milk and the potential for harm to the infant is unknown, women should not breastfeed during Herceptin therapy.

Fertility
Whether Herceptin can impair reproductive capacity when administered to pregnant women is unknown.
Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 times the weekly human maintenance dose of 2 mg/kg body weight Herceptin. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) fetal development period was observed. However, the studies revealed no evidence of harm to the fetuses or impaired fertility.

4.7 Effects on ability to drive and use machines

Herceptin has a minor influence on the ability to drive and use machines. Dizziness and somnolence may occur during treatment with Herceptin (see "Undesirable effects"). Patients experiencing infusion-related symptoms (see "Warnings and precautions") should be advised not to drive or use machines until their symptoms have fully resolved.

4.8 Undesirable effects

The most serious and/or frequently reported undesirable effects during treatment with Herceptin are cardiotoxicity, infusion reactions, hepatotoxicity (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, dyspnoea, 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, anaemia 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 oedema 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).
Adverse drug reactions and adverse events reported with the use of intravenous Herceptin alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting are listed below.
The frequency statements relate to the maximum percentage frequencies of adverse reactions observed in pivotal clinical trials.

Infections and infestations
Very common: Infection (24%), nasopharyngitis (17%).
Common: Cystitis, influenza, pharyngitis, skin infection, sinusitis, rhinitis, upper respiratory tract infection, urinary tract infection, neutropenic sepsis.
Frequency not known: Meningitis, bronchitis.

Benign, malignant and unspecified neoplasms (including cysts and polyps)
Frequency not known: Progressive malignant neoplasia, progressive neoplasia.

Blood and lymphatic system disorders
Very common: Neutropenia (47%), anaemia (28%), febrile neutropenia (23%), thrombocytopenia (16%), leukopenia (15%).
Frequency not known: Hypoprothrombinaemia, leukaemia, immune thrombocytopenia.

Immune system disorders
Common: Hypersensitivity.
Rare: Anaphylactic reaction, anaphylactic shock.

Metabolism and nutrition disorders
Very common: Anorexia (46%), weight loss (23%), decreased appetite (20%), weight gain
(15%).
Frequency not known: Hyperkalaemia, tumour lysis syndrome.

Psychiatric disorders
Very common: Insomnia (11%).

Common: Depression, anxiety.
Frequency not known: Lethargy, paraneoplastic cerebellar degeneration.

Nervous system disorders
Very common: Paraesthesia (50%), headache (25%), dizziness (21%), dysgeusia (19%), hypoaesthesia (11%), $tremor.
Common: Taste impairment, increased muscle tone (hypertonia), peripheral neuropathy, light- headedness, somnolence.
Frequency not known: Lethargy, coma, cerebrovascular disorders.

Eye disorders
Very common: Conjunctivitis (38%), increased lacrimation (21%).
Common: Dry eye.
Frequency not known: Papilloedema, retinal haemorrhage, madarosis.

Ear and labyrinth disorders
Uncommon: Deafness.

Cardiac disorders*
Very common: Ejection fraction decreased (11%), $cardiac flutter, $irregular heartbeat.
Common: $Supraventricular tachyarrhythmia, cardiac failure (congestive), cardiomyopathy,
$palpitations.
Uncommon: Pericardial effusion.
Frequency not known: Cardiogenic shock, gallop rhythm, tachycardia.

Vascular disorders
Very common: Hot flushes (17%), lymphoedema (11%).
Common: $Hypotension, $hypertension, vasodilatation.

Respiratory, thoracic and mediastinal disorders
Very common: Epistaxis (18%), rhinorrhoea (18%), cough (16%), oropharyngeal pain (15%), dyspnoea (14%).
Common: Asthma, lung disorder, pleural effusion, pneumonia.
Uncommon: Pneumonitis, $wheezing.
Frequency not known: Interstitial lung disease including pulmonary infiltrates, pulmonary fibrosis, respiratory failure, respiratory arrest, acute pulmonary oedema, acute respiratory distress, bronchospasm, laryngeal oedema, orthopnoea, exertional dyspnoea, hiccups, acute respiratory distress syndrome, respiratory distress syndrome, decreased oxygen saturation, hypoxia, Cheyne-Stokes respiration.

Gastrointestinal disorders
Very common: Nausea (78%), diarrhoea (50%), vomiting (50%), stomatitis (40%), constipation
(27%), abdominal pain (20%), dyspepsia (14%), $lip swelling.
Common: Dry mouth, haemorrhoids.
Uncommon: Pancreatitis.
Frequency not known: Gastritis.

