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.

For a full list of excipients, (see section 6.1).

3. **PHARMACEUTICAL FORM**

Powder for concentrate for solution for infusion.

Herceptin is a white to pale yellow lyophilised powder.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

**Breast Cancer**

**Metastatic Breast Cancer (MBC)**

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

- 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 metastatic breast cancer, not previously treated with trastuzumab.

**Early Breast Cancer (EBC)**

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

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

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

Herceptin should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory 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).

**MBC**

**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 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 Summary of Product Characteristics for anastrozole or other aromatase inhibitors).

**EBC**

*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).

**MGC**

**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 (MBC and EBC) and Gastric Cancer (MGC)**

**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, whatever occurs first.

**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 Summary of Product Characteristics for paclitaxel, docetaxel or aromatase inhibitor for information on dose reduction or delays.

**Missed doses**
If the patient misses 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 given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg respectively) should then be given according to the previous schedule.

If the patient misses a dose of Herceptin by more than one week, a re-loading dose of Herceptin should be given over approximately 90 minutes (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg). Subsequent Herceptin maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should then be given (weekly regimen: every week; three-weekly regimen every 3 weeks) from that point.

**Special patient populations**
Clinical data show that the disposition of Herceptin is not altered based on age or serum creatinine (see section 5.2). In clinical trials, elderly patients did not receive reduced doses of Herceptin. Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. However in a population pharmacokinetic analysis, age and renal impairment were not shown to affect trastuzumab disposition.

**Paediatric population**
Herceptin is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy.

**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 use and handling of Herceptin refer to section 6.6.

4.3 Contraindications

Hypersensitivity to trastuzumab, murine proteins, or to any of the excipients.
Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

4.4 Special warnings and precautions for use

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.

Cardiotoxicity

General considerations

Heart failure (New York Heart Association [NYHA] class II-IV) has been observed in patients receiving Herceptin therapy alone or in combination with paclitaxel or docetaxel, particularly following anthracycline (doxorubicin or epirubicin)–containing chemotherapy. This may be moderate to severe and has been associated with death (see section 4.8).

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, ECG, echocardiogram, or MUGA scan or magnetic resonance imaging. A careful risk-benefit assessment should be made before deciding to treat with Herceptin.

Because the half-life of Herceptin is approximately 4-5 weeks Herceptin may persist in the circulation for up to 20-25 weeks after stopping Herceptin treatment. Patients who receive anthracyclines after stopping Herceptin may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 25 weeks 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. Caution should be exercised in treating patients with symptomatic heart failure, a history of hypertension or documented coronary artery disease, and in early breast cancer, in those patients with a left ventricular ejection fraction (LVEF) of 55 % or less.

If LVEF drops 10 ejection fraction (EF) 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, 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 medications for this purpose. Discontinuation of Herceptin therapy should be strongly considered in
patients who develop clinically significant heart failure unless the benefits for an individual patient are deemed to outweigh the risks.

The safety of continuation or resumption of Herceptin in patients who experience cardiotoxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal (H0648g, H0649g, M77001, BO16216, BO16348, BO18255, NSABP B31, NCCTG N9831, BCIRG 006, MO16432) trials improved with standard medical treatment. This included diuretics, cardiac glycosides, beta-blockers and/or angiotensin-converting enzyme inhibitors. 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 metastatic breast cancer setting.

Patients with metastatic breast cancer who have previously received anthracyclines are also at risk of cardiotoxicity with Herceptin treatment, although the risk is lower than with concurrent use of Herceptin and anthracyclines.

Early breast cancer (EBC)

For patients with early breast cancer, 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.

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).

In EBC, the following patients were excluded from the HERA trial, there are no data about the benefit-risk balance, and therefore treatment can not be recommended in such patients:

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

In patients with early breast cancer eligible for neoadjuvant-adjuvant treatment, Herceptin should only be used concurrently with anthracyclines in chemotherapy-naive patients and only with low-dose anthracycline regimens (maximum cumulative doses: doxorubicin 180 mg/m² or epirubicin 360 mg/m²).

If patients have been treated concurrently with low-dose anthracyclines and Herceptin in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery.

The following patients were excluded from the NOAH trial in the neoadjuvant-adjuvant setting and this treatment is not recommended for such patients:

- New York Heart Association (NYHA) class greater or equal II heart disease
- Left ventricular ejection fraction (LVEF) of <55% by MUGA scan or echocardiography
- History of documented congestive cardiac failure, angina pectoris requiring antianginal medication, evidence of transmural infarction on ECG, poorly controlled hypertension (e.g. systolic > 180 mm Hg or diastolic >100 mm Hg), clinically significant valvular heart disease, or high-risk uncontrolled arrhythmias.

Experience of concurrent administration of trastuzumab with low dose anthracycline regimens is currently limited. In the NOAH trial, Herceptin was administered concurrently with neoadjuvant chemotherapy that contained three cycles of neoadjuvant doxorubicin (cumulative doxorubicin dose 180 mg/m²). The incidence of symptomatic cardiac dysfunction was low in the Herceptin arm (2 of 115 patients, 1.7%).

Only few patients in the NOAH trial were > 65 years of age. Therefore, clinical experience in this age group is limited, and therefore neoadjuvant-adjuvant treatment is not recommended for patients older than 65 years.

