PROFESSIONAL INFORMATION

WARNINGS

Cardiomyopathy: Herceptin administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with Herceptin. Discontinuation of Herceptin treatment should be strongly considered in patients who develop a clinically significant decrease in left ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who received Herceptin in combination with anthracyclines and cyclophosphamide (see section 4.4).

Hypersensitivity reactions including anaphylaxis, infusion reactions, pulmonary events.

Herceptin administration can result in severe hypersensitivity reactions (including anaphylaxis), infusion reactions and pulmonary events. These may be fatal. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnoea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of Herceptin should be strongly considered for patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome (see section 4.4).

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Herceptin® 21 mg/mL IV powder for concentrate for solution for infusion

Bacteriostatic Water for Injection for Herceptin® Diluent for Herceptin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Reconstituted Herceptin concentrate contains 21 mg/mL trastuzumab.*

Multidose vial: Each multidose vial contains 440 mg of trastuzumab.

Single-dose vial: Each single dose vial contains 150 mg of trastuzumab.

Bacteriostatic Water for Injection for Herceptin: Each vial contains 20 mL sterile bacteriostatic water for injection with 1,1 % m/v benzyl alcohol as preservative for use with the multidose vials only.

*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.

Sugar free

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White to pale yellow lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Metastatic breast cancer (MBC)

Herceptin is indicated for the treatment of patients with metastatic breast cancer whose tumours over-express HER2:

- As monotherapy for the treatment of those patients who have received at least two chemotherapy regimens for their metastatic disease.
- In combination with paclitaxel or 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 patients with hormone-receptor positive metastatic breast cancer.

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).
- In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- In combination with neoadjuvant chemotherapy followed by adjuvant Herceptin, for locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter.

Herceptin should only be used in patients whose tumours have either HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay.

Herceptin should only be used in patients whose tumours have HER2 overexpression at a 3+ level as determined by immunohistochemistry.

Metastatic gastric-adenocarcinoma (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-oesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

Herceptin should only be used in patients with metastatic gastric-adenocarcinoma whose tumours have HER2 overexpression as defined by IHC 2+ and a confirmatory silver *in situ* hybridisation (SISH) or fluorescence *in situ* hybridisation (FISH) result, or by an IHC 3+ result. Accurate and validated assay methods should be used (see section 4.4).

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

4.2 Posology and method of administration

HER2 testing is mandatory prior to initiation of Herceptin therapy.

Herceptin should be administered by a qualified healthcare professional.

It is important to check the product labels to ensure that the correct formulation (Herceptin 21 mg/mL IV or Herceptin 600 mg SC) is being administered to the patient as prescribed. Herceptin IV formulation is not intended for subcutaneous administration and should be administered via intravenous infusion only.

Herceptin should be administered as an intravenous infusion. **Do not administer as an intravenous push or bolus.**

Early breast cancer (EBC), Metastatic breast cancer (MBC) and Metastatic gastric-adenocarcinoma (MGC):

Weekly schedule

The following loading and subsequent doses are recommended for monotherapy and in combination with paclitaxel or docetaxel.

Loading dose: The recommended initial loading dose is 4 mg/kg body weight Herceptin administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see sections 4.4 and 4.8). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses: The recommended weekly dose of Herceptin is 2 mg/kg body weight, beginning one week after the loading dose. If the loading dose was well tolerated, the subsequent dose can be administered as a 30-minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see sections 4.4 and 4.8).

Administration in combination with paclitaxel or docetaxel

Paclitaxel or docetaxel in metastatic disease may be administered the day following the first dose of Herceptin or immediately after the subsequent doses of Herceptin if the preceding dose of Herceptin 21 mg/mL IV was well tolerated.

Administration in combination with an aromatase inhibitor

In the pivotal trial Herceptin and anastrozole were administered on day 1. There were no restrictions on the relative timing of Herceptin and anastrozole at administration. For the anastrozole dose, refer to the anastrozole professional information.

Three weekly schedule

Initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes. If the prior dosage was well tolerated, the dose can be administered as a 30-minute infusion.

Duration of treatment

Patients with MBC or MGC should be treated with Herceptin until progression of disease. Patients with EBC should be treated with Herceptin for 1 year or until disease recurrence, whichever occurs first. Extending treatment in EBC beyond 1 year has been shown to be not more effective than treatment for one year.