Hepatobiliary disorders
Common: Hepatocellular injury, hepatitis, liver tenderness.

Rare: Jaundice.

Skin and subcutaneous tissue disorders
Very common: Alopecia (94%), palmar-plantar erythrodysaesthesia syndrome (26%), rash
(24%), erythema (23%), nail disorder (17%), nail toxicity (11%), $face oedema.
Common: Acne, dermatitis, dry skin, subcutaneous bleeding, hyperhidrosis, maculopapular rash, pruritus, onychoclasis.
Uncommon: Urticaria.
Frequency not known: Angioedema, onychorrhexis, Stevens-Johnson syndrome.

Musculoskeletal and connective tissue disorders
Very common: Myalgia (35%), arthralgia (28%), $muscle tightness.
Common: Arthritis, back pain, bone pain, muscle spasms, neck pain, pain in the extremities, musculoskeletal pain.

Renal and urinary disorders
Common: Renal disorder.
Frequency not known: Membranous glomerulonephritis, glomerulonephropathy, renal failure, dysuria.

Reproductive system and breast disorders
Common: Breast inflammation/mastitis, breast pain.

General disorders and administration site conditions

Very common: Infusion-related reactions (74%), fatigue (53%), asthenia (51%), influenza-like illness (23%), mucosal inflammation (23%), peripheral oedema (17%), chills (15%), pain (12%), fever (12%), chest pain (11%).
Common: Oedema, malaise.
$ Denotes that the incidence shown is a sum of the incidences of multiple terms. Percentages for individual adverse reactions are not available.

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

Description of selected undesirable effects
Immunogenicity
In a neoadjuvant-adjuvant study (BO22227), anti-trastuzumab antibodies (both treatment- induced and treatment-enhanced) were detected in 10.1% (30/296) of patients during a median follow-up exceeding 70 months. Neutralising antibodies were found in post-baseline samples in 2 of 30 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 & 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.
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.

Reporting of suspected adverse reactions after marketing authorisation is very important. It allows continued monitoring of the benefit/risk balance of the

medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reaction via the ElViS (Electronic Vigilance System) online portal. Information can be found at www.swissmedic.ch.

4.9 Overdose

There is no experience with overdosage in human clinical trials. Single doses higher than 10 mg/kg body weight have not been tested.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action
Trastuzumab is a recombinant humanised monoclonal IgG1 kappa antibody produced in CHO (Chinese hamster ovary) cells that has murine hypervariable regions of the variable region. The antibody binds specifically to the extracellular domain of human epidermal growth factor receptor 2 (HER2).
The HER2 proto-oncogene (or c-erbB2) codes for a transmembrane, receptor-like, single- stranded protein of 185 kDa that is structurally related to the epidermal growth factor receptor. 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 of IHC3+ or FISH+ for HER2 positivity. HER2 gene amplification results in an increase in HER2 protein expression on the surface of these tumour cells and consequently in potent HER2 activation.

Pharmacodynamics
Studies have shown that breast cancer patients with tumours that overexpress HER2 have shorter disease-free survival than patients with tumours that do not overexpress HER2.
Trastuzumab has been shown, both *in vitro* and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted 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 tumours exhibit HER2 overexpression or HER2 gene amplification. HER2 overexpression should be diagnosed using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks (see “Dosage/Administration”). HER2 gene amplification should be detected using fluorescence *in situ* hybridisation (FISH) or chromogenic *in situ* hybridisation (CISH) of fixed tumour 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 obtain accurate and reproducible results, testing must be performed in specialised laboratories that can ensure validation of the testing procedures.

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

Staining intensity	**Staining pattern**	**HER2 overexpression**
0	No staining is observed or membrane staining is observed in <10% of the tumour cells	Negative
1+	Weak/barely perceptible membrane staining is detected in >10% of the tumour cells. The cells are only	Negative
2+	Weak to moderate complete membrane staining is detected in >10% of the tumour cells.	Equivocal
3+	Moderate to strong complete membrane staining is detected in >10% of the tumour cells.	Positive