Infusion reactions, allergic-like reactions and hypersensitivity

Serious adverse reactions to Herceptin infusion that have been reported infrequently include dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachyarrhythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria and angioedema (see section 4.8). 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). 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. A risk for interactions with the concomitant use of other medicinal products cannot be excluded.

4.6 Fertility, pregnancy and lactation

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 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 of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 6 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the foetus. If a pregnant woman is treated with Herceptin, close monitoring by a multidisciplinary team is desirable.

Lactation

A study conducted in lactating cynomolgus monkeys at doses 25 times that of the weekly human maintenance dose of 2 mg/kg Herceptin demonstrated that trastuzumab is secreted in the milk. The presence of trastuzumab in the serum of infant monkeys was not associated with any adverse effects on their growth or development from birth to 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 6 months after the last dose.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable Effects

Amongst the most serious and/or common adverse reactions reported in Herceptin usage to date are cardiotoxicity, infusion-related reactions, haematotoxicity (in particular neutropenia) and pulmonary adverse events.

In this section, the following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness.
List of adverse reactions
Presented in the following table are adverse reactions that have been reported in association with the use of Herceptin alone or in combination with chemotherapy in pivotal clinical trials and in the post-marketing setting. Pivotal trials included:

- H0648g and H0649g: Herceptin as a monotherapy or in combination with paclitaxel in metastatic breast cancer.
- M77001: Docetaxel, with or without Herceptin in metastatic breast cancer.
- BO16216: Anastrozole with or without Herceptin in HER2 positive and hormone receptor positive metastatic breast cancer.
- BO16348: Herceptin as a monotherapy following adjuvant chemotherapy in HER2 positive breast cancer.
- BO18255: Herceptin in combination with a fluoropyrimidine and cisplatin versus chemotherapy alone as first-line therapy in HER2 positive advanced gastric cancer.
- B-31, N9831: Herceptin administered sequential to adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel.
- BCIRG 006: Herceptin administered sequential to adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with docetaxel or Herceptin administered in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- MO16432: Herceptin administered concurrently in combination with the neoadjuvant regimen of doxorubicin plus paclitaxel, paclitaxel and cyclophosphamide plus methotrexate plus 5-fluorouracil, followed by postoperative adjuvant Herceptin monotherapy.

All the terms included are based on the highest percentage seen in pivotal clinical trials.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Adverse reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Pneumonia</td>
<td>Common (&lt;1 %)</td>
</tr>
<tr>
<td></td>
<td>Neutropenic sepsis</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Cystitis</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Herpes zoster</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>Common</td>
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<tr>
<td></td>
<td>Influenza</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Nasopharyngitis</td>
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</tr>
<tr>
<td></td>
<td>Sinusitis</td>
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</tr>
<tr>
<td></td>
<td>Skin infection</td>
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</tr>
<tr>
<td></td>
<td>Rhinitis</td>
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<tr>
<td></td>
<td>Upper respiratory tract infection</td>
<td>Common</td>
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<tr>
<td></td>
<td>Urinary tract infection</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Erysipelas</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Cellulitis</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl. Cysts and polyps)</td>
<td>Malignant neoplasm progression</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Neoplasm progression</td>
<td>Not known</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Febrile Neutropenia</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
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<td></td>
<td>Neutropenia</td>
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<tr>
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<td>Thrombocytopenia</td>
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<td>White blood cell count decreased/leukopenia</td>
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</tr>
<tr>
<td></td>
<td>Hypoprothrombinaemia</td>
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</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td>Common</td>
</tr>
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<td></td>
<td>Anaphylactic reaction</td>
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<tr>
<td></td>
<td>Anaphylactic shock</td>
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<tr>
<td>System organ class</td>
<td>Adverse reaction</td>
<td>Frequency</td>
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<tr>
<td>--------------------</td>
<td>-----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight Decreased/Weight Loss</td>
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<td>Anorexia</td>
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</tr>
<tr>
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<td>Hyperkalaemia</td>
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<td>Psychiatric disorders</td>
<td>Anxiety</td>
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<td>Depression</td>
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<tr>
<td></td>
<td>Insomnia</td>
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<tr>
<td></td>
<td>Thinking abnormal</td>
<td>Common</td>
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<tr>
<td>Nervous system disorders</td>
<td>Tremor</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Very common</td>
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<tr>
<td></td>
<td>Headache</td>
<td>Very common</td>
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<tr>
<td></td>
<td>Peripheral neuropathy</td>
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<tr>
<td></td>
<td>Paraesthesia</td>
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<tr>
<td></td>
<td>Hypertonia</td>
<td>Common</td>
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<tr>
<td></td>
<td>Somnolence</td>
<td>Common</td>
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<tr>
<td></td>
<td>Dysgeusia</td>
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<td></td>
<td>Ataxia</td>
<td>Common</td>
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<tr>
<td></td>
<td>Paresis</td>
<td>Rare</td>
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<tr>
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<td>Brain oedema</td>
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<td>Eye disorders</td>
<td>Conjunctivitis</td>
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<tr>
<td></td>
<td>Lacrimation increased</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Dry eye</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Papilloedema</td>
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</tr>
<tr>
<td></td>
<td>Retinal haemorrhage</td>
<td>Not known</td>
</tr>
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<td>Ear and Labyrinth Disorders</td>
<td>Deafness</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Blood pressure decreased</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Blood pressure increased</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Heart beat irregular</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Palpitation</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Cardiac flutter</td>
<td>Very common</td>
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<tr>
<td></td>
<td>Cardiac failure (congestive)</td>
<td>Common (2 %)</td>
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<td>Supraventricular tachyarrhythmia</td>
<td>Common</td>
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<tr>
<td></td>
<td>Cardiomyopathy</td>
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</tr>
<tr>
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<td>Ejection fraction decreased*</td>
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<td>Pericardial effusion</td>
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<td>Cardiogenic shock</td>
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<td>Pericarditis</td>
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<td>Bradycardia</td>
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<td>Gallop rhythm present</td>
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<tr>
<td>Vascular disorders</td>
<td>Hot flush</td>
<td>Very Common</td>
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<tr>
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<td>Hypotension</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Vasodilatation</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Wheezing</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea</td>
<td>Very common (14 %)</td>
</tr>
<tr>
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<td>Cough</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Epistaxis</td>
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<td></td>
<td>Rhinorrhea</td>
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</tr>
<tr>
<td></td>
<td>Asthma</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Lung disorder</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pleural effusion</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Pulmonary fibrosis</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Respiratory distress</td>
<td>Not known</td>
</tr>
<tr>
<td>System organ class</td>
<td>Adverse reaction</td>
<td>Frequency</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Lung infiltration</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Acute pulmonary oedema</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation decreased</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Laryngeal oedema</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Orthopnoea</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Very common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Lip swelling</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Haemorrhoids</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatocellular Injury</td>
<td>Common</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Liver Tenderness</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Hepatic Failure</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Erythema</td>
<td>Very common</td>
</tr>
<tr>
<td>Rash</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Swelling face</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Nail disorder</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Angioedema</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>Very common</td>
</tr>
<tr>
<td>Muscle tightness</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary conditions</td>
<td>Renal disorder</td>
<td>Common</td>
</tr>
<tr>
<td>Glomerulonephritis membranous</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephropathy</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>System organ class</td>
<td>Adverse reaction</td>
<td>Frequency</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal disorders</td>
<td>Oligohydramnios</td>
<td>Not known</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Breast inflammation/mastitis</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Chest pain</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Influenza-like symptoms</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Infusion related reaction</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Peripheral oedema</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Mucosal inflammation</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Oedema</td>
<td>Common</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Contusion</td>
<td>Common</td>
</tr>
</tbody>
</table>

