

## 1. NAME OF THE MEDICINAL PRODUCT

Herceptin 150 mg powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 150 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.

The reconstituted Herceptin solution contains 21 mg/mL of trastuzumab.

### Excipient with known effect

Each 150 mg vial contains 0.6 mg of polysorbate 20

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to pale yellow lyophilised powder.

## 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).

### Metastatic gastric cancer

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

Herceptin should only be used in patients with metastatic gastric cancer (MGC) whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory SISH or FISH result, or by an IHC 3+ result. Accurate and validated assay methods should be used (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 intravenous formulation is not intended for subcutaneous administration and should be administered via an intravenous infusion 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

### Metastatic breast cancer

#### *Three-weekly schedule*

The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

#### *Weekly schedule*

The recommended initial loading dose of Herceptin is 4 mg/kg body weight. The recommended weekly maintenance dose of Herceptin is 2 mg/kg body weight, beginning one week after the loading dose.

#### *Administration in combination with paclitaxel or docetaxel*

In the pivotal trials (H0648g, M77001), paclitaxel or docetaxel was administered the day following the first dose of Herceptin (for dose, see the Summary of Product Characteristics (SmPC) for paclitaxel or docetaxel) and immediately after the subsequent doses of Herceptin if the preceding dose of Herceptin was well tolerated.

#### *Administration in combination with an aromatase inhibitor*

In the pivotal trial (BO16216) Herceptin and anastrozole were administered from day 1. There were no restrictions on the relative timing of Herceptin and anastrozole at administration (for dose, see the SmPC for anastrozole or other aromatase inhibitors).

### Early breast cancer

#### *Three-weekly and weekly schedule*

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

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

See section 5.1 for chemotherapy combination dosing.

### Metastatic gastric cancer

#### *Three-weekly schedule*

The recommended initial loading dose is 8 mg/kg body weight. The recommended maintenance dose at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

### Breast cancer and gastric cancer

#### *Duration of treatment*

Patients with MBC or MGC 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 but they should be monitored carefully for complications of neutropenia during this time. Refer to the SmPC for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

If left ventricular ejection fraction (LVEF) percentage drops  $\geq 10$  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 has missed a dose of Herceptin by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

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

### *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

Herceptin loading dose should be administered as a 90-minute intravenous infusion. Do not administer as an intravenous push or bolus. Herceptin intravenous infusion should be administered by a health-care provider prepared to manage anaphylaxis and an emergency kit should be available. Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms (see sections 4.4 and 4.8). Interruption or slowing the rate of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

For instructions on reconstitution of Herceptin intravenous formulation before administration, see section 6.6.

## **4.3 Contraindications**

- Hypersensitivity to trastuzumab, murine proteins, or to any of the 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 (AC) exposure, should undergo baseline cardiac assessment including history and physical examination, 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  $\geq 10$  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 combination in the adjuvant treatment setting.

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin and was more marked when Herceptin was administered concurrently with taxanes than when administered sequentially to taxanes. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months. 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 in patients who were administered Herceptin concurrently with a taxane following anthracycline therapy up to 2.37% 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<sup>2</sup>.

### *Neoadjuvant-adjuvant treatment*

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

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<sup>2</sup>).

The incidence of symptomatic cardiac dysfunction was 1.7% in the Herceptin arm.

The pivotal trial BO22227 was designed to demonstrate non-inferiority of treatment with Herceptin subcutaneous formulation versus treatment with Herceptin intravenous formulation based on co-primary PK and efficacy endpoints (trastuzumab C<sub>trough</sub> at pre-dose Cycle 8, and pCR rate at definitive surgery, respectively) (See Section 5.1. of Herceptin subcutaneous formulation SmPC). In the pivotal trial BO22227, Herceptin was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m<sup>2</sup>); at a median follow-up exceeding 70 months, the incidence of cardiac failure/congestive cardiac failure was 0.3% in the Herceptin intravenous arm.

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

### Infusion-related reactions (IRRs) and hypersensitivity

Serious IRRs to Herceptin infusion including dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema have been reported (see section 4.8). Pre-medication may be used to reduce risk of occurrence of these events. The majority of these events occur during or within 2.5 hours of the start of the first infusion. Should an infusion reaction occur the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms (see section 4.2). These symptoms can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of Herceptin. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with Herceptin (see section 4.3).

