Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Herceptin 600 mg solution for injection in vial

2. Qualitative and quantitative composition

One vial of 5 mL contains 600 mg of trastuzumab, a humanised IgG1 monoclonal antibody produced by mammalian (Chinese hamster ovary) cell suspension culture and purified by affinity and ion exchange chromatography including specific viral inactivation and removal procedures.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection

Clear to opalescent solution, colourless to yellowish.

4. Clinical particulars

4.1 Therapeutic indications

Breast cancer

Metastatic breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive metastatic breast cancer (MBC):

- as monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease. Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.

- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable.

- in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.

- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive MBC, not previously treated with trastuzumab.

Early breast cancer

Herceptin is indicated for the treatment of adult patients with HER2 positive early breast cancer (EBC).

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section 5.1).

- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.

- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant Herceptin therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections 4.4 and 5.1).

Herceptin should only be used in patients with metastatic or early breast cancer whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay (see sections 4.4 and 5.1).

4.2 Posology and method of administration

HER2 testing is mandatory prior to initiation of therapy (see sections 4.4 and 5.1). Herceptin treatment should only be initiated by a physician experienced in the administration of cytotoxic chemotherapy (see section 4.4), and should be administered by a healthcare professional only.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous fixed dose) is being administered to the patient, as prescribed. Herceptin subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulations and vice versa, using the three-weekly (q3w) dosing regimen, was investigated in study MO22982 (see section 4.8).

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 another trastuzumab-containing product (e.g. trastuzumab emtansine or trastuzumab deruxtecan).

Posology

The recommended dose for Herceptin subcutaneous formulation is 600 mg irrespective of the patient's body weight. No loading dose is required. This dose should be administered subcutaneously over 2-5 minutes every three weeks.

In the pivotal trial (BO22227) Herceptin subcutaneous formulation was administered in the neoadjuvant/adjuvant setting in patients with early breast cancer. The preoperative chemotherapy regimen consisted of docetaxel (75 mg/m²) followed by FEC (5FU, epirubicin and cyclophosphamide) at a standard dose.

See section 5.1 for chemotherapy combination dosing.

Duration of treatment

Patients with MBC should be treated with Herceptin until progression of disease. Patients with EBC should be treated with Herceptin for 1 year or until disease recurrence, whichever occurs first; extending treatment in EBC beyond one year is not recommended (see section 5.1).

Dose reduction

No reductions in the dose of Herceptin were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression butthey should be monitored carefully for complications of neutropenia during this time. Refer to the Summary of Product Characteristics (SmPC) for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

If left ventricular ejection fraction (LVEF) percentage drops ≥ 10 points from baseline AND to below 50 %, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if symptomatic congestive heart failure (CHF) has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

Missed doses

If the patient misses a dose of Herceptin subcutaneous formulation, it is recommended to administer the next 600 mg dose (i.e. the missed dose) as soon as possible. The interval between consecutive Herceptin subcutaneous formulation administrations should not be less than three weeks.

Special populations

Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. In a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

Paediatric population

There is no relevant use of Herceptin in the paediatric population.

Method of administration

The 600 mg dose should be administered as a subcutaneous injection only over 2-5 minutes every three weeks. The injection site should be alternated between the left and right thigh. New injections should be given at least 2.5 cm from the old site and never into areas where the skin is red, bruised, tender, or hard. During the treatment course with Herceptin subcutaneous formulation other medicinal products for subcutaneous administration should preferably be injected at different sites. Patients should be observed for 30 minutes after the first injection and for 15 minutes after subsequent injections for signs or symptoms of administration-related reactions (see sections 4.4 and 4.8).

For instructions on use and handling of Herceptin subcutaneous formulation refer to section 6.6.

4.3 Contraindications

- Hypersensitivity to trastuzumab, murine proteins, hyaluronidase or to any of the other excipients listed in section 6.1.
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures (see section 5.1).

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

Cardiac dysfunction

General considerations

Patients treated with Herceptin are at increased risk for developing CHF (New York Heart Association [NYHA] Class II-IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. These may be moderate to severe and have been associated with death (see section 4.8). In addition, caution should be exercised in treating patients with increased cardiac risk, e.g. hypertension, documented coronary artery disease, CHF, LVEF of <55%, older age.

All candidates for treatment with Herceptin, but especially those with prior anthracycline and cyclophosphamide exposure, should undergo baseline cardiac assessment including history and physical examination and electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan or magnetic resonance imaging. Monitoring may help to identify patients who develop cardiac dysfunction. Cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Herceptin. A careful risk-benefit assessment should be made before deciding to treat with Herceptin.

Trastuzumab may persist in the circulation for up to 7 months after stopping Herceptin treatment based on population pharmacokinetic analysis of all available data (see section 5.2). Patients who receive anthracyclines after stopping Herceptin may possibly be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Formal cardiological assessment should be considered in patients in whom there are cardiovascular concerns following baseline screening. In all patients' cardiac function should be monitored during treatment (e.g. every 12 weeks). Monitoring may help to identify patients who develop cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Herceptin therapy has been seen.

The safety of continuation or resumption of Herceptin in patients who experience cardiac dysfunction has not been prospectively studied. If LVEF percentage drops ≥ 10 points from baseline AND to below 50%, treatment should be suspended and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or declined further, or symptomatic CHF has developed, discontinuation of Herceptin should be strongly considered, unless the benefits for the individual patient are

deemed to outweigh the risks. All such patients should be referred for assessment by a cardiologist and followed up.

If symptomatic cardiac failure develops during Herceptin therapy, it should be treated with standard medicinal products for CHF. Most patients who developed CHF or asymptomatic cardiac dysfunction in pivotal trials improved with standard CHF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on therapy without additional clinical cardiac events.

Metastatic breast cancer

Herceptin and anthracyclines should not be given concurrently in combination in the MBC setting.

Patients with MBC who have previously received anthracyclines are also at risk of cardiac dysfunction with Herceptin treatment, although the risk is lower than with concurrent use of Herceptin and anthracyclines.

Early breast cancer

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

Patients with history of myocardial infarction (MI), angina pectoris requiring medical treatment, history of or existing CHF (NYHA Class II –IV), LVEF of < 55%, other cardiomyopathy, cardiac arrhythmia requiring medical treatment, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medical treatment eligible), and hemodynamic effective pericardial effusion were excluded from adjuvant and neoadjuvant EBC pivotal trials with Herceptin and therefore treatment cannot be recommended in such patients.