+ 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

Note: Specific percentage frequencies have been provided in brackets for terms that have been reported in association with a fatal outcome with the frequency designation ‘common’ or ‘very common’. The specific percentage frequencies relate to total number of these events, both fatal and non-fatal.

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

**Description of selected adverse reactions**

**Cardiotoxicity**

Cardiotoxicity (heart failure), NYHA 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).

In 3 pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (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 to a taxane ($0.3-0.4\%$). The rate was highest in patients who were administered Herceptin concurrently with a taxane ($2.0\%$).

The safety of continuation or resumption of Herceptin in patients who experience cardiotoxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal trials (H0648g, H0649g, M77001, BO16216, BO16348, BO18255, B-31, N9831, BCIRG 006, MO16432) improved with standard medical treatment. This included diuretics, cardiac glycosides, beta-blockers and/or angiotensin-converting enzyme inhibitors. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued on therapy with Herceptin without additional clinical cardiac events (for information on identification of risk factors and management see section 4.4).

In the neoadjuvant setting, the experience of concurrent administration of Herceptin and low dose anthracycline regimen is limited.
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, but are not limited to, chills, fever, rash, nausea and vomiting, dyspnoea and headache (see section 4.4). 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.

Haematotoxicity
Febrile neutropenia occured very commonly. Commonly occurring adverse reactions included anaemia, leukopenia, thrombocytopenia and neutropenia. 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.

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. Doses up to this level were well tolerated.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC03

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 follows:

<table>
<thead>
<tr>
<th>Score</th>
<th>Staining pattern</th>
<th>HER2 overexpression assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No staining is observed or membrane staining is observed in &lt; 10 % of the tumour cells</td>
<td>Negative</td>
</tr>
<tr>
<td>1+</td>
<td>A faint/barely perceptible membrane staining is detected in &gt; 10 % of the tumour cells. The cells are only stained in part of their membrane.</td>
<td>Negative</td>
</tr>
<tr>
<td>2+</td>
<td>A weak to moderate complete membrane staining is detected in &gt; 10 % of the tumour cells.</td>
<td>Equivocal</td>
</tr>
<tr>
<td>3+</td>
<td>Strong complete membrane staining is detected in &gt; 10 % of the tumour cells.</td>
<td>Positive</td>
</tr>
</tbody>
</table>

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 overexpression or HER2 gene amplification in gastric cancer
Only an accurate and validated assay should be used to detect HER2 overexpression 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 overexpression 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 follows:

<table>
<thead>
<tr>
<th>Score</th>
<th>Surgical specimen - staining pattern</th>
<th>Biopsy specimen – staining pattern</th>
<th>HER2 overexpression assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No reactivity or membranous reactivity in &lt; 10 % of tumour cells</td>
<td>No reactivity or membranous reactivity in any tumour cell</td>
<td>Negative</td>
</tr>
<tr>
<td>1+</td>
<td>Faint/barely perceptible membranous reactivity in ≥ 10 % of tumour cells; cells are reactive only in part of their membrane</td>
<td>Tumour cell cluster with a faint/barely perceptible membranous reactivity irrespective of percentage of tumour cells stained</td>
<td>Negative</td>
</tr>
<tr>
<td>2+</td>
<td>Weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10 % of tumour cells</td>
<td>Tumour cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained</td>
<td>Equivocal</td>
</tr>
<tr>
<td>3+</td>
<td>Strong complete, basolateral or lateral membranous reactivity in ≥ 10 % of tumour cells</td>
<td>Tumour cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumour cells stained</td>
<td>Positive</td>
</tr>
</tbody>
</table>

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**

**MBC**

Herceptin has been used in clinical trials as monotherapy for patients with metastatic breast cancer who have tumours that overexpress HER2 and who have failed 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/m² infused over 3 hours) with or without Herceptin. In the pivotal trial of docetaxel (100 mg/m² 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 MBC*

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Herceptin¹</td>
<td>Herceptin plus paclitaxel² N=68</td>
</tr>
<tr>
<td>Response rate (95 %CI)</td>
<td>18 % (13 - 25)</td>
<td>49 % (36 - 61)</td>
</tr>
<tr>
<td>Median duration of response (months) (95 %CI)</td>
<td>9.1 (5.6-10.3)</td>
<td>8.3 (7.3-8.8)</td>
</tr>
<tr>
<td>Median TTP (months) (95 %CI)</td>
<td>3.2 (2.6-3.5)</td>
<td>7.1 (6.2-12.0)</td>
</tr>
<tr>
<td>Median Survival (months) (95 %CI)</td>
<td>16.4 (12.3-ne)</td>
<td>24.8 (18.6-33.7)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Herceptin(^1) N=105</td>
<td>Herceptin plus paclitaxel(^3) N=32</td>
</tr>
<tr>
<td>Response rate (95 %CI)</td>
<td>24 % (15 - 35)</td>
<td>59 % (41-76)</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>10.1 (2.8-35.6)</td>
<td>10.5 (1.8-21)</td>
</tr>
<tr>
<td>Median TTP (months) (95 %CI)</td>
<td>3.4 (2.8-4.1)</td>
<td>12.2 (6.2-ne)</td>
</tr>
<tr>
<td>Median Survival (months) (95 %CI)</td>
<td>ne</td>
<td>ne</td>
</tr>
</tbody>
</table>

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 % vs. 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 % vs. 6.5 %; p=0.377).

**EBC**

Early breast cancer is defined as non-metastatic primary invasive carcinoma of the breast.

In the adjuvant setting, Herceptin was investigated in 4 large multicentre, randomised, trials.

- The HERA study was designed to compare one year of three-weekly Herceptin treatment versus observation in patients with HER2 positive early breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). Patients assigned to receive Herceptin were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for one year.

- The NCCTG N9831 and NSABP B-31 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 early breast cancer 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 early breast cancer 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 NCCTG N9831 and NSABP B-31 studies, early breast cancer was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node positive or HER2 positive and lymph node negative with high risk features (tumor size > 1 cm and ER negative or tumor size > 2 cm, regardless of hormonal status).
In the BCIRG 006 study HER2 positive, early breast cancer 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 HERA trial are summarized in the following table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Observation</th>
<th>Herceptin 1 Year</th>
<th>P-value vs Observation</th>
<th>Hazard Ratio vs Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1693</td>
<td>N = 1693</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No. patients with event</td>
<td>219 (12.9 %)</td>
<td>127 (7.5 %)</td>
<td>&lt; 0.0001</td>
<td>0.54</td>
</tr>
<tr>
<td>- No. patients without event</td>
<td>1474 (87.1 %)</td>
<td>1566 (92.5 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No. patients with event</td>
<td>208 (12.3 %)</td>
<td>113 (6.7 %)</td>
<td>&lt; 0.0001</td>
<td>0.51</td>
</tr>
<tr>
<td>- No. patients without event</td>
<td>1485 (87.7 %)</td>
<td>1580 (93.3 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant disease-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No. patients with event</td>
<td>184 (10.9 %)</td>
<td>99 (5.8 %)</td>
<td>&lt; 0.0001</td>
<td>0.50</td>
</tr>
<tr>
<td>- No. patients without event</td>
<td>1508 (89.1 %)</td>
<td>1594 (94.2 %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study BO16348 (HERA): 12 months follow-up

For the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8 % vs 78.2 %) in favour of the Herceptin arm.

In the NCCTG N9831 and NSABP B-31 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/m², given every 3 weeks for 4 cycles.
- intravenous cyclophosphamide, at 600 mg/m² over 30 minutes, given every 3 weeks for 4 cycles.