In general, FISH is considered positive if the ratio of the HER2 gene copy number per tumour 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 tumour cell if no chromosome 17 control is used.
In general, CISH is considered positive if there are more than 5 copies of the HER2 gene per nucleus in more than 50% of tumour 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 metastatic gastric cancer or cancer of the gastro-oesophageal 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 additional HER2 gene amplification status is also required, either silver-enhanced *in situ* hybridisation (SISH) or a FISH technique must be used. To obtain accurate and reproducible results, testing must be performed in specialised laboratories that can ensure validation of the testing procedures. For full instructions on assay performance and interpretation, please refer to the package inserts of validated FISH and SISH assays.
In the ToGA study, patients whose tumours 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 tumours 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* hybridisation, e.g. FISH or SISH of fixed tumour 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**
0	No reactivity or membranous reactivity in <10% of tumour cells	No reactivity or membranous reactivity in any tumour cell	Negative
1+	Faint/barely perceptible membranous reactivity in ≥10% of tumour cells; cells are reactive only in part of their membrane	Tumour cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumour cells stained	Negative
2+	Weak to moderate complete or basolateral membranous reactivity in ≥10% of tumour cells	Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells	Equivocal
3+	Strong complete, basolateral or lateral membranous reactivity in ≥10% of tumour cells	Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage	Positive

In general, the FISH or SISH assay result is considered positive if the ratio of the HER2 gene copy number per tumour 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 efficacy
Metastatic breast cancer
Herceptin has been used in clinical trials as monotherapy for patients with metastatic breast cancer who have tumours that overexpress HER2 and who have 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 for the treatment of patients who have not received chemotherapy for their metastatic breast cancer. Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m2 infused over 3 hours) with or without Herceptin. In the pivotal study of docetaxel (100 mg/m2 infused over 1 hour) with or without Herceptin, 60% of

patients had received prior anthracycline-based adjuvant chemotherapy. Patients were treated with Herceptin until disease progression.
The efficacy of Herceptin combined with paclitaxel in patients receiving no adjuvant anthracycline chemotherapy has not been studied. Nevertheless, Herceptin plus docetaxel was effective in all patients – whether they received adjuvant anthracycline or not.
The HER2 overexpression assay used to qualify patients in the pivotal study (Herceptin monotherapy and Herceptin plus paclitaxel) was based on immunohistochemical staining of

HER2 in fixed material from breast cancer tumours using monoclonal murine antibodies CB11 and 4D5. These tissues were fixed in formalin or Bouin's fluid. This clinical trial assay was performed in a central laboratory utilising a 0 to 3+ scale. Patients classified as staining 2+ or
3+ were included, while those staining 0 or 1+ were excluded. More than 70% of patients enrolled exhibited 3+ overexpression. The data suggest that beneficial effects were greater
among those patients with higher levels of overexpression of HER2 (3+).
In the pivotal study of docetaxel with or without Herceptin, immunohistochemistry was the main method of testing for HER2 overexpression. A minority of patients were tested using FISH. In this study 87% of included patients displayed IHC3+ overexpression and 95% were IHC3+- and/or FISH-positive.

Combination therapy with Herceptin and paclitaxel or docetaxel:
The following table summarises the efficacy results from the monotherapy and combination therapy studies (with paclitaxel or docetaxel):

Parameter	**Combination therapy**				**Monothera**
	Herceptin + paclitaxel 1	**Paclitaxel 1**	**Herceptin + docetaxel 2**	**Docetaxel 2**	**Herceptin1 n=172**
Median duration of response (months) (95% confidence	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	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 (months) (95%	24.8 (18.6-	17.9 (11.2-	31.2 (27.3-	22.7 (19.1-	16.4 (12.3-ND)
Response rate (%) (95% confidence	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 IHC3+ patient subgroup
2 Full analysis population (intention-to-treat)

Combination treatment with Herceptin and anastrozole:
Herceptin has been studied in combination with anastrozole for first-line treatment of HER2- overexpressing, hormone receptor-positive (e.g. oestrogen receptor [ER]-positive and/or progesterone receptor [PR]-positive) postmenopausal patients with metastatic breast cancer who have not received chemotherapy for their metastatic disease. Patients with cerebral metastases were also excluded. Progression-free survival was significantly improved in the Herceptin plus anastrozole arm compared to anastrozole alone (4.8 months versus 2.4 months, p=0.0016). The following parameters were also improved by addition of Herceptin: overall response (16.5% versus 6.7%), clinical benefit rate (42.7% versus 27.9%) and time to progression (4.8 months versus 2.4 months). For time to response and duration of response no difference could be found between the two arms. The median overall survival

was extended by 4.6 months for patients in the combination arm. The difference was not statistically significant. However, it must be borne in mind that more than half the patients in the anastrozole alone arm crossed over to a Herceptin-containing regimen after disease progression. Fifty-two percent of patients receiving Herceptin plus anastrozole survived for at least 2 years compared to 45% of patients receiving anastrozole only at the start of treatment (statistically non-significant difference).