Adjuvant treatment

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

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin (intravenous formulation) was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when Herceptin (intravenous formulation) was administered concurrently with taxanes than when

administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. In one of the 3 pivotal studies conducted in which a median follow-up of 5.5 years was available (BCIRG006) a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events was observed (up to 2.37 %) in patients who were administered Herceptin concurrently with a taxane following anthracycline therapy, compared to approximately 1 % in the two comparator arms (anthracycline plus cyclophosphamide followed by taxane and taxane, carboplatin and Herceptin).

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low LVEF (<55%) at baseline, prior to or following the initiation of paclitaxel treatment, decline in LVEF by 10-15 points, and prior or concurrent use of anti-hypertensive medicinal products. 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 body mass index (BMI) >25 kg/m^2.

Neoadjuvant-adjuvant treatment

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

If patients have been treated concurrently with a full course of low-dose anthracyclines and Herceptin in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery. In other situations, the decision on the need for additional cytotoxic chemotherapy is determined based on individual factors.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited to two trials (MO16432 and BO22227).

In the pivotal trial MO16432, Herceptin was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2) . The incidence of symptomatic cardiac dysfunction was 1.7% in the Herceptin arm .

In the pivotal trial BO22227, Herceptin was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m^2); at a median follow-up exceeding 70 months, the incidence of cardiac failure/congestive cardiac failure was 0.3% in the Herceptin intravenous arm and 0.7% in the Herceptin subcutaneous arm. In patients with lower body weights (<59 kg, the lowest body weight quartile) the fixed dose used in the Herceptin subcutaneous arm was not associated with an increased risk of cardiac events or significant drop in LVEF.

Clinical experience is limited in patients above 65 years of age.

Administration-related reactions

Administration-related reactions (ARRs) are known to occur with Herceptin subcutaneous formulation. Pre-medication may be used to reduce risk of occurrence of ARRs.

Although serious ARRs, including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, were not reported in the clinical trial with the Herceptin subcutaneous formulation, caution should be exercised as these have been associated with the intravenous formulation. Patients should be observed for ARRs for 30 minutes after the first injection and for 15 minutes after subsequent injections. ARRs considered mild in severity can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions to intravenous Herceptin have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions were associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal ARR. Therefore, these patients should not be treated with Herceptin (see section 4.3).

Pulmonary events

Caution is recommended with Herceptin subcutaneous formulation as severe pulmonary events have been reported with the use of the intravenous formulation in the post-marketing setting (see section 4.8). These events have occasionally been fatal and may occur as part of an infusion-related reaction or with delayed onset. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients 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 (see section 4.3). Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes.

Sodium

Herceptin contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. Clinically significant interactions between Herceptin and the concomitant medicinal products used in clinical trials have not been observed.

Effect of trastuzumab on the pharmacokinetics of other antineoplastic agents

Pharmacokinetic data from studies BO15935 and M77004 in women with HER2-positive MBC suggested that exposure to paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) was not altered in the presence of trastuzumab (8 mg/kg or 4 mg/kg IV loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w IV, respectively).
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 was unclear.

Data from study JP16003, a single-arm study of Herceptin (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m2 IV) in Japanese women with HER2- positive MBC, suggested that concomitant administration of Herceptin had no effect on the single dose pharmacokinetics of docetaxel. Study JP19959 was a substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer to study the pharmacokinetics of capecitabine and cisplatin when used with or without Herceptin. The results of this substudy suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus Herceptin. However, capecitabine itself showed higher concentrations and a longer half-life when combined with Herceptin. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Herceptin.

Pharmacokinetic data from Study H4613g/GO01305 in patients with metastatic or locally advanced inoperable HER2-positive cancer suggested that trastuzumab had no impact on the PK of carboplatin.

Effect of antineoplastic agents on trastuzumab pharmacokinetics

By comparison of simulated serum trastuzumab concentrations after Herceptin monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2- positive MBC (study JP16003) no evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetics of trastuzumab was found.

Comparison of PK results from two Phase II studies (BO15935 and M77004) and one Phase III study (H0648g) in which patients were treated concomitantly with Herceptin and paclitaxel and two Phase II studies in which Herceptin was administered as monotherapy (W016229 and MO16982), in women with HER2-positive MBC indicates that individual and mean trastuzumab trough serum concentrations varied within and across

studies but there was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab. Comparison of trastuzumab PK data from Study M77004 in which women with HER2-positive MBC were treated concomitantly with Herceptin, paclitaxel and doxorubicin to trastuzumab PK data in studies where Herceptin was administered as monotherapy (H0649g) or in combination with anthracycline plus cyclophosphamide or paclitaxel (Study H0648g), suggested no effect of doxorubicin and paclitaxel on the pharmacokinetics of trastuzumab.

Pharmacokinetic data from Study H4613g/GO01305 suggested that carboplatin had no impact on the PK of trastuzumab.

The administration of concomitant anastrozole did not appear to influence the pharmacokinetics of trastuzumab.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception

Women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for 7 months after treatment has concluded (see section 5.2).

Pregnancy

Reproduction studies have been conducted in Cynomolgus monkeys at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin intravenous formulation and have revealed no evidence of impaired fertility or harm to the fetus. Placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) fetal development period was observed. It is not known whether Herceptin can affect reproductive capacity. As animal reproduction studies are not always predictive of human response, Herceptin should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

In the post-marketing setting, cases of fetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the fetus, have been reported in pregnant women receiving Herceptin. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Herceptin, or if a patient becomes pregnant while receiving Herceptin or within 7 months following last dose of Herceptin, close monitoring by a multidisciplinary team is desirable.

Breast-feeding

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

trastuzumab in utero and the presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 1 month of age. It is not known whether trastuzumab is secreted in human milk. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during Herceptin therapy and for 7 months after the last dose.

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

Herceptin has a minor influence on the ability to drive or use machines (see section 4.8). Dizziness and somnolence may occur during treatment with Herceptin (see section 4.8). Patients experiencing administration-related symptoms (see section 4.4) should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

Amongst the most serious and/or common adverse reactions reported in Herceptin usage (intravenous and subcutaneous formulations) to date are cardiac dysfunction, administration-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

The safety profile of Herceptin subcutaneous formulation (evaluated in 298 and 297 patients treated with the intravenous and subcutaneous formulations respectively) from the pivotal trial in EBC was overall similar to the known safety profile of the intravenous formulation.