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

- intravenous paclitaxel - 80 mg/m² as a continuous i.v. infusion, given every week for 12 weeks.
  or
- intravenous paclitaxel - 175 mg/m² as a continuous i.v. infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).
The efficacy results from the joint analysis of the NCCTG 9831 and NSABP B-31 trials are summarized in the table below. 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>
<thead>
<tr>
<th>Parameter</th>
<th>AC→P (n=1697)</th>
<th>AC→PH (n=1672)</th>
<th>Hazard Ratio vs AC→P (95% CI) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients with event (%)</td>
<td>261 (15.4)</td>
<td>133 (7.9)</td>
<td>0.48 (0.39, 0.59) p&lt;0.0001</td>
</tr>
<tr>
<td>Distant Recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients with event</td>
<td>174</td>
<td>90</td>
<td>0.47 (0.37, 0.60) p&lt;0.0001</td>
</tr>
<tr>
<td>Death (OS event):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients with event</td>
<td>92</td>
<td>62</td>
<td>0.67 (0.48, 0.92) p=0.014</td>
</tr>
</tbody>
</table>

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

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 % vs 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.

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/m² as an i.v. 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/m² as an i.v. infusion over 1 hour, given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each subsequent cycle)

which was followed by:
- carboplatin – at target AUC = 6 mg/mL/min administered by IV infusion over 30-60 minutes repeated every 3 weeks for a total of 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 the tables below. 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.
Overview of Efficacy Analyses BCIRG 006  AC→D versus AC→DH

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

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

Overview of Efficacy Analyses BCIRG 006  AC→D versus DCarbH

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

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 % vs 80.9 %) in favour of the AC→DH (Herceptin) arm and 4.6 percentage points (85.5 % vs 80.9 %) in favour of the DCarbH (Herceptin) arm compared to AC→D.

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) vs AC→D (AC→T); hazard ratio 0.97, 95% CI [0.60, 1.55] for AC→DH (AC→TH) vs 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 the following table:

<table>
<thead>
<tr>
<th></th>
<th>AC→PH (vs. AC→P) (NSABP B-31 and NCCTG N9831)</th>
<th>AC→DH (vs. AC→D) (BCIRG 006)</th>
<th>DCarbH (vs. AC→D) (BCIRG 006)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy analysis DFS</td>
<td>0.48 (0.39, 0.59)</td>
<td>0.61 (0.49, 0.77)</td>
<td>0.67 (0.54, 0.83)</td>
</tr>
<tr>
<td>Hazard ratios (95% CI)</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.0003</td>
</tr>
<tr>
<td>Post-hoc exploratory analysis</td>
<td>0.64 (0.53, 0.77)</td>
<td>0.70 (0.57, 0.87)</td>
<td>0.71 (0.57, 0.87)</td>
</tr>
<tr>
<td>with DFS and symptomatic cardiac events Hazard ratios (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel; Carb: carboplatin; H: trastuzumab

CI = confidence interval

**Neoadjuvant-adjuvant treatment**

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 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 early breast cancer. 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/m² and paclitaxel 150 mg/m², administered 3-weekly for 3 cycles,

which was followed by

- Paclitaxel 175 mg/m² 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 MO16432 are summarized in the table below. The median duration of follow-up in the Herceptin arm was 3.8 years.
Parameter | Chemo + Herceptin (n=115) | Chemo only (n=116) | Hazard Ratio (95% CI) | p-value
--- | --- | --- | --- | ---
Event-free survival | | | | 
No. patients with event | 46 | 59 | 0.65 (0.44, 0.96) | 0.0275
Total pathological complete response* (95% CI) | 40% (31.0, 49.6) | 20.7% (13.7, 29.2) | | P=0.0014
Overall survival | | | | 
No. patients with event | 22 | 33 | 0.59 (0.35, 1.02) | 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 % vs. 52 %).

**MGC**

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$^2$ orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle)

or

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

Either of which was administered with:

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

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

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

FP + H: Fluoropyrimidine/cisplatin + Herceptin
FP: Fluoropyrimidine/cisplatin
* 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)].

**Immunogenicity**

903 breast cancer patients treated with Herceptin, alone or in combination with chemotherapy, have been evaluated for antibody production. Human anti-trastuzumab antibodies were detected in one patient, who had no allergic manifestations.

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

**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 in Breast and Gastric cancer. See section 4.2 for information on paediatric use.

**5.2 Pharmacokinetic properties**

The pharmacokinetics of trastuzumab have been studied in patients with metastatic breast cancer, early breast cancer and advanced gastric cancer patients. Formal drug-drug interaction studies have not been performed with Herceptin.

**Breast Cancer**

Short duration intravenous infusions of 10, 50, 100, 250, and 500 mg trastuzumab once weekly in patients demonstrated non-linear pharmacokinetics where clearance decreased with increasing dose.

**Half-life**

The elimination half-life is of 28-38 days and subsequently the washout period is up to 27 weeks (190 days or 5 elimination half-lives).

**Steady State pharmacokinetics**

Steady state should be reached by approximately 25 weeks. In a population pharmacokinetic (two compartment, model-dependent) assessment of Phase I, II and III clinical trials in metastatic breast cancer, the median predicted AUC at steady state over a three-week period was three times 578 mg•day/l (1677 mg•day/l) with 3 weekly doses of 2 mg/kg and 1793 mg•day/l with every one three week dose of 6 mg/kg; the estimated median peak concentrations were 104 mg/l and 189 mg/l, respectively. In patients with early breast cancer administered Herceptin at a loading dose of 8 mg/kg followed every three weeks by 6 mg/kg, using model-independent or non-compartmental analyses (NCA) the mean steady state trough concentration measured at cycle 13 (week 37) was 63 mg/l, which was comparable to that reported previously in patients with metastatic breast cancer receiving the weekly regimen.
**Clearance (CL)**
The typical trastuzumab clearance (for a body weight of 68 kg) was 0.241 l/day.