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration have also been reported. Fatalities have occurred within hours and up to one week following infusion. On very rare occasions, patients have experienced the onset of infusion symptoms and pulmonary symptoms more than six hours after the start of the Herceptin infusion. Patients should be warned of the possibility of such a late onset and should be instructed to contact their physician if these symptoms occur.

## Pulmonary events

Severe pulmonary events have been reported with the use of Herceptin in the post-marketing setting (see section 4.8). These events have occasionally been fatal. 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. These events may occur as part of an infusion-related reaction or with a delayed onset. 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.

## Excipient with known effect

Herceptin contains 0.6 mg of polysorbate 20 in each 150mg vial, which is equivalent to 0.083mg/mL (after reconstitution with 7.2mL sterile water for injection). Polysorbates may cause allergic reactions.

## **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- $\alpha$  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/m<sup>2</sup> 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

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 foetus. Placental transfer of trastuzumab during the early (days 20–50 of gestation) and late (days 120–150 of gestation) foetal 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 foetus.

In the post-marketing setting, cases of foetal renal growth and/or function impairment in association with oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving Herceptin. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herceptin, or if a patient becomes pregnant while receiving Herceptin or within 7 months following the 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 infusion-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, infusion-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

#### Tabulated list of adverse reactions

In this section, the following categories of frequency have been used: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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

| <b>System organ class</b>                                            | <b>Adverse reaction</b>                     | <b>Frequency</b> |
|----------------------------------------------------------------------|---------------------------------------------|------------------|
| 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      |

| System organ class                              | Adverse reaction                                           | Frequency   |
|-------------------------------------------------|------------------------------------------------------------|-------------|
|                                                 | Thrombocytopenia                                           | Very common |
|                                                 | Hypoprothrombinaemia                                       | Not known   |
|                                                 | Immune thrombocytopenia                                    | Not known   |
| Immune system disorders                         | Hypersensitivity                                           | Common      |
|                                                 | <sup>+</sup> Anaphylactic reaction                         | Rare        |
|                                                 | <sup>+</sup> 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                        | <sup>1</sup> 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                               | <sup>1</sup> Blood pressure decreased                      | Very common |
|                                                 | <sup>1</sup> Blood pressure increased                      | Very common |
|                                                 | <sup>1</sup> Heart beat irregular                          | Very common |
|                                                 | <sup>1</sup> Cardiac flutter                               | Very common |
|                                                 | Ejection fraction decreased*                               | Very common |
|                                                 | <sup>+</sup> Cardiac failure (congestive)                  | Common      |
|                                                 | <sup>+</sup> <sup>1</sup> Supraventricular tachyarrhythmia | Common      |
|                                                 | Cardiomyopathy                                             | Common      |
|                                                 | <sup>1</sup> Palpitation                                   | Common      |
|                                                 | Pericardial effusion                                       | Uncommon    |
|                                                 | Cardiogenic shock                                          | Not known   |
|                                                 | Gallop rhythm present                                      | Not known   |
| Vascular disorders                              | Hot flush                                                  | Very common |
|                                                 | <sup>+</sup> <sup>1</sup> Hypotension                      | Common      |
|                                                 | Vasodilatation                                             | Common      |
| Respiratory, thoracic and mediastinal disorders | <sup>+</sup> Dyspnoea                                      | Very common |
|                                                 | Cough                                                      | Very common |
|                                                 | Epistaxis                                                  | Very common |
|                                                 | Rhinorrhoea                                                | Very common |
|                                                 | <sup>+</sup> Pneumonia                                     | Common      |
|                                                 | Asthma                                                     | Common      |
|                                                 | Lung disorder                                              | Common      |
|                                                 | <sup>+</sup> Pleural effusion                              | Common      |
|                                                 | <sup>+</sup> <sup>1</sup> Wheezing                         | Uncommon    |
|                                                 | Pneumonitis                                                | Uncommon    |