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

Some adverse events / reactions were reported with a higher frequency for the subcutaneous formulation:

- Serious adverse events (most of which were identified because of in-patient hospitalisation or prolongation of existing hospitalisation): 14.1 % for the intravenous formulation versus 21.5 % for the subcutaneous formulation. The difference in serious adverse event rates between formulations was mainly due to infections with or without neutropenia (4.4 % versus 8.1 %) and cardiac disorders (0.7 % versus 1.7 %);

- Post-operative wound infections (severe and/or serious): 1.7 % versus 3.0 % for the intravenous formulation versus subcutaneous formulation, respectively;
- Administration-related reactions: 37.2 % versus 47.8 % for the intravenous formulation versus subcutaneous formulation, respectively during the treatment phase;
- Hypertension: 4.7 % versus 9.8 % for the intravenous formulation versus subcutaneous formulation respectively.

Tabulated list of adverse reactions with the intravenous formulation

In this section, the following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Presented in Table 1 are adverse reactions that have been reported in association with the use of intravenous Herceptin alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting.

All the terms included are based on the highest percentage seen in pivotal clinical trials. In addition, terms reported in the post marketing setting are included in Table 1.

Table 1: Undesirable effects reported with intravenous Herceptin monotherapy or in combination with chemotherapy in pivotal clinical trials (N = 8386) and in post-marketing

System organ class	**Adverse reaction**	**Frequency**
Infections and infestations	Infection	Very common
	Nasopharyngitis	Very common
	Neutropenic sepsis	Common
	Cystitis	Common
	Influenza	Common
	Sinusitis	Common
	Skin infection	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
	Pharyngitis	Common
Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)	Malignant neoplasm progression	Not known
	Neoplasm progression	Not known
Blood and lymphatic system disorders	Febrile neutropenia	Very common
	Anaemia	Very common
	Neutropenia	Very common
	White blood cell count decreased/leukopenia	Very common
	Thrombocytopenia	Very common

System organ class	Adverse reaction	Frequency
	Hypoprothrombinaemia	Not known
	Immune thrombocytopenia	Not known
Immune system disorders	Hypersensitivity	Common
	+Anaphylactic reaction	Rare
	+Anaphylactic shock	Rare
Metabolism and nutrition disorders	Weight decreased/Weight loss	Very common
	Anorexia	Very common
	Tumour lysis syndrome	Not known
	Hyperkalaemia	Not known
Psychiatric disorders	Insomnia	Very common
	Anxiety	Common
	Depression	Common
Nervous system disorders	[1]Tremor	Very common
	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common
	Dysgeusia	Very common
	Peripheral neuropathy	Common
	Hypertonia	Common
	Somnolence	Common
Eye disorders	Conjunctivitis	Very common
	Lacrimation increased	Very common
	Dry eye	Common
	Papilloedema	Not known
	Retinal haemorrhage	Not known
Ear and labyrinth disorders	Deafness	Uncommon
Cardiac disorders	[1] Blood pressure decreased	Very common
	[1] Blood pressure increased	Very common
	[1] Heart beat irregular	Very common
	[1]Cardiac flutter	Very common
	Ejection fraction decreased*	Very common
	+Cardiac failure (congestive)	Common
	+[1]Supraventricular tachyarrhythmia	Common
	Cardiomyopathy	Common
	[1]Palpitation	Common
	Pericardial effusion	Uncommon
	Cardiogenic shock	Not known
	Gallop rhythm present	Not known
Vascular disorders	Hot flush	Very common
	+[1] Hypotension	Common
	Vasodilatation	Common
Respiratory, thoracic and mediastinal disorders	+Dyspnoea	Very common
	Cough	Very common
	Epistaxis	Very common
	Rhinorrhoea	Very common
	+Pneumonia	Common
	Asthma	Common
	Lung disorder	Common
	+Pleural effusion	Common
	+[1]Wheezing	Uncommon
	Pneumonitis	Uncommon
	+Pulmonary fibrosis	Not known
	+Respiratory distress	Not known
	+Respiratory failure	Not known

System organ class	Adverse reaction	Frequency
	[+]Lung infiltration	Not known
	[+]Acute pulmonary oedema	Not known
	[+]Acute respiratory distress syndrome	Not known
	[+]Bronchospasm	Not known
	[+]Hypoxia	Not known
	[+]Oxygen saturation decreased	Not known
	Laryngeal oedema	Not known
	Orthopnoea	Not known
	Pulmonary oedema	Not known
	Interstitial lung disease	Not known
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	[1] Lip swelling	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Haemorrhoids	Common
	Dry mouth	Common
Hepatobiliary disorders	Hepatocellular Injury	Common
	Hepatitis	Common
	Liver Tenderness	Common
	Jaundice	Rare
Skin and subcutaneous tissue disorders	Erythema	Very common
	Rash	Very common
	[1] Swelling face	Very common
	Alopecia	Very common
	Nail disorder	Very common
	Palmar-plantar erythrodysaesthesia syndrome	Very common
	Acne	Common
	Dry skin	Common
	Ecchymosis	Common
	Hyperhydrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Dermatitis	Common
	Urticaria	Uncommon
	Angioedema	Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	[1]Muscle tightness	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck pain	Common
	Pain in extremity	Common
Renal and urinary disorders	Renal disorder	Common
	Glomerulonephritis membranous	Not known
	Glomerulonephropathy	Not known

System organ class	Adverse reaction	Frequency
	Renal failure	Not known
Pregnancy, puerperium and perinatal conditions	Oligohydramnios	Not known
	Renal hypoplasia	Not known
	Pulmonary hypoplasia	Not known
Reproductive system and breast disorders	Breast inflammation/mastitis	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Mucosal inflammation	Very common
	Peripheral oedema	Very common
	Malaise	Common
	Oedema	Common
Injury, poisoning and procedural complications	Contusion	Common

+ Denotes adverse reactions that have been reported in association with a fatal outcome.
1 Denotes adverse reactions that are reported largely in association with administration-related reactions. Specific percentages for these are not available.
* Observed with combination therapy following anthracyclines and combined with taxanes

Description of selected adverse reactions

Cardiac dysfunction

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

In 3 pivotal EBC clinical trials of adjuvant intravenous Herceptin given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (specifically symptomatic congestive heart failure) was similar in patients who were administered chemotherapy alone (ie did not receive Herceptin) and in patients who were administered Herceptin sequentially after a taxane (0.3-0.4 %). The rate was highest in patients who were administered Herceptin concurrently with a taxane (2.0 %). In the neoadjuvant setting, the experience of concurrent administration of Herceptin and low dose anthracycline regimen is limited (see section 4.4).

When Herceptin was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6 % of patients in the one-year arm after a median follow-up of 12 months. In study

BO16348, after a median follow-up of 8 years the incidence of severe CHF (NYHA Class III & IV) in the Herceptin 1 year treatment arm was 0.8 %, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6 %.
Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥50 % after the event) was evident for 71.4 % of Herceptin-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5 % of patients. Approximately 17 % of cardiac dysfunction related events occurred after completion of Herceptin.