Early breast cancer
In the adjuvant setting, Herceptin was investigated in four multicentre, randomised phase III
trials:
The BO16348 (HERA) study was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2-positive early breast cancer following surgery, established chemotherapy and (where applicable) radiotherapy. In addition, two-year and one-year Herceptin treatments were compared. Patients assigned to receive Herceptin were given an initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight every three 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 tumours at least 1 cm in diameter.
The efficacy results from the BO16348 (HERA) study are summarised in the following table:

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

12 months

Median follow-up
8 years

Parameter	No Herceptin, observation only n=1693	Herceptin 1 year only n=1693	No Herceptin, observation 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

The co-primary endpoint of disease-free survival after 1 year versus observation was within the pre- defined 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 randomised after the cut-off date for the 12-month median follow-up.

The efficacy results in the interim analysis exceeded the statistical limits pre-defined 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 to an

absolute benefit, in terms of 2-year disease-free survival, of 7.6 percentage points (85.8% vs 78.2%) in favour of the Herceptin arm.
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 favour of 1-year Herceptin treatment.
In this final analysis, extending Herceptin treatment to two 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 analysed 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 tumours, defined as HER2-positive and positive axillary lymph nodes or HER2-positive and negative axillary lymph nodes 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 after AC chemotherapy. Paclitaxel was administered as follows:
– intravenous paclitaxel 80 mg/m2 as a continuous i.v. infusion, given every week for 12 weeks
or
– intravenous paclitaxel 175 mg/m2 as a continuous i.v. infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).
In the NCCTG 9831 and NSABP B-31 studies, Herceptin i.v. was administered weekly together with chemotherapy: initial 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 B-31 at the time of the definitive DFS analysis*:

Parameter	AC→P n=1679	AC→P+H n=1672	p value	Hazard ratio

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

* 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 pre-specified 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 favour of the AC→PH (Herceptin) arm.
The pre-planned 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 combined with 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 node-negative patients at high risk, defined as negative (pN0) lymph node involvement and at least 1 of the following factors: tumour size >2 cm, oestrogen 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/m2 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/m2 as an i.v. infusion over 1 hour, given every 3 weeks for 6 cycles (day 2 of 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 six cycles.
Herceptin i.v. was administered weekly with chemotherapy: initial 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 treatment with chemotherapy, Herceptin was administered every 3 weeks (initial 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 arm.
The efficacy results from the BCIRG 006 study are summarised in the following tables:

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	Hazard ratio vs AC→D (95% CI)
Disease-free survival - Number of patients with event	195 (18.2%)	134 (12.5%)	<0.0001	0.61 (0.49-0.77)
- Number of patients without				
Distant metastases - Number of patients with event	144 (13.4%)	95 (8.8%)	<0.0001	0.59 (0.46-0.77)
- Number of patients without		979		
Death (overall survival event) - Number of patients with event	80 (7.5%)	49 (4.6%)	0.0024	0.58 (0.40-0.83)
- Number of patients without	993	1025		

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	Hazard ratio vs AC→D (95% CI)
Disease-free survival - Number of patients with event	195 (18.2%)	145 (13.5%)	0.0003	0.67 (0.54-0.83)
- Number of patients without				
Distant metastases - Number of patients with event	144 (13.4%)	103 (9.6%)	0.0008	0.65 (0.50-0.84)
- Number of patients without		972		

Death (overall survival event) - Number of patients with event - Number of patients without	80 (7.5%) 993	56 (5.2%) 1019	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 the BCIRG 006 study reflects an absolute benefit in 3-year disease-free survival of 5.8 percentage points (86.7% vs
80.9%) in favour of the AC→DH (Herceptin) arm and 4.6 percentage points (85.5% vs 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% 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 noticed in this subgroup of patients (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 HER-2 positive breast cancer.
Median duration of follow-up in the Herceptin arm was 3.8 years. Pathological complete response is defined as the absence of invasive tumour 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 response (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 favour of the Herceptin arm.