| System organ class                              | Adverse reaction                                 | Frequency   |
|-------------------------------------------------|--------------------------------------------------|-------------|
|                                                 | <sup>+</sup> Pulmonary fibrosis                  | Not known   |
|                                                 | <sup>+</sup> Respiratory distress                | Not known   |
|                                                 | <sup>+</sup> Respiratory failure                 | Not known   |
|                                                 | <sup>+</sup> Lung infiltration                   | Not known   |
|                                                 | <sup>+</sup> Acute pulmonary oedema              | Not known   |
|                                                 | <sup>+</sup> Acute respiratory distress syndrome | Not known   |
|                                                 | <sup>+</sup> Bronchospasm                        | Not known   |
|                                                 | <sup>+</sup> Hypoxia                             | Not known   |
|                                                 | <sup>+</sup> 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 |
|                                                 | <sup>1</sup> 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 |
|                                                 | <sup>1</sup> Swelling face                       | Very common |
|                                                 | Alopecia                                         | Very common |
|                                                 | Nail disorder                                    | Very common |
|                                                 | Palmar-plantar erythrodysesthesia syndrome       | Very common |
|                                                 | Acne                                             | Common      |
|                                                 | Dry skin                                         | Common      |
|                                                 | Ecchymosis                                       | Common      |
|                                                 | Hyperhidrosis                                    | Common      |
|                                                 | Maculopapular rash                               | Common      |
|                                                 | Pruritus                                         | Common      |
|                                                 | Onychoclasia                                     | Common      |
|                                                 | Dermatitis                                       | Common      |
|                                                 | Urticaria                                        | Uncommon    |
|                                                 | Angioedema                                       | Not known   |
| Musculoskeletal and connective tissue disorders | Arthralgia                                       | Very common |
|                                                 | <sup>1</sup> Muscle tightness                    | Very common |
|                                                 | Myalgia                                          | Very common |
|                                                 | Arthritis                                        | Common      |
|                                                 | Back pain                                        | Common      |
|                                                 | Bone pain                                        | Common      |
|                                                 | Muscle spasms                                    | Common      |
|                                                 | Neck Pain                                        | Common      |

| System organ class                                   | Adverse reaction              | Frequency   |
|------------------------------------------------------|-------------------------------|-------------|
|                                                      | Pain in extremity             | Common      |
| Renal and urinary disorders                          | Renal disorder                | Common      |
|                                                      | Glomerulonephritis membranous | Not known   |
|                                                      | Glomerulonephropathy          | Not known   |
|                                                      | 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 Infusion-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 associated with the use of Herceptin and has been associated with a fatal outcome (see section 4.4). 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 clinical trials of adjuvant 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  $\geq 50$  % after the event) was evident for 71.4 % of Herceptin-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5 % of patients. Approximately 17 % of cardiac dysfunction related events occurred after completion of Herceptin.

In the 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.

#### *Infusion reactions, allergic-like reactions and hypersensitivity*

It is estimated that approximately 40 % of patients who are treated with Herceptin will experience some form of infusion-related reaction. However, the majority of infusion-related reactions are mild to moderate in intensity (NCI-CTC grading system) and tend to occur earlier in treatment, i.e. during infusions one, two and three and lessen in frequency in subsequent infusions. Reactions include chills, fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, respiratory distress, rash, nausea, vomiting and headache (see section 4.4). The rate of infusion-related reactions 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.

Severe anaphylactic reactions requiring immediate additional intervention can occur usually during either the first or second infusion of Herceptin (see section 4.4) and have been associated with a fatal outcome.

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).

Details of risk minimisation measures that are consistent with the EU Risk Management Plan are presented in (section 4.4) Warnings and Precautions.

#### 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 developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 30 patients in the Herceptin intravenous arm.

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

There are no immunogenicity data available for Herceptin in gastric cancer.

#### 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 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 (see details below).

#### **Ireland**

HPRA Pharmacovigilance

Website: [www.hpra.ie](http://www.hpra.ie)

#### **Malta**

ADR Reporting Website: <https://medicinesauthority.gov.mt/adrportal>

## **4.9 Overdose**

There is no experience with overdose in human clinical trials. Single doses of Herceptin alone greater than 10 mg/kg have not been administered in the clinical trials; a maintenance dose of 10 mg/kg q3w following a loading dose of 8 mg/kg has been studied in a clinical trial with metastatic gastric cancer patients. Doses up to this level were well tolerated.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FD01

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 of HER2-positivity rates in gastric cancer (GC) using immunohistochemistry

(IHC) and fluorescence *in situ* hybridization (FISH) or chromogenic *in situ* hybridization (CISH) have shown that there is a broad variation of HER2-positivity ranging from 6.8 % to 34.0 % for IHC and 7.1 % to 42.6 % for FISH. 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 in Breast Cancer

| 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.