The effects of patient characteristics (such as age or serum creatinine) on the disposition of trastuzumab have been evaluated. The data suggest that the disposition of trastuzumab is not altered in any of these groups of patients (see section 4.2), however, studies were not specifically designed to investigate the impact of renal impairment upon pharmacokinetics.

**Volume of distribution**
In all clinical studies, the volume of distribution of the central ($V_c$) and the peripheral ($V_p$) compartment was 3.02 l and 2.68 l, respectively, in the typical patient.

**Circulating shed antigen**
Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in the serum of some patients with HER2 overexpressing breast cancers. Determination of shed antigen in baseline serum samples revealed that 64% (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/ml (median = 11 ng/ml). Patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations of trastuzumab. However, with weekly dosing, most patients with elevated shed antigen levels achieved target serum concentrations of trastuzumab by week 6 and no significant relationship has been observed between baseline shed antigen and clinical response.

**Advanced Gastric Cancer**

**Steady state pharmacokinetics**
A two compartment nonlinear population pharmacokinetic model, based on data from Phase III study BO18255, was used to estimate the steady state pharmacokinetics in patients with advanced gastric cancer administered trastuzumab at a loading dose of 8 mg/kg followed by a 3-weekly maintenance dose of 6 mg/kg. The observed serum levels of trastuzumab were lower and thus total clearance was estimated to be higher in AGC patients compared to breast cancer patients receiving the same dosing regimen. The reason for this is unknown. At high concentrations, total clearance is dominated by linear clearance, and the half-life in AGC patients is approximately 26 days. The median predicted steady-state AUC values (over a period of 3 weeks at steady state) is equal to 1213 mg•day/L, the median steady-state $C_{\text{max}}$ is equal to 132 mg/l and the median steady-state $C_{\text{min}}$ values is equal to 27.6 mg/L.

There are no data on the level of circulating extracellular domain of the HER2 receptor (shed antigen) in the serum of gastric cancer patients.

**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

L-histidine hydrochloride
L-histidine
α,α-trehalose dihydrate
polysorbate 20

6.2 Incompatibilities

Herceptin should not be mixed or diluted with other 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

4 years

After reconstitution with water for injections the reconstituted solution is physically and chemically stable for 48 hours at 2°C – 8°C. Any remaining reconstituted solution should be discarded.

Solutions of Herceptin for infusion are physically and chemically stable in polyvinylchloride, polyethylene or polypropylene bags containing sodium chloride 9 mg/ml (0.9%) solution for injection for 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. The product is not intended to be stored after reconstitution and dilution unless this has taken place under controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

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

Appropriate aseptic technique should be used. Each vial of Herceptin is reconstituted with 7.2 ml of water for injections (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 reconstitution:
1) Using a sterile syringe, slowly inject 7.2 ml of water for injections 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.

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 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. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for 24 hours (do not store above 30°C).

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

Herceptin is for single-use only, as the product contains no preservatives. Any unused 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 Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

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 August 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Roche Diagnostics GmBH, Pharma Biotechnology Production
Nonnenwald 2
82372 Penzberg
Germany

Genentech Inc.
1000 New Horizons Way
Vacaville, CA 95688
USA

Name and address of the manufacturer(s) responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable

• OTHER CONDITIONS

Risk Management Plan
The MAH commits to performing the trials and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 10.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).
In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

The MAH will continue to submit periodic safety update reports (PSURs) on a six-monthly basis.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT

Herceptin 150 mg powder for concentrate for solution for infusion
Trastuzumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

The vial contains 150 mg trastuzumab. After reconstitution 1 ml concentrate contains 21 mg of trastuzumab

3. LIST OF EXCIPIENTS

L-histidine hydrochloride, L-histidine, polysorbate 20, α,α-trehalose dehydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution and dilution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY


8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2ºC – 8 ºC).
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1//00/145/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted
## MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

### VIAL LABEL

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Herceptin 150 mg powder for infusion</td>
</tr>
<tr>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Intravenous use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2. METHOD OF ADMINISTRATION</strong></th>
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</thead>
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<table>
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<tr>
<th><strong>3. EXPIRY DATE</strong></th>
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<tbody>
<tr>
<td>EXP</td>
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<tr>
<th><strong>4. BATCH NUMBER</strong></th>
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<tr>
<td>Lot</td>
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<thead>
<tr>
<th><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></th>
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<table>
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<tr>
<th><strong>6. OTHER</strong></th>
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</table>
Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What Herceptin is and what it is used for
2. Before you use Herceptin
3. How to use Herceptin
4. Possible side effects
5. How to store Herceptin
6. Further information

1. WHAT HERCEPTIN IS AND WHAT IT IS USED FOR

Herceptin contains the active substance trastuzumab, which is a monoclonal antibody. Monoclonal antibodies attach to specific proteins or antigens. Trastuzumab is designed to bind selectively to an antigen called human epidermal growth factor receptor 2 (HER2). HER2 is found in large amounts on the surface of some cancer cells where it stimulates their growth. When Herceptin binds to HER2 it stops the growth of such cells and causes them to die.