In the pivotal metastatic trials of intravenous Herceptin, the incidence of cardiac dysfunction varied between 9 % and 12 % when it was combined with paclitaxel compared with 1 % – 4 % for paclitaxel alone. For monotherapy, the rate was 6 % – 9 %. The highest rate of cardiac dysfunction was seen in patients receiving Herceptin concurrently with anthracycline/cyclophosphamide (27 %), and was significantly higher than for anthracycline/cyclophosphamide alone (7 % – 10 %). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic CHF was 2.2 % in patients receiving Herceptin and docetaxel, compared with 0 % in patients receiving docetaxel alone. Most of the patients (79 %) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF.

Administration-related reactions/hypersensitivity

Administration-related reactions (ARRs)/hypersensitivity reactions such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache were seen in Herceptin clinical trials (see section 4.4). The rate of ARRs of all grades varied between studies depending on the indication, the data collection methodology, and whether trastuzumab was given concurrently with chemotherapy or as monotherapy.

Anaphylactoid reactions have been observed in isolated cases.

Haematotoxicity

Febrile neutropenia, leukopenia, anaemia, thrombocytopenia and neutropenia occurred very commonly. The frequency of occurrence of hypoprothrombinemia is not known. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Pulmonary events

Severe pulmonary adverse reactions occur in association with the use of Herceptin and have been associated with a fatal outcome. These include, but are not limited to, pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency (see section 4.4).

Description of selected adverse reactions with the subcutaneous formulation

Administration-related reactions

In the pivotal trial, the rate of all grade ARRs was 37.2 % with the Herceptin intravenous formulation and 47.8 % with the Herceptin subcutaneous formulation; severe grade 3 reactions were reported in 2.0 % and 1.7 % of the patients, respectively during the treatment phase; no severe grade 4 or 5 reactions were observed. All of the severe ARRs with the Herceptin subcutaneous formulation occurred during concurrent administration with chemotherapy. The most frequent severe reaction was drug hypersensitivity.

The systemic reactions included hypersensitivity, hypotension, tachycardia, cough, and dyspnoea. The local reactions included erythema, pruritus, oedema, rash and pain at the site of the injection.

Infections

The rate of severe infections (NCI CTCAE grade ≥3) was 5.0 % versus 7.1 %, in the Herceptin intravenous formulation arm and the Herceptin subcutaneous formulation arm respectively.

The rate of serious infections (most of which were identified because of in-patient hospitalisation or prolongation of existing hospitalisation) was 4.4 % in the Herceptin intravenous formulation arm and 8.1 % in the Herceptin subcutaneous formulation arm. The difference between formulations was mainly observed during the adjuvant treatment phase (monotherapy) and was mainly due to postoperative wound infections, but also to various other infections such as respiratory tract infections, acute pyelonephritis and sepsis. They resolved within a mean of 13 days in the Herceptin intravenous treatment arm and a mean of 17 days in the Herceptin subcutaneous treatment arm.

Hypertensive events

In the pivotal trial BO22227, there were more than twice as many patients reporting all grade hypertension with the Herceptin subcutaneous formulation (4.7 % versus 9.8 % in the intravenous and subcutaneous formulations respectively), with a greater proportion of patients with severe events (NCI CTCAE grade ≥3) <1 % versus 2.0 % the intravenous and subcutaneous formulations respectively. All but one patient who reported severe hypertension had a history of hypertension before they entered the study. Some of the severe events occurred on the day of the injection.

Immunogenicity

In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1% (30/296) of patients treated with Herceptin intravenous and 15.9 % (47/295) of patients receiving Herceptin subcutaneous vial developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the Herceptin intravenous arm and 3 of 47 in the Herceptin subcutaneous arm. 21.0 % of patients treated with Herceptin subcutaneous formulation developed antibodies against the excipient hyaluronidase (rHuPH20).

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

Details of risk minimisation measures that are consistent with the EU Risk Management Plan are presented in Section 4.4.

Switching treatment between Herceptin intravenous and Herceptin subcutaneous formulation and vice versa

Study MO22982 investigated switching between the Herceptin intravenous and Herceptin subcutaneous formulation with a primary objective to evaluate patient preference for either the intravenous or the subcutaneous route of trastuzumab administration. In this trial, 2 cohorts (one using subcutaneous formulation in vial and one using subcutaneous formulation in administration system) were investigated using a 2-arm, cross-over design with 488 patients being randomized to one of two different three-weekly Herceptin treatment sequences (IV [Cycles 1-4]→ SC [Cycles 5-8], or SC [Cycles 1-4]→ IV [Cycles 5-8]). Patients were either naïve to Herceptin IV treatment (20.3%) or pre-exposed to Herceptin IV (79.7%). For the sequence IV→SC (SC vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre-switching (Cycles 1-4) and post-switching (Cycles 5-8) as 53.8% vs. 56.4%, respectively; for the sequence SC→IV (SC vial and SC formulation in administration system cohorts combined), adverse event rates (all grades) were described pre- and post-switching as 65.4% vs. 48.7%, respectively. Pre-switching rates (Cycles 1-4) for serious adverse events, grade 3 adverse events and treatment discontinuations due to adverse events were low (<5%) and similar to post-switching rates (Cycles 5-8). No grade 4 or grade 5 adverse events were reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Single doses of up to 960 mg of Herceptin subcutaneous formulation have been administered with no reported untoward effects.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Herceptin subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). Overexpression of HER2 is observed in 20% - 30% of primary breast cancers. Studies indicate that breast cancer patients whose tumours overexpress HER2 have a shortened disease-free survival compared to patients whose tumours do not overexpress HER2. The extracellular domain of the receptor (ECD, p105) can be shed into the blood stream and measured in serum samples.

Mechanism of action

Trastuzumab binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). *In vitro*, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Detection of HER2 overexpression or HER2 gene amplification

Detection of HER2 overexpression or HER2 gene amplification in breast cancer

Herceptin should only be used in patients whose tumours have HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay. HER2 overexpression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks (see section 4.4). 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 ensure accurate and reproducible results, the testing must be performed in a specialised laboratory, which can ensure validation of the testing procedures.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 2:

Table 2: Recommended scoring system to evaluate the IHC staining patterns

Score	**Staining pattern**	**HER2 overexpression assessment**
0	No staining is observed or membrane staining is observed in < 10 % of the tumour cells	Negative
1+	A faint/barely perceptible membrane staining is detected in > 10 % of the tumour 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 tumour cells.	Equivocal
3+	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 greater 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. Official recommendations on HER2 testing may also apply.