#### *Detection of HER2 over expression or HER2 gene amplification in gastric cancer*

Only an accurate and validated assay should be used to detect HER2 over expression or HER2 gene amplification. IHC is recommended as the first testing modality and in cases where HER2 gene amplification status is also required, either a silver-enhanced *in situ* hybridization (SISH) or a FISH technique must be applied. SISH technology is however, recommended to allow for the parallel evaluation of tumor histology and morphology. To ensure validation of testing procedures and the generation of accurate and reproducible results, HER2 testing must be performed in a laboratory staffed by trained personnel. Full instructions on assay performance and results interpretation should be taken from the product information leaflet provided with the HER2 testing assays used.

In the ToGA (BO18255) trial, patients whose tumours were either IHC3+ or FISH positive were defined as HER2 positive and thus included in the trial. Based on the clinical trial 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 for SISH and FISH techniques for the detection of HER2 gene amplification in gastric cancer patients.

HER2 over expression should be detected using an immunohistochemistry (IHC)-based assessment of fixed tumour blocks; HER2 gene amplification should be detected using *in situ* hybridisation using either SISH or FISH on fixed tumour blocks.

The recommended scoring system to evaluate the IHC staining patterns is as stated in Table 3:

Table 3 Recommended Scoring System to Evaluate the IHC Staining Patterns in Gastric Cancer

| Score | Surgical specimen - staining pattern                                                                                        | Biopsy specimen – staining pattern                                                                                                                    | HER2 overexpression assessment |
|-------|-----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| 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, basolateral or lateral 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 stained | 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 of tumour cells stained           | Positive                       |

In general, SISH or 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.

### Clinical efficacy and safety

#### Metastatic breast cancer

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<sup>2</sup> infused over 3 hours) with or without Herceptin. In the pivotal trial of docetaxel (100 mg/m<sup>2</sup> 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 metastatic breast cancer*

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

Table 4 Efficacy Results from the Monotherapy and Combination Therapy Studies

| Parameter                                                        | Monotherapy                         | Combination Therapy                               |                                     |                                                  |                                    |
|------------------------------------------------------------------|-------------------------------------|---------------------------------------------------|-------------------------------------|--------------------------------------------------|------------------------------------|
|                                                                  | Herceptin <sup>1</sup><br><br>N=172 | Herceptin plus<br>paclitaxel <sup>2</sup><br>N=68 | Paclitaxel <sup>2</sup><br><br>N=77 | Herceptin plus<br>docetaxel <sup>3</sup><br>N=92 | Docetaxel <sup>3</sup><br><br>N=94 |
| <b>Response rate<br/>(95 %CI)</b>                                | 18 %<br>(13 - 25)                   | 49 %<br>(36 - 61)                                 | 17 %<br>(9 - 27)                    | 61 %<br>(50-71)                                  | 34 %<br>(25-45)                    |
| <b>Median duration<br/>of response<br/>(months)<br/>(95 %CI)</b> | 9.1<br>(5.6-10.3)                   | 8.3<br>(7.3-8.8)                                  | 4.6<br>(3.7-7.4)                    | 11.7<br>(9.3 – 15.0)                             | 5.7<br>(4.6-7.6)                   |
| <b>Median TTP<br/>(months)<br/>(95 %CI)</b>                      | 3.2<br>(2.6-3.5)                    | 7.1<br>(6.2-12.0)                                 | 3.0<br>(2.0-4.4)                    | 11.7<br>(9.2-13.5)                               | 6.1<br>(5.4-7.2)                   |
| <b>Median Survival<br/>(months)<br/>(95 %CI)</b>                 | 16.4<br>(12.3-ne)                   | 24.8<br>(18.6-33.7)                               | 17.9<br>(11.2-23.8)                 | 31.2<br>(27.3-40.8)                              | 22.74<br>(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 5:

Table 5 Efficacy Results from the Non-Comparative Monotherapy and Combination Therapy Studies