Your doctor may prescribe Herceptin for the treatment of breast and gastric cancer when:
- You have early breast cancer, with high levels of a protein called HER2.
- You have metastatic breast cancer (i.e. breast cancer that has spread beyond the original tumour) with high levels of HER2. Herceptin may be prescribed in combination with the chemotherapy agents paclitaxel or docetaxel as first treatment for metastatic breast cancer or it may be prescribed alone if other treatments have proved unsuccessful. It is also used in combination with medicines called aromatase inhibitors with patients with high levels of HER2 and hormone receptor-positive metastatic breast cancer (i.e. cancer that is sensitive to the presence of female sex hormones)
- You have metastatic gastric cancer with high levels of HER2, when it is in combination with the other cancer medicines capecitabine or 5-flourouracil and cisplatin.

2. BEFORE YOU USE HERCEPTIN

Do not use Herceptin
- If you are allergic to trastuzumab, to murine (mouse) proteins, or to any of the other ingredients.
- If you have severe breathing problems at rest due to your cancer or if you need oxygen treatment.
Tell your doctor before you use Herceptin

Your doctor will closely supervise your therapy. You should tell your doctor before you use Herceptin:

- If you have had heart failure, coronary artery disease, heart valve disease (heart murmurs) or high blood pressure. Talk to your doctor about this because Herceptin can cause heart failure.

- If you suffer from breathlessness. Herceptin can cause breathing difficulties, especially when it is first given. This could be more serious if you are already breathless. Very rarely, patients with severe breathing difficulties before treatment have died when they were given Herceptin.

- If you have ever had any other treatment for cancer.

- Especially if you have ever had a medicine called doxorubicin or epirubicin. These medicinal products can damage heart muscle and increase the risk of heart problems with Herceptin.

If you receive Herceptin with paclitaxel, docetaxel, an aromatase inhibitor, capecitabine, 5-fluorouracil, or cisplatin you should also read the patient information leaflets for these products.

Treatment with Herceptin may affect the heart. Therefore, your heart function will be checked before and during the treatment with Herceptin. If you develop any signs of heart failure (i.e., inadequate pumping of blood by the heart), you may have to stop Herceptin.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

It may take up to 6 months for Herceptin to be removed from the body. Therefore you should tell your doctor or pharmacist that you have had Herceptin if you start any new medication in the 6 months after stopping treatment.

Use in children and adolescents
At present, Herceptin is not recommended for anyone under the age of 18 years because there is not enough information in this age group.

Pregnancy and breast-feeding
Before starting treatment, you must tell your doctor if you are pregnant, if you think you are pregnant or if you intend to become pregnant. You should use effective contraception during treatment with Herceptin and for at least 6 months after treatment has concluded. In rare cases, a reduction in the amount of (amniotic) fluid that surrounds the developing baby within the womb has been observed in pregnant women receiving Herceptin. This condition may be harmful to your baby in the womb and has been associated with impaired lung maturation resulting in foetal death. Your doctor will advise you of the risks and benefits of taking Herceptin during pregnancy.

Do not breast-feed your baby during Herceptin therapy and for 6 months after the last dose of Herceptin.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
We do not know whether Herceptin could affect your ability to drive a car or operate machines. However, if you experience symptoms, such as chills or fever, during an infusion of Herceptin (see section 4), you should not drive or use machines until these symptoms disappear.
3. **HOW TO USE HERCEPTIN**

Herceptin is given as an intravenous infusion (“drip”) directly into your veins. The first dose of your treatment is given over 90 minutes and you will be observed by a health professional while it is being given in case you have any side effects. If the first dose is well tolerated the next doses may be given over 30 minutes (see section 2 under “Tell your doctor before you use Herceptin”).

Before starting the treatment your doctor will determine the amount of HER2 in your tumour. Only patients with a large amount of HER2 will be treated with Herceptin. Your doctor will prescribe a dose and treatment regimen that is right for you. The dose of Herceptin depends on your body weight. The number of infusions you receive will depend on how you respond to the treatment. Your doctor will discuss this with you.

For early breast cancer, metastatic breast cancer and metastatic gastric cancer, Herceptin is given every 3 weeks. Herceptin may also be given once a week for metastatic breast cancer.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Herceptin can cause side effects, although not everybody gets them. Some of these side effects may be serious and may lead to hospitalisation.

During a Herceptin infusion, chills, fever and other flu like symptoms may occur. These are very common (affects more than 1 user in 10). Other infusion-related symptoms are: feeling sick (nausea), vomiting, pain, increased muscle tension and shaking, headache, dizziness, breathing difficulties, wheezing, high or low blood pressure, heart rhythm disturbances (palpitations, heart fluttering or irregular heart beat), swelling of the face and lips, rash and feeling tired. Some of these symptoms can be serious and some patients have died (see 2. under “Tell your doctor before you use Herceptin”).