For any other method that may be used for the assessment of HER2 protein or gene expression, the analyses should only be performed by laboratories that provide adequate state-of-the-art performance of validated methods. Such methods must clearly be precise and accurate enough to demonstrate

overexpression of HER2 and must be able to distinguish between moderate (congruent with 2+) and strong (congruent with 3+) overexpression of HER2.

Clinical efficacy and safety

Metastatic breast cancer

Intravenous formulation

Herceptin has been used in clinical trials as monotherapy for patients with MBC who have tumours that overexpress HER2 and who have failed 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 disease. Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m^2 infused over 3 hours) with or without Herceptin. In the pivotal trial of docetaxel (100 mg/m^2 infused over 1 hour) with or without Herceptin, 60 % of the patients had received prior anthracycline-based adjuvant chemotherapy. Patients were treated with Herceptin until progression of disease.

The efficacy of Herceptin in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been studied. However, Herceptin plus docetaxel was efficacious in patients whether or not they had received prior adjuvant anthracyclines.

The test method for HER2 overexpression used to determine eligibility of patients in the pivotal Herceptin monotherapy and Herceptin plus paclitaxel clinical trials employed immunohistochemical staining for HER2 of fixed material from breast tumours using the murine monoclonal antibodies CB11 and 4D5. These tissues were fixed in formalin or Bouin's fixative. This investigative clinical trial assay performed in a central laboratory utilised a 0 to 3+ scale. Patients classified as staining 2+ or 3+ were included, while those staining 0 or 1+ were excluded. Greater 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+).

The main test method used to determine HER2 positivity in the pivotal trial of docetaxel, with or without Herceptin, was immunohistochemistry. A minority of patients was tested using fluorescence *in-situ* hybridisation (FISH). In this trial, 87 % of patients entered had disease that was IHC3+, and 95 % of patients entered had disease that was IHC3+ and/or FISH-positive.

Weekly dosing in metatstatic breast cancer

The efficacy results from the monotherapy and combination therapy studies are summarised in Table 3:

Table 3: Efficacy results from the monotherapy and combination therapy studies

Parameter	**Monotherapy**	**Combination Therapy**			
	Herceptin[1] N=172	**Herceptin plus paclitaxel[2] N=68**	**Paclitaxel[2] N=77**	**Herceptin plus docetaxel[3] N=92**	**Docetaxel[3] N=94**
Response rate (95 %CI)	18 % (13-25)	49 % (36- 61)	17 % (9-27)	61 % (50-71)	34 % (25-45)
Median duration of response (months) (95 %CI)	9.1 (5.6-10.3)	8.3 (7.3-8.8)	4.6 (3.7-7.4)	11.7 (9.3–15.0)	5.7 (4.6-7.6)
Median TTP (months) (95 %CI)	3.2 (2.6-3.5)	7.1 (6.2-12.0)	3.0 (2.0-4.4)	11.7 (9.2-13.5)	6.1 (5.4-7.2)
Median Survival (months) (95 %CI)	16.4 (12.3-ne)	24.8 (18.6-33.7)	17.9 (11.2-23.8)	31.2 (27.3-40.8)	22.74 (19.1-30.8)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

1. Study H0649g: IHC3+ patient subset
2. Study H0648g: IHC3+ patient subset
3. Study M77001: Full analysis set (intent-to-treat), 24 months results

Combination treatment with Herceptin and anastrozole

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

Three -weekly dosing in metastatic breast cancer

The efficacy results from the non-comparative monotherapy and combination therapy studies are summarised in Table 4:

Table 4: Efficacy results from the non-comparative monotherapy and combination therapy studies

Parameter	**Monotherapy**		**Combination Therapy**	
	Herceptin[1] **N=105**	**Herceptin[2]** **N=72**	**Herceptin plus paclitaxel[3]** **N=32**	**Herceptin plus docetaxel[4]** **N=110**
Response rate (95 %CI)	24 % (15-35)	27 % (14-43)	59 % (41-76)	73 % (63-81)
Median duration of response (months) (range)	10.1 (2.8-35.6)	7.9 (2.1-18.8)	10.5 (1.8-21)	13.4 (2.1-55.1)
Median TTP (months) (95 %CI)	3.4 (2.8-4.1)	7.7 (4.2-8.3)	12.2 (6.2-ne)	13.6 (11-16)
Median Survival (months) (95 %CI)	ne	ne	ne	47.3 (32-ne)

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.

1. Study WO16229: loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule
2. Study MO16982: loading dose 6 mg/kg weekly x 3; followed by 6 mg/kg 3-weekly schedule
3. Study BO15935
4. Study MO16419

Sites of progression

The frequency of progression in the liver was significantly reduced in patients treated with the combination of Herceptin and paclitaxel, compared to paclitaxel alone (21.8 % versus 45.7 %; p=0.004). More patients treated with Herceptin and paclitaxel progressed in the central nervous system than those treated with paclitaxel alone (12.6 % versus 6.5 %; p=0.377).

Early breast cancer (adjuvant setting)

Intravenous formulation

Early breast cancer is defined as non-metastatic primary invasive carcinoma of the breast.
In the adjuvant treatment setting, Herceptin was investigated in 4 large multicentre, randomised, trials.

- Study BO16348 was designed to compare one and two years of three-weekly Herceptin treatment versus observation in patients with HER2

positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). In addition, comparison of two years of Herceptin treatment versus one year of Herceptin treatment was performed. Patients assigned to receive Herceptin were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years.

- Studies NSABP B-31 and NCCTG N9831 that comprise the joint analysis were designed to investigate the clinical utility of combining Herceptin treatment with paclitaxel following AC chemotherapy, additionally the NCCTG N9831 study also investigated adding Herceptin sequentially to AC→P chemotherapy in patients with HER2 positive EBC following surgery.
- Study BCIRG 006 study was designed to investigate combining Herceptin treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2 positive EBC following surgery.

Early breast cancer in the BO16348 Study was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative if tumors at least 1 cm in diameter.

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

In the BCIRG 006 study HER2 positive, EBC was defined as either lymph node positive or high-risk node negative patients with no (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, estrogen receptor and progesterone receptor negative, histological and/or nuclear grade 2-3, or age < 35 years.