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

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.
- The NSABP B-31 and NCCTG N9831 studies 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.
- The 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 HERA trial 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 the BO16348 trial following 12 months\* and 8 years\*\* median follow-up are summarized in Table 6:

Table 6 Efficacy Results from Study BO16348

| Parameter                       | Median follow-up<br>12 months* |                                 | Median follow-up<br>8 years** |                                    |
|---------------------------------|--------------------------------|---------------------------------|-------------------------------|------------------------------------|
|                                 | Observation<br>N=1693          | Herceptin<br>1 Year<br>N = 1693 | Observation<br>N= 1697***     | Herceptin<br>1 Year<br>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<sup>2</sup>, given every 3 weeks for 4 cycles.
- intravenous cyclophosphamide, at 600 mg/ m<sup>2</sup> over 30 minutes, given every 3 weeks for 4 cycles.

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

- intravenous paclitaxel - 80 mg/m<sup>2</sup> as a continuous intravenous infusion, given every week for 12 weeks.
- or
- intravenous paclitaxel - 175 mg/m<sup>2</sup> 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 7. 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 7 Summary of Efficacy results from the joint analysis of the NSABP B-31 and NCCTG N9831 trials at the time of the definitive DFS analysis\*

| Parameter                                            | AC→P<br>(n=1679) | AC→PH<br>(n=1672) | Hazard Ratio vs<br>AC→P<br>(95% CI)<br>p-value |
|------------------------------------------------------|------------------|-------------------|------------------------------------------------|
| Disease-free survival<br>No. patients with event (%) | 261 (15.5)       | 133 (8.0)         | 0.48 (0.39, 0.59)<br>p<0.0001                  |
| Distant Recurrence<br>No. patients with event        | 193 (11.5)       | 96 (5.7)          | 0.47 (0.37, 0.60)<br>p<0.0001                  |
| Death (OS event):<br>No. patients with event         | 92 (5.5)         | 62 (3.7)          | 0.67 (0.48, 0.92)<br>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→P H 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 8 below:

Table 8 Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831

| Parameter                                        | AC→P<br>(N=2032) | AC→PH<br>(N=2031) | p-value versus<br>AC→P | Hazard Ratio<br>versus<br>AC→P<br>(95% CI) |
|--------------------------------------------------|------------------|-------------------|------------------------|--------------------------------------------|
| Death (OS event):<br>No. patients with event (%) | 418 (20.6%)      | 289 (14.2%)       | < 0.0001               | 0.64<br>(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<sup>2</sup> 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<sup>2</sup> 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 9 and 10. 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 9 Overview of Efficacy Analyses BCIRG 006 AC→D versus AC→DH

| Parameter                                        | AC→D<br>(n=1073) | AC→DH<br>(n=1074) | Hazard Ratio vs<br>AC→D<br>(95 % CI)<br>p-value |
|--------------------------------------------------|------------------|-------------------|-------------------------------------------------|
| Disease-free survival<br>No. patients with event | 195              | 134               | 0.61 (0.49, 0.77)<br>p<0.0001                   |
| Distant recurrence<br>No. patients with event    | 144              | 95                | 0.59 (0.46, 0.77)<br>p<0.0001                   |
| Death (OS event)<br>No. patients with event      | 80               | 49                | 0.58 (0.40, 0.83)<br>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 10 Overview of Efficacy Analyses BCIRG 006 AC→D versus DCarbH

| Parameter                                        | AC→D<br>(n=1073) | DCarbH<br>(n=1074) | Hazard Ratio vs<br>AC→D<br>(95 % CI) |
|--------------------------------------------------|------------------|--------------------|--------------------------------------|
| Disease-free survival<br>No. patients with event | 195              | 145                | 0.67 (0.54, 0.83)<br>p=0.0003        |
| Distant recurrence<br>No. patients with event    | 144              | 103                | 0.65 (0.50, 0.84)<br>p=0.0008        |
| Death (OS event)<br>No. patients with event      | 80               | 56                 | 0.66 (0.47, 0.93)<br>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 11:

Table 11 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<br>(vs. AC→P)<br>(NSABP B-31 and<br>NCCTG N9831)* | AC→DH<br>(vs. AC→D)<br>(BCIRG 006) | DCarbH<br>(vs. AC→D)<br>(BCIRG 006) |
|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|------------------------------------|-------------------------------------|
| Primary efficacy analysis<br>DFS Hazard ratios<br>(95 % CI)<br>p-value                                                             | 0.48<br>(0.39, 0.59)<br>p<0.0001                        | 0.61<br>(0.49, 0.77)<br>p< 0.0001  | 0.67<br>(0.54, 0.83)<br>p=0.0003    |
| Long term follow-up efficacy<br>analysis**<br>DFS Hazard ratios<br>(95 % CI)<br>p-value                                            | 0.61<br>(0.54, 0.69)<br>p<0.0001                        | 0.72<br>(0.61, 0.85)<br>p<0.0001   | 0.77<br>(0.65, 0.90)<br>p=0.0011    |
| Post-hoc exploratory analysis<br>with DFS and symptomatic<br>cardiac events<br>Long term follow-up**<br>Hazard ratios<br>(95 % CI) | 0.67<br>(0.60, 0.75)                                    | 0.77<br>(0.66, 0.90)               | 0.77<br>(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) arm 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)

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<sup>2</sup> and paclitaxel 150 mg/m<sup>2</sup>, administered 3-weekly for 3 cycles,

which was followed by

- Paclitaxel 175 mg/m<sup>2</sup> 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 12. The median duration of follow-up in the Herceptin arm was 3.8 years.

Table 12 Efficacy Results from MO16432

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

### Metastatic gastric cancer

Herceptin has been investigated in one randomised, open-label phase III trial ToGA (BO18255) in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine - 1000 mg/m<sup>2</sup> orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle)

or

- intravenous 5-fluorouracil - 800 mg/m<sup>2</sup>/day as a continuous intravenous infusion over 5 days, given every 3 weeks for 6 cycles (days 1 to 5 of each cycle)

Either of which was administered with:

- cisplatin - 80 mg/m<sup>2</sup> every 3 weeks for 6 cycles on day 1 of each cycle.

The efficacy results from study BO18225 are summarized in Table 13:

Table 13 Efficacy Results from BO18225

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

FP + H: Fluoropyrimidine/cisplatin + Herceptin

FP: Fluoropyrimidine/cisplatin

a Odds ratio

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

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

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

### 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 and gastric cancer (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

The pharmacokinetics of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects, including patients with HER2 positive MBC, EBC, AGC or other tumor types, and healthy volunteers, in 18 Phase I, II and III trials receiving Herceptin IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to non-linear elimination, total clearance increased with decreasing concentration. Therefore, no constant value for half-life of trastuzumab can be deduced. The  $t_{1/2}$  decreases with decreasing concentrations within a dosing interval (see Table 16). MBC and EBC patients had similar PK parameters (e.g. clearance (CL), the central compartment volume ( $V_c$ )) and population-predicted steady-state exposures ( $C_{min}$ ,  $C_{max}$  and AUC). Linear clearance was 0.136 L/day for MBC, 0.112 L/day for EBC and 0.176 L/day for AGC. The non-linear elimination parameter values were 8.81 mg/day for the maximum elimination rate ( $V_{max}$ ) and 8.92

$\mu\text{g/mL}$  for the Michaelis-Menten constant ( $K_m$ ) for the MBC, EBC, and AGC patients. The central compartment volume was 2.62 L for patients with MBC and EBC and 3.63 L for patients with AGC. In the final population PK model, in addition to primary tumor type, body-weight, serum aspartate aminotransferase and albumin were identified as a statistically significant covariates affecting the exposure of trastuzumab. However, the magnitude of effect of these covariates on trastuzumab exposure suggests that these covariates are unlikely to have a clinically meaningful effect on trastuzumab concentrations.

The population predicted PK exposure values (median with 5th - 95th Percentiles) and PK parameter values at clinically relevant concentrations ( $C_{\text{max}}$  and  $C_{\text{min}}$ ) for MBC, EBC and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 14 (Cycle 1), Table 15 (steady-state), and Table 16 (PK parameters).