CNS metastases
The HERA trial showed a 0.3% difference in the CNS as the site of first metastatic relapse (1.2% of Herceptin patients vs 0.9% of control patients). Overall, however, the incidence of CNS metastases (first and subsequent relapse) was similar in the two treatment groups (23 patients in the observation group vs 25 in the Herceptin group), indicating the probability of an approximately equal incidence of CNS micrometastases in the two treatment groups at the end of adjuvant chemotherapy.
According to the joint analysis of studies NCCTG N9831 and NSAPB B-31, isolated brain metastases occurred more often as first events in the Herceptin group than in the control group (12 vs 4 in study N9831 and 21 vs 11 in study B-31). After occurrence of the first distant metastases, the patients of study B-31 were followed for further relapses. In total, brain metastases were diagnosed in this study as a first or subsequent event in 28 Herceptin patients and 35 control patients (hazard ratio 0.79, p=0.35).
The incidence of brain metastases in the Herceptin group was thus no higher than in the control group. The differing frequency of brain metastases as first event in the control patients is probably attributable to an earlier relapse in another organ system.

Metastatic adenocarcinoma of the stomach or gastro-oesophageal junction:

The efficacy results from study BO18255 are summarised in the following table. Patients taking part in the study had not previously been treated for metastatic gastric or gastro- oesophageal junction adenocarcinoma. The primary endpoint was overall survival. At the time of analysis a total of 349 of the randomised 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 tumours with higher concentrations of HER2 protein (IHC 2+/FISH+ and IHC 3+/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 for Herceptin +
capecitabine/5-FU and cisplatin, respectively.

Summary of efficacy data (study BO18255):

Population/Parameter	**FP n=290**	**H+FP 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%	1.70a (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 (0.53-1.02)	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
Gastro-oesophageal 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
H+FP: Herceptin + fluoropyrimidine/cisplatin
a Odds ratio
b Subgroup p values not given as power was insufficient to demonstrate differences between study arms.

5.2 Pharmacokinetic properties

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.

Absorption

Not applicable.

Distribution
The following tables show the population-predicted PK exposures (with 5th-95th percentiles) and PK parameter values at clinically relevant concentrations (Cmax and Cmin) 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 tumour type	N	Cmin (µg/ml)	Cmax (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	Cmin,ss	Cmax,ss	AUCss (µg.day/	Time to steady state	Total CL range at steady
8 mg/kg + 6 mg/kg	MBC/EB	119	47.4 (5-115)	179 (107-	1794 (673-	12	0.173-
	AGC	274	32.9 (6.1-	131 (72.5-	1338 (557-	9	0.189-
4 mg/kg + 2 mg/kg qw	MBC/EB	119	66.1 (14.9-	109 (51.0-	1765 (647-	12	0.201-

Metabolism
Not applicable.

Elimination
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 Cmin,ss, or about 97% washout) 7 months after the last dose.

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 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 gastro-oesophageal junction cancer.

Linearity/non-linearity
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 (Vmax) for non-linear elimination was 8.81 mg/day and the Michaelis-Menten constant (Km) 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.

Kinetics in specific patient groups
Hepatic impairment
Detailed pharmacokinetic studies have not been carried out in patients with hepatic impairment.

Renal impairment
Detailed pharmacokinetic studies have not been carried out in patients with renal impairment. A population pharmacokinetic analysis showed that renal impairment does not affect trastuzumab disposition.
Serum creatinine has not been shown to influence the pharmacological disposition of trastuzumab.

Elderly patients
Detailed pharmacokinetic studies have not been carried out in elderly patients. Patient age had no effect on trastuzumab pharmacokinetics.

5.3 Preclinical safety data

Safety pharmacology/Long-term toxicity (or repeat-dose toxicity)
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.
Two non-clinical toxicity studies to evaluate cardiotoxic effects of Herceptin were conducted in cynomolgus monkeys.
The effects of Herceptin were investigated in animals suffering from overt heart damage caused by prior exposure to doxorubicin. At the end of treatment with Herceptin there were no changes in parameters indicative of myocardial cell necrosis. The results showed changes in one parameter – mitral valve E point to septal separation (EPSS) – but not in another two – fractional shortening (FS) and velocity of circumferential shortening (Vcf) – that would have indicated cardiac dysfunction.
One study compared the adverse effects of doxorubicin and Herceptin combination therapy on cardiac function and red and white blood cells with the corresponding side effects of each of the drugs administered alone. The

side effects of combination therapy were somewhat more severe and were more prolonged than those of doxorubicin monotherapy. Herceptin monotherapy did not show any undesirable effects.

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

Reproductive toxicity
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Herceptin vial:
L-Histidine hydrochloride monohydrate, L-histidine, α,α-trehalose dihydrate, polysorbate 20 (produced from genetically modified maize).

Vial with 20 ml of solvent (bacteriostatic water for injection):
benzyl alcohol (E1519) (220 mg), water for injection.