The efficacy results from study BO16348 following 12 months* and 8 years** median follow-up are summarized in the Table 5:

Table 5: Efficacy results from study BO16348

	Median follow-up 12 months*		Median follow-up 8 years**	
Parameter	Observation N=1693	Herceptin 1 Year N = 1693	Observation N= 1697***	Herceptin 1 Year N = 1702***
Disease-free survival				
- No. patients with event	219 (12.9 %)	127 (7.5 %)	570 (33.6 %)	471 (27.7 %)
- No. patients without event	1474 (87.1 %)	1566 (92.5 %)	1127 (66.4 %)	1231 (72.3 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.54		0.76	
Recurrence-free survival				

- No. patients with event	208 (12.3 %)	113 (6.7 %)	506 (29.8 %)	399 (23.4 %)
- No. patients without event	1485 (87.7 %)	1580 (93.3 %)	1191 (70.2 %)	1303 (76.6 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease-free survival				
- No. patients with event	184 (10.9 %)	99 (5.8 %)	488 (28.8 %)	399 (23.4 %)
- No. patients without event	1508 (89.1 %)	1594 (94.6 %)	1209 (71.2 %)	1303 (76.6 %)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death)				
- No. patients with event	40 (2.4 %)	31 (1.8 %)	350 (20.6 %)	278 (16.3 %)
- No. patients without event	1653 (97.6 %)	1662 (98.2 %)	1347 (79.4 %)	1424 (83.7 %)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

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

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

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

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

In the NSABP B-31 and NCCTG N9831 studies Herceptin was administered in combination with paclitaxel, following AC chemotherapy.

Doxorubicin and cyclophosphamide were administered concurrently as follows:

- intravenous push doxorubicin, at 60 mg/ m^2, given every 3 weeks for 4 cycles.

- intravenous cyclophosphamide, at 600 mg/ m^2 over 30 minutes, given every 3 weeks for 4 cycles.

Paclitaxel, in combination with Herceptin, was administered as follows:

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

or

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

The efficacy results from the joint analysis of the NSABP B-31 and NCCTG 9831 trials at the time of the definitive analysis of DFS* are summarized in Table 6. The median duration of follow up was 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm.

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

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

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

* at median duration of follow up of 1.8 years for the patients in the AC→P arm and 2.0 years for patients in the AC→PH arm

** p value for OS did not cross the pre-specified statistical boundary for comparison of AC→PH vs. AC→P

For the primary endpoint, DFS, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit, in terms of 3-year disease-free survival rate estimates of 11.8 percentage points (87.2 % versus 75.4 %) in favour of the AC→PH (Herceptin) arm.
At the time of a safety update after a median of 3.5-3.8 years follow up, an analysis of DFS reconfirms the magnitude of the benefit shown in the

definitive analysis of DFS. Despite the cross-over to Herceptin in the control arm, the addition of Herceptin to paclitaxel chemotherapy resulted in a 52 % decrease in the risk of disease recurrence. The addition of Herceptin to paclitaxel chemotherapy also resulted in a 37 % decrease in the risk of death.

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

The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in Table 7:

Table 7: Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831

Parameter	AC→P (N=2032)	AC→PH (N=2031)	p-value versus AC→P	Hazard Ratio versus AC→P (95% CI)
Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	< 0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: trastuzumab

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

In the BCIRG 006 study 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:

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

or

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

which was followed by:

- carboplatin – at target AUC = 6 mg/mL/min administered by intravenous infusion over 30-60 minutes repeated every 3 weeks for a total of six cycles

Herceptin was administered weekly with chemotherapy and 3 weekly thereafter for a total of 52 weeks.

The efficacy results from the BCIRG 006 are summarized in Tables 8 and 9. The median duration of follow up was 2.9 years in the AC→D arm and 3.0 years in each of the AC→DH and DCarbH arms.

Table 8: Overview of efficacy analyses BCIRG 006 AC→D versus AC→DH

Parameter	AC→D (n=1073)	AC→DH (n=1074)	Hazard Ratio vs AC→D (95 % CI) p-value
Disease-free survival No. patients with event	195	134	0.61 (0.49, 0.77) p<0.0001
Distant recurrence No. patients with event	144	95	0.59 (0.46, 0.77) p<0.0001
Death (OS event) No. patients with event	80	49	0.58 (0.40, 0.83) p=0.0024

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

Table 9: Overview of efficacy analyses BCIRG 006 AC→D versus DCarbH

Parameter	AC→D (n=1073)	DCarbH (n=1074)	Hazard Ratio vs AC→D (95 % CI)
Disease-free survival No. patients with event	195	145	0.67 (0.54, 0.83) p=0.0003
Distant recurrence No. patients with event	144	103	0.65 (0.50, 0.84) p=0.0008
Death (OS event) No. patients with event	80	56	0.66 (0.47, 0.93) p=0.0182

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

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

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

In addition, a post-hoc exploratory analysis was performed on the data sets from the joint analysis (JA) NSABP B-31/NCCTG N9831* and BCIRG006 clinical studies combining DFS events and symptomatic cardiac events and summarised in Table 10:

Table 10: Post-hoc exploratory analysis results from the joint analysis NSABP B-31/NCCTG N9831* and BCIRG006 clinical studies combining DFS events and symptomatic cardiac events

	AC→PH (vs. AC→P) (NSABP B-31 and NCCTG N9831)*	AC→DH (vs. AC→D) (BCIRG 006)	DCarbH (vs. AC→D) (BCIRG 006)
Primary efficacy analysis DFS Hazard ratios (95 % CI) p-value	0.48 (0.39, 0.59) p<0.0001	0.61 (0.49, 0.77) p< 0.0001	0.67 (0.54, 0.83) p=0.0003
Long term follow-up efficacy analysis** DFS Hazard ratios (95 % CI) p-value	0.61 (0.54, 0.69) p<0.0001	0.72 (0.61, 0.85) p<0.0001	0.77 (0.65, 0.90) p=0.0011
Post-hoc exploratory analysis with DFS and symptomatic cardiac events Long term follow-up** Hazard ratios (95 % CI)	0.67 (0.60, 0.75)	0.77 (0.66, 0.90)	0.77 (0.66, 0.90)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel; Carb: carboplatin; H: trastuzumab
CI = confidence interval
* At the time of the definitive analysis of DFS. Median duration of follow up was 1.8 years in the AC→P arm and 2.0 years in the AC→PH arm
** Median duration of long-term follow-up for the Joint Analysis clinical studies was 8.3 years (range: 0.1 to 12.1) for the AC→PH arm and 7.9 years (range: 0.0 to 12.2) for the AC→P arm; Median duration of long-term follow-up for the BCIRG 006 study was 10.3 years in both the AC→D arm

(range: 0.0 to 12.6) and the DCarbH arm (range: 0.0 to 13.1), and was 10.4 years (range: 0.0 to 12.7) in the AC→DH arm

Early breast cancer – (neoadjuvant-adjuvant setting)

Intravenous formulation

So far, no results are available which compare the efficacy of Herceptin administered with chemotherapy in the adjuvant setting with that obtained in the neo-adjuvant/adjuvant setting.