Table 14 Population Predicted Cycle 1 PK Exposure Values (median with 5th - 95th Percentiles) for Herceptin IV Dosing Regimens in MBC, EBC and AGC Patients

| Regimen             | Primary tumor type | N   | $C_{\text{min}}$<br>( $\mu\text{g/mL}$ ) | $C_{\text{max}}$<br>( $\mu\text{g/mL}$ ) | $\text{AUC}_{0-21\text{days}}$<br>( $\mu\text{g}\cdot\text{day/mL}$ ) |
|---------------------|--------------------|-----|------------------------------------------|------------------------------------------|-----------------------------------------------------------------------|
| 8mg/kg + 6mg/kg q3w | MBC                | 805 | 28.7<br>(2.9 - 46.3)                     | 182<br>(134 - 280)                       | 1376<br>(728 - 1998)                                                  |
|                     | EBC                | 390 | 30.9<br>(18.7 - 45.5)                    | 176<br>(127 - 227)                       | 1390<br>(1039 - 1895)                                                 |
|                     | AGC                | 274 | 23.1<br>(6.1 - 50.3)                     | 132<br>(84.2 - 225)                      | 1109<br>(588 - 1938)                                                  |
| 4mg/kg + 2mg/kg qw  | MBC                | 805 | 37.4<br>(8.7 - 58.9)                     | 76.5<br>(49.4 - 114)                     | 1073<br>(597 - 1584)                                                  |
|                     | EBC                | 390 | 38.9<br>(25.3 - 58.8)                    | 76.0<br>(54.7 - 104)                     | 1074<br>(783 - 1502)                                                  |

Table 15 Population Predicted Steady State PK Exposure Values (median with 5th - 95th Percentiles) for Herceptin IV Dosing Regimens in MBC, EBC and AGC Patients

| Regimen             | Primary tumor type | N   | $C_{\text{min,ss}}$<br>( $\mu\text{g/mL}$ ) | $C_{\text{max,ss}}$<br>( $\mu\text{g/mL}$ ) | $\text{AUC}_{\text{ss}, 0-21\text{days}}$<br>( $\mu\text{g}\cdot\text{day/mL}$ ) | Time to steady-state***<br>(week) |
|---------------------|--------------------|-----|---------------------------------------------|---------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------|
| 8mg/kg + 6mg/kg q3w | MBC                | 805 | 44.2<br>(1.8 - 85.4)                        | 179<br>(123 - 266)                          | 1736<br>(618 - 2756)                                                             | 12                                |
|                     | EBC                | 390 | 53.8<br>(28.7 - 85.8)                       | 184<br>(134 - 247)                          | 1927<br>(1332 - 2771)                                                            | 15                                |
|                     | AGC                | 274 | 32.9<br>(6.1 - 88.9)                        | 131<br>(72.5 - 251)                         | 1338<br>(557 - 2875)                                                             | 9                                 |
| 4mg/kg + 2mg/kg qw  | MBC                | 805 | 63.1<br>(11.7 - 107)                        | 107<br>(54.2 - 164)                         | 1710<br>(581 - 2715)                                                             | 12                                |
|                     | EBC                | 390 | 72.6<br>(46 - 109)                          | 115<br>(82.6 - 160)                         | 1893<br>(1309 - 2734)                                                            | 14                                |

\* $C_{\text{min,ss}}$  –  $C_{\text{min}}$  at steady state

\*\* $C_{\text{max,ss}}$  =  $C_{\text{max}}$  at steady state

\*\*\* time to 90% of steady-state

Table 16 Population Predicted PK Parameter Values at Steady State for Herceptin IV Dosing Regimens in MBC, EBC and AGC Patients

| Regimen             | Primary tumor type | N   | Total CL range from $C_{max,ss}$ to $C_{min,ss}$ (L/day) | $t_{1/2}$ range from $C_{max,ss}$ to $C_{min,ss}$ (day) |
|---------------------|--------------------|-----|----------------------------------------------------------|---------------------------------------------------------|
| 8mg/kg + 6mg/kg q3w | MBC                | 805 | 0.183 - 0.302                                            | 15.1 - 23.3                                             |
|                     | EBC                | 390 | 0.158 - 0.253                                            | 17.5 - 26.6                                             |
|                     | AGC                | 274 | 0.189 - 0.337                                            | 12.6 - 20.6                                             |
| 4mg/kg + 2mg/kg qw  | MBC                | 805 | 0.213 - 0.259                                            | 17.2 - 20.4                                             |
|                     | EBC                | 390 | 0.184 - 0.221                                            | 19.7 - 23.2                                             |

#### *Trastuzumab washout*

Trastuzumab washout period was assessed following q1w or q3w intravenous administration using the population PK model. The results of these simulations indicate that at least 95% of patients will reach concentrations that are  $<1 \mu\text{g/mL}$  (approximately 3% of the population predicted  $C_{min,ss}$ , or about 97% washout) by 7 months.