These effects mainly occur with the first infusion (“drip” into your vein) and during the first few hours after the start of the infusion. They are usually temporary. You will be observed by a health care professional during the infusion and for at least six hours after the start of the first infusion and for two hours after the start of other infusions. If you develop a reaction, they will slow down or stop the infusion and may give you treatment to counteract the side effects. The infusion may be continued after the symptoms improve.

Occasionally, symptoms start later than six hours after the infusion begins. If this happens to you, contact your doctor immediately. Sometimes, symptoms may improve and then get worse later.

Other side effects can occur at any time during treatment with Herceptin, not just related to an infusion. Heart problems can sometimes occur during treatment and occasionally after treatment has stopped and can be serious. They include weakening of the heart muscle possibly leading to heart failure, inflammation (i.e. swollen, red, hot, and in pain) of the lining around the heart and heart rhythm disturbances. This can lead to symptoms such as:

- breathlessness (including breathlessness at night),
- cough,
- fluid retention (swelling) in the legs or arms,
- palpitations (heart fluttering or irregular heart beat).

Your doctor will monitor your heart regularly during treatment but you should tell your doctor immediately if you notice any of the above symptoms.

If you experience any of the above symptoms after treatment with Herceptin has been stopped, you should consult your doctor and inform him/her that you have previously been treated with Herceptin.
Very common side effects of Herceptin (affects more than 1 user in 10):

- diarrhoea,
- weakness,
- skin rashes,
- chest pain,
- abdominal pain,
- joint pain,
- febrile neutropenia
- and muscle pain
- conjunctivitis
- watery eyes
- nose bleeds
- runny nose
- tremor
- hot flush
- dizziness

Other common side effects of Herceptin (affects 1 to 10 users in 100):

- allergic reactions
- abnormal blood counts (anaemia, low platelet count and low white blood count)
- constipation
- heartburn (dyspepsia)
- infections including bladder and skin infections
- shingles
- inflammation of the breast
- inflammation of the pancreas or liver
- kidney disorders
- increased muscle tone /tension (hypertonia)
- numbness or tingling of the fingers and toes
- nail disorders
- hair loss
- inability to sleep (insomnia)
- sleepiness (somnolence)
- bruising
- haemorrhoids

- itchiness
- dry mouth and skin
- dry eyes
- sweating
- feeling weak and unwell
- anxiety
- depression
- abnormal thinking
- loss of appetite
- weight loss
- altered taste
- asthma
- lung disorders
- back pain
- neck pain
- bone pain
- acne
- leg cramps

Other rare side effects of Herceptin, (affects 1 to 10 users in 10,000) are:

- Weakness
- Inflammation/scarring of the lungs
- Jaundice

Other side effects that have been reported with Herceptin use (frequency cannot be estimated from the available data):

- Abnormally low clotting factor
- Anaphylactic reactions
- High potassium levels
- Swelling of the brain
- Swelling /bleeding at the back of the eyes
- Shock
- Swelling of the lining of the heart
- Slow heart rate
- Abnormal heart rhythm
- Respiratory distress
- Respiratory Failure
- Acute accumulation of fluid in the lungs
- Acute narrowing of the airways
- Abnormally low oxygen levels in the blood
- Swelling of the throat
- Difficulty in breathing when lying flat
- Liver damage/failure
- Swelling of the face, lips and throat
- Rash (itchy, bumpy)
- Kidney failure
- Abnormally low levels of fluid around baby in womb

Some of the side effects you experience may be due to your underlying breast cancer. If you receive Herceptin in combination with chemotherapy, some of them may also be due to the chemotherapy.

If you experience any of the side effects mentioned in this leaflet or notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE HERCEPTIN

Keep out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the vial label after EXP.

Store in a refrigerator (2°C – 8°C).

Infusion solutions should be used immediately after dilution. Do not use Herceptin if you notice any particulate matter or discoloration prior to administration.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Herceptin contains

- The active substance is trastuzumab. Each vial contains 150 mg trastuzumab that has to be dissolved in 7.2 ml of water for injection. The resulting solution contains approximately 21 mg/ml trastuzumab.

- The other ingredient(s) are L-histidine hydrochloride, L-histidine, α,α-trehalose dihydrate, polysorbate 20.
What Herceptin looks like and contents of the pack

Herceptin is a powder for concentrate for solution for infusion, that is supplied in a glass vial with a rubber stopper containing 150 mg of trastuzumab. The powder is a white to pale yellow pellet. Each carton contains 1 vial of powder.

Marketing Authorisation Holder

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

Manufacturer
Roche Pharma AG
Emil-Barell-Strasse 1
D-79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.
Herceptin should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted Herceptin may result in problems with the amount of Herceptin that can be withdrawn from each vial.

Instructions for Reconstitution:
1) Using a sterile syringe, slowly inject 7.2 ml of water for injections in the vial containing the lyophilised Herceptin, directing the stream into the lyophilised cake.
2) Swirl vial gently to aid reconstitution. DO NOT SHAKE!
Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for approximately 5 minutes. The reconstituted Herceptin results in a colourless to pale yellow transparent solution and should be essentially free of visible particulates.

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 and added to a polyvinylchloride, polyethylene or polypropylene infusion bag containing 250 ml of 0.9 % sodium chloride solution. Do not use with glucose-containing solutions. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for 24 hours (do not store above 30°C).