In the neoadjuvant-adjuvant treatment setting, study MO16432, a multicentre randomised trial, was designed to investigate the clinical efficacy of concurrent administration of Herceptin with neoadjuvant chemotherapy including both an anthracycline and a taxane, followed by adjuvant Herceptin, up to a total treatment duration of 1 year. The study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory EBC. Patients with HER2+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant Herceptin, or neoadjuvant chemotherapy alone.

In study MO16432, Herceptin (8 mg/kg loading dose, followed by 6 mg/kg maintenance every 3 weeks) was administered concurrently with 10 cycles of neoadjuvant chemotherapy

as follows:

- Doxorubicin 60mg/m^2 and paclitaxel 150 mg/m^2, administered 3-weekly for 3 cycles,

which was followed by
- Paclitaxel 175 mg/m^2 administered 3-weekly for 4 cycles,

which was followed by
- CMF on day 1 and 8 every 4 weeks for 3 cycles

which was followed after surgery by
- additional cycles of adjuvant Herceptin (to complete 1 year of treatment)

The efficacy results from Study MO16432 are summarized in Table 11. The median duration of follow-up in the Herceptin arm was 3.8 years.

Table 11: Efficacy results from MO16432

Parameter	Chemo + Herceptin (n=115)	Chemo only (n=116)	
Event-free survival No. patients with event	46	59	Hazard Ratio (95 % CI) 0.65 (0.44, 0.96) p=0.0275
Total pathological complete response* (95 % CI)	40 % (31.0, 49.6)	20.7 % (13.7, 29.2)	P=0.0014
Overall survival No. patients with event	22	33	Hazard Ratio (95 % CI) 0.59 (0.35, 1.02) p=0.0555

* defined as absence of any invasive cancer both in the breast and axillary nodes

An absolute benefit of 13 percentage points in favour of the Herceptin arm was estimated in terms of 3-year event-free survival rate (65 % versus. 52 %).

Subcutaneous formulation

Study BO22227 was designed to demonstrate non-inferiority of treatment with Herceptin subcutaneous formulation versus Herceptin intravenous formulation based on co-primary PK and efficacy endpoints (trastuzumab C_{trough} at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively). A total of 595 patients with HER2-positive, operable or locally advanced breast cancer (LABC) including inflammatory breast cancer received eight cycles of either Herceptin intravenous formulation or Herceptin subcutaneous formulation concurrently with chemotherapy (4 cycles of docetaxel, 75 mg/m^2 intravenous infusion, followed by 4 cycles of FEC ([5-Fluorouracil, 500 mg/m^2; epirubicin, 75 mg/m^2; cyclophosphamide, 500 mg/m^2 each intravenous bolus or infusion]), followed by surgery, and continued therapy with Herceptin intravenous formulation or Herceptin subcutaneous formulation as originally randomized for 10 additional cycles, for a total of one year of treatment.

The analysis of the efficacy co-primary endpoint, pCR, defined as absence of invasive neoplastic cells in the breast, resulted in rates of 40.7 % (95 % CI: 34.7, 46.9) in the Herceptin intravenous arm and 45.4 % (95 % CI: 39.2 %, 51.7 %) in the Herceptin subcutaneous arm, a difference of 4.7 percentage points in favour of the Herceptin subcutaneous arm. The lower boundary of the one-sided 97.5 % confidence interval for the difference in pCR rates was -4.0, establishing the non-inferiority of Herceptin subcutaneous for the co-primary endpoint

Table 12: Summary of pathological Complete Response (pCR)

	Herceptin IV (N = 263)	Herceptin SC (N=260)
pCR (absence ofinvasive neoplastic cells in breast	107 (40.7%)	118 (45.4%)
Non-responders	156 (59.3%)	142 (54.6%)
Exact 95% CI for pCR Rate*	(34.7; 46.9)	(39.2; 51.7)

Difference in pCR (SC minus IV arm)	4.70
Lower bound one-sided 97.5% CI for the difference in pCR**	-4.0

*Confidence interval for one sample binomial using Pearson-Clopper method
**Continuity correction of Anderson and Hauck (1986) has been used in this calculation

Analyses with longer term follow-up of a median duration exceeding 40 months supported the non-inferior efficacy of Herceptin subcutaneous compared to Herceptin intravenous with comparable results of both EFS and OS (3-year EFS rates of 73% in the Herceptin intravenous arm and 76% in the Herceptin subcutaneous arm, and 3-year OS rates of 90% in the Herceptin intravenous arm and 92% in the Herceptin subcutaneous arm).

For non-inferiority of the PK co-primary endpoint, steady-state trastuzumab C_{trough} value at the end of treatment Cycle 7, refer to section 5.2. Pharmacokinetic Properties. For the comparative safety profile see section 4.8.

The final analysis at a median follow-up exceeding 70 months showed similar EFS and OS between patients who received Herceptin IV and those who received Herceptin SC. The 6-year EFS rate was 65% in both arms (ITT population: HR=0.98 [95% CI: 0.74;1.29]) and the OS rate, 84% in both arms (ITT population: HR=0.94 [95% CI: 0.61;1.45]).

Study MO28048 investigating the safety and tolerability of Herceptin subcutaneous formulation as adjuvant therapy in HER2 positive EBC patients who were enrolled in either a Herceptin subcutaneous vial cohort (N=1868 patients, including 20 patients receiving neoadjuvant therapy) or a Herceptin subcutaneous administration system cohort (N=710 patients, including 21 patients receiving neoadjuvant therapy) resulted in no new safety signals. Results were consistent with the known safety profile for Herceptin intravenous and Herceptin subcutaneous formulations. In addition, treatment of lower body weight patients with Herceptin subcutaneous fixed dose in adjuvant EBC was not associated with increased safety risk, adverse events and serious adverse events, compared to the higher body weight patients. The final results of study BO22227 at a median follow-up exceeding 70 months were also consistent with the known safety profile for Herceptin IV and Herceptin SC, and no new safety signals were observed.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Herceptin in all subsets of the paediatric population for breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of trastuzumab at a dose of 600 mg administered three-weekly by the subcutaneous route was compared to the intravenous route (8 mg/kg loading dose, 6 mg/kg maintenance every three weeks) in the phase III study BO22227. The pharmacokinetic results for the co primary endpoint, C_{trough} pre dose Cycle 8, showed non-inferiority of the Herceptin subcutaneous compared to the Herceptin intravenous dose adjusted by body weight.