#### *Circulating shed HER2 ECD*

The exploratory analyses of covariates with information in only a subset of patients suggested that patients with greater shed HER2-ECD level had faster nonlinear clearance (lower  $K_m$ ) ( $P < 0.001$ ). There was a correlation between shed antigen and SGOT/AST levels; part of the impact of shed antigen on clearance may have been explained by SGOT/AST levels.

Baseline levels of the shed HER2-ECD observed in MGC patients were comparable to those in MBC and EBC patients and no apparent impact on trastuzumab clearance was observed.

### **5.3 Preclinical safety data**

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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Histidine hydrochloride monohydrate  
 Histidine  
 $\alpha, \alpha$ -trehalose dihydrate  
 Polysorbate 20 (E432)

## 6.2 Incompatibilities

This medicinal product must not be mixed or diluted with other medicinal products except those mentioned under section 6.6.

Do not dilute with glucose solutions since these cause aggregation of the protein.

## 6.3 Shelf life

### Unopened vial

4 years

### Aseptic reconstitution and dilution:

After aseptic reconstitution with sterile water for injection, chemical and physical stability of the reconstituted solution has been demonstrated for 48 hours at 2°C – 8°C.

After aseptic dilution in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/mL (0.9 %) solution for injection, chemical and physical stability of Herceptin has been demonstrated for up to 30 days at 2°C – 8°C, and 24 hours at temperatures not exceeding 30°C.

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

## 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze the reconstituted solution.

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

## 6.5 Nature and contents of container

### *Herceptin vial:*

One 15 mL clear glass type I vial with butyl rubber stopper laminated with a fluoro-resin film containing 150 mg of trastuzumab.

Each carton contains one vial.

## 6.6 Special precautions for disposal and other handling

Herceptin IV is provided in sterile, preservative-free, non-pyrogenic, single use vials.

Appropriate aseptic technique should be used for reconstitution and dilution procedures. Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed.

### Aseptic preparation, handling and storage:

Aseptic handling must be ensured when preparing the infusion. Preparation should be:

- performed under aseptic conditions by trained personnel in accordance with good practice rules especially with respect to the aseptic preparation of parenteral products.

- prepared in a laminar flow hood or biological safety cabinet using standard precautions for the safe handling of intravenous agents.
- followed by adequate storage of the prepared solution for intravenous infusion to ensure maintenance of the aseptic conditions

Each vial of Herceptin is reconstituted with 7.2 mL of sterile water for injection (not supplied). Use of other reconstitution solvents should be avoided.

This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overage of 4 % ensures that the labelled dose of 150 mg can be withdrawn from each vial.

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

The reconstituted solution should not be frozen.

#### Instructions for aseptic reconstitution:

- 1) Using a sterile syringe, slowly inject 7.2 mL of sterile water for injection in the vial containing the lyophilised Herceptin, directing the stream into the lyophilised cake.
- 2) Swirl the vial gently to aid reconstitution. DO NOT SHAKE!

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

#### Instructions for aseptic dilution of the reconstituted solution

Determine the volume of the solution required:

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

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

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

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

The appropriate amount of solution should be withdrawn from the vial using a sterile needle and syringe and added to an infusion bag containing 250 mL of 0.9 % sodium chloride solution. Do not use with glucose-containing solutions (see section 6.2). The bag should be gently inverted to mix the solution in order to avoid foaming.

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

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

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

**7. MARKETING AUTHORISATION HOLDER**

Roche Registration GmbH  
Emil-Barell-Strasse 1  
79639 Grenzach-Wyhlen  
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**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/00/145/001

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 28 August 2000  
Date of latest renewal: 28 July 2010

**10. DATE OF REVISION OF THE TEXT**

17 October 2025

Detailed information on this medicinal product is available on the website of the European Medicines Agency <https://www.ema.europa.eu>.