6.2 Incompatibilities

No incompatibility has been observed between Herceptin and polyvinylchloride, polyethylene or polypropylene bags.
Glucose (5%) solution must not be used, as it causes protein aggregation.
In the absence of compatibility studies, Herceptin must not be mixed or diluted with other medicinal products.

6.3 Shelf life

48 months

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Herceptin 150 mg for single-dose use
Shelf life of reconstituted concentrate
The concentrate reconstituted with sterile water for injection is physically and chemically stable for up to 48 hours at 2°C to 8°C.
For microbiological reasons the reconstituted concentrate should immediately be further diluted in the infusion solution. If not, the storage time and conditions of the ready-to-use solution prior to use are the responsibility of

the user and should not exceed 24 hours at 2°C to 8°C unless reconstitution has been carried out under controlled and validated aseptic conditions.
Do not freeze the reconstituted concentrate.

Shelf life of ready-to-use Herceptin 150 mg solution for infusion
The ready-to-use Herceptin infusion solution (diluted in sodium chloride 0.9%) is physically and chemically stable for up to 30 days at 2°C to 8°C and 24 hours at room temperature (≤30°C).
For microbiological reasons the Herceptin infusion solution should be used immediately. If not used immediately, the storage time and conditions of the infusion solution prior to use are the responsibility of the user and should not exceed 24 hours at 2°C to 8°C unless reconstitution and dilution have been carried out under controlled and validated aseptic conditions.

Herceptin 440 mg for multidose use
Shelf life of reconstituted concentrate
The Herceptin concentrate reconstituted with the bacteriostatic water for injection supplied with the 440 mg vial of Herceptin is stable for 28 days at 2°C to 8°C. It contains a preservative and is therefore suitable for multidose use. Any remaining reconstituted concentrate 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 sterile water for injection, with only one dose of Herceptin taken from each vial. The concentrate reconstituted with sterile water for injection should be used immediately. Any unused portion should be discarded.
Do not freeze the reconstituted concentrate.

Shelf life of ready-to-use Herceptin 440 mg solution for infusion
The ready-to-use Herceptin infusion solution (diluted in sodium chloride 0.9%) is physically and chemically stable for up to 24 hours at 2°C to 8°C and thereafter for 24 hours at temperatures up to 30°C.

For microbiological reasons the Herceptin infusion solution should be used immediately. If not used immediately, the storage time and conditions prior to use are the responsibility of the user. The storage time should not exceed 24 hours at 2°C to 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.

6.4 Special precautions for storage

Store in the refrigerator (2-8°C). Keep out of the reach of children.

6.5 Nature and contents of container

150 mg single-dose vials:
1 vial containing Herceptin (trastuzumab) [A]

440 mg multidose vials:
Pack containing 1 vial of Herceptin (trastuzumab) and 1 vial with 20 ml of solvent [A]

6.6 Special precautions for disposal and other handling

Instructions for handling
Instructions for handling Herceptin 150 mg for single-dose use
Preparation for administration:
Each vial of Herceptin is reconstituted with 7.2 ml of sterile water for injection (not supplied). Other reconstitution solvents must not be used. This yields 7.4 ml of solution for single-dose use containing 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. 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 injection onto the Herceptin lyophilised powder for concentrate for solution for infusion in the vial.
2. Rock the vial gently to and fro. DO NOT SHAKE.
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 colourless to pale yellow transparent solution.

Instructions for handling Herceptin 440 mg for multidose use
Preparation for administration:
An appropriate aseptic technique should be used. Each vial of Herceptin is reconstituted with
20 ml of the enclosed bacteriostatic water for injection containing 1.1% benzyl alcohol. This yields a solution for multidose use containing 21 mg/ml trastuzumab at a pH of approximately
6.0. Use of other solvents for reconstitution should be avoided.
To prepare a single dose in patients hypersensitive to benzyl alcohol, water for injection (not supplied) can also be used. Such preparations must 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. Rapid expulsion from a syringe should likewise be avoided.

Instructions for reconstitution:

1. Using a sterile syringe, slowly inject 20 ml of bacteriostatic water onto the Herceptin lyophilized powder for concentrate for solution for infusion in the vial.

7. Marketing Authorization Holder

F. HOFFMAN-LA ROCHE LTD
Address: Grenzacherstrase 124, 4058 Basel
Country: Switzerland

8. Marketing Authorization Number

CTD 20372

9. Date of first authorization/renewal of the authorization

23 Jan 2026

10. Date of revision of the text

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