The mean C_{trough} during the neoadjuvant treatment phase, at the pre dose Cycle 8 time point, was higher in the Herceptin subcutaneous arm (78.7 µg/mL) than the Herceptin intravenous arm (57.8 µg/mL) of the study. During the adjuvant phase of treatment, at the pre-dose Cycle 13 time point, the mean C_{trough} values were 90.4 µg/mL and 62.1 µg/mL, respectively. Based on the observed data in study BO22227, steady state with the intravenous formulation was reached at cycle 8. With Herceptin subcutaneous formulation, concentrations were approximately at steady-state following Cycle 7 dose (pre-dose Cycle 8) with small increase in concentration (<15%) up to cycle 13. The mean C_{trough} at the subcutaneous pre- dose cycle 18 was 90.7 µg/mL and is similar to that of cycle 13, suggesting no further increase after cycle 13.

The median T_{max} following subcutaneous administration was approximately 3 days, with high interindividual variability (range 1-14 days). The mean C_{max} was expectedly lower in the Herceptin subcutaneous formulation (149 µg/mL) than in the intravenous arm (end of infusion value: 221 µg/mL).

The mean $AUC_{0\text{-}21\ days}$ following the Cycle 7 dose was approximately 10 % higher with the Herceptin subcutaneous formulation as compared to the Herceptin intravenous formulation, with mean AUC values of 2268 µg/mL•day and 2056 µg/mL•day, respectively. The $AUC_{0\text{-}21\ days}$ following Cycle 12 dose was approximately 20 % higher with the Herceptin subcutaneous formulation than the Herceptin intravenous dose, with mean AUC values of 2610 µg/mL•day and 2179 µg/mL•day, respectively. Due to the significant impact of body weight on trastuzumab clearance and the use of a fixed dose for the subcutaneous administration the difference in exposure between subcutaneous and intravenous administration was dependent on body weight: in patients with a body weight < 51 kg, mean steady state AUC of trastuzumab was about 80% higher after subcutaneous than after intravenous treatment whereas in the highest BW group (> 90 kg) AUC was 20% lower after subcutaneous than after intravenous treatment.

A population PK model with parallel linear and nonlinear elimination from the central compartment was constructed using pooled Herceptin SC and Herceptin IV PK data from the phase III study BO22227 to describe the observed PK concentrations following Herceptin IV and Herceptin SC administration in EBC patients. Bioavailability of trastuzumab given as the subcutaneous formulation was estimated to be 77.1%, and the first order absorption rate constant was estimated to be 0.4 day-1. Linear clearance was 0.111 L/day and the central compartment volume (V_c) was 2.91 L. The Michaelis-Menten parameter values were 11.9 mg/day and 33.9 µg/mL for V_{max} and K_m, respectively. Body weight and serum alanine aminotransferase

(SGPT/ALT) showed a statistically significant influence on PK, however, simulations demonstrated that no dose adjustments are required in EBC patients. The population predicted PK exposure parameter values (median with 5th - 95th Percentiles) for Herceptin SC dosing regimens in EBC patients are shown in Table 13 below.

Table 13 Population Predicted PK Exposure Values (median with 5th - 95th Percentiles) for the Herceptin SC 600 mg Q3W Dosing Regimen in EBC patients

Primary tumor type and Regimen	**Cycle**	**N**	**C_{min} (µg/mL)**	**C_{max} (µg/mL)**	**$AUC_{0\text{-}21days}$ (µg.day/mL)**
EBC 600 mg Herceptin SC q3w	Cycle 1	297	28.2 (14.8 - 40.9)	79.3 (56.1 - 109)	1065 (718 - 1504)
	Cycle 7 (steady state)	297	75.0 (35.1 - 123)	149 (86.1 - 214)	2337 (1258 - 3478)

Trastuzumab washout

Trastuzumab washout period was assessed following subcutaneous administration using the population PK model. The results of these simulations indicate that at least 95% of patients will reach concentrations that are <1 µg/mL (approximately 3% of the population predicted $C_{min,ss}$, or about 97% washout) by 7 months.

5.3 Preclinical safety data

Herceptin Intravenous

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

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

Herceptin Subcutaneous

A single dose study in rabbits and a 13-week repeat dose toxicity study in Cynomolgus monkeys were conducted. The rabbit study was performed to specifically examine local tolerance aspects. The 13-week study was performed to confirm that the change in route of administration and the use of the novel excipient recombinant human hyaluronidase (rHuPH20) did not have an effect on the Herceptin safety characteristics. Herceptin subcutaneous formulation was locally and systemically well tolerated.

Hyaluronidase is found in most tissues of the human body. Non-clinical data for recombinant human hyaluronidase reveal no special hazard for humans based on conventional studies of repeated dose toxicity including safety pharmacology endpoints. Reproductive toxicology studies with rHuPH20 revealed embryofetal toxicity in mice at high systemic exposure, but did not show teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Herceptin subcutaneous formulation is a ready to use solution which should not be mixed or diluted with other products.

No incompatibilities between Herceptin subcutaneous formulation and polypropylene or polycarbonate syringe material or stainless-steel transfer and injection needles and polyethylene Luer cone stoppers have been observed.

6.3 Shelf life

21 months.

Once transferred from the vial to the syringe the medicinal product is physically and chemically stable for 28 days at 2°C – 8°C and for 6 hours (cumulative time in the vial and the syringe) at ambient temperature (max. 30°C) in diffused daylight.
As Herceptin does not contain any antimicrobial-preservative, from a microbiological point of view, the medicine should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Once removed from the refrigerator Herceptin subcutaneous formulation must be administered within 6 hours and should not be kept above 30°C.

For storage conditions of the opened medicinal product, see section 6.3 and 6.6.

6.5 Nature and contents of container

One 6 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film containing 5 mL of solution (600 mg of trastuzumab).

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

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

Herceptin is for single-use only.

As Herceptin does not contain any antimicrobial-preservative, from a microbiological point of view, the medicine should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. After transfer of the solution to the syringe, it is recommended to replace the transfer needle by a syringe closing cap to avoid drying of the solution in the needle and not compromise the quality of the medicinal product. The hypodermic injection needle must be attached to the syringe immediately prior to administration followed by volume adjustment to 5 mL.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

1

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.

7. Marketing Authorization Holder

F. Hoffmann-La Roche Ltd, Basel, Switzerland by F. Hoffmann-La Roche Ltd Switzerland, Wurmisweg, Kaiseraugst, CH-4303

8. Marketing Authorization Number

H2021/CTD 8039/16461

9. Date of first authorization/renewal of the authorization

23 Jan 2026

10. Date of revision of the text

15th March 2023