Missed doses

If the patient misses a dose of Herceptin by one week or less, then the usual maintenance dose of Herceptin (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 Herceptin maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.
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) as soon as possible. Subsequent Herceptin maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively.

Dose reduction

No reductions in the dose of Herceptin were made during clinical trials. Patients may continue Herceptin therapy during periods of reversible, chemotherapy-induced, myelosuppression but they should be

monitored carefully for complications of neutropenia during this time. The specific instructions to reduce or withhold the dose of chemotherapy should be followed.

Special populations

Elderly: Data suggests that the disposition of Herceptin is not altered based on age (see section 5.2). In clinical trials, elderly patients did not receive reduced doses of Herceptin.

Children: Herceptin is not recommended for use in children below 18 years of age because the safety and efficacy in paediatric patients have not been established.

For “Handling and disposal” including instructions for reconstitution: see section 6.6

For “Incompatibilities” see section 6.2

4.3 Contraindications

- Patients with known hypersensitivity to trastuzumab, murine proteins, or to any of the excipients in Herceptin.
- Patients with severe dyspnoea at rest due to complications of advanced malignancy or the requirement for supplementary oxygen therapy.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

General

HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures (see section 4.1).

Herceptin therapy should only be initiated under supervision of a medical practitioner experienced in the treatment of cancer patients. **Refer to boxed warning.** No data are available on re-treatment of patients with previous exposure to Herceptin in the adjuvant or neoadjuvant setting.

Cardiotoxicity

General considerations

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

Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping Herceptin treatment (see section 5.2). Patients who receive anthracycline after stopping Herceptin are also at increased risk of cardiac dysfunction.

If possible, medical practitioners should avoid anthracycline-based therapy for up to 7 months after stopping Herceptin. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Candidates for treatment with Herceptin, especially those with prior exposure to an anthracycline, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG) and echocardiogram or multigated acquisition scanning (MUGA) scan. Monitoring may help to identify patients who develop cardiac dysfunction, including signs and symptoms of CHF. 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. If LVEF percentage drops 10 points from baseline and to below 50 %, Herceptin should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or if clinically significant CHF has developed, discontinuation of Herceptin should be strongly considered**.**

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 medical practitioner should consider discontinuing therapy if no clinical benefit of Herceptin therapy has been seen.

The safety of continuation or resumption of Herceptin in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during Herceptin therapy, Herceptin should be stopped and patients treated with standard medicines for heart failure (HF). In the pivotal trials, most patients who developed HF or asymptomatic cardiac dysfunction improved with standard HF treatment consisting of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a β-blocker. The majority of patients with cardiac symptoms and evidence of a clinical benefit of Herceptin treatment continued with Herceptin without additional clinical cardiac events.

Metastatic breast cancer (MBC)

Herceptin and anthracyclines should not be given concurrently in the metastatic breast cancer setting.

Early breast cancer (EBC)

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

Patients with history of myocardial infarction (MI), angina pectoris requiring medication, history of or present CHF (NYHA Class II - IV), other cardiomyopathy, cardiac dysrhythmia requiring medication, clinically significant cardiac valvular disease, uncontrolled hypertension, and haemodynamic significant pericardial effusion were excluded from adjuvant breast cancer clinical trials with Herceptin.

Adjuvant treatment

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

In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Herceptin was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence 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.

Risk factors for a cardiac event identified in four large adjuvant studies included advanced age (> 50 years), low level of baseline and declining LVEF (< 55 %), low LVEF prior to or following the initiation of paclitaxel treatment, Herceptin treatment, and prior or concurrent use of anti-hypertensive medicines. In patients receiving Herceptin after completion of adjuvant chemotherapy, the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Herceptin and a high body mass index (BMI >25 kg/m^2).

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, Herceptin concurrently with anthracyclines should be used with caution and only in chemotherapy-naïve patients. The maximum cumulative doses of the low-dose anthracycline regimens should not exceed 180 mg/m^2 (doxorubicin) or 360 mg/m^2 (epirubicin).

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

Clinical experience in the neoadjuvant-adjuvant setting is limited in patients above 65 years of age.

Infusion-related reactions (IRRs), allergic-like reactions, and hypersensitivity

Serious infusion-related adverse reactions to Herceptin infusion that have been reported include dyspnoea, hypotension, wheezing, hypertension, bronchospasm, supraventricular tachydysrythmia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, angioedema, chills, fever, rash, nausea and vomiting and headache (see section 4.8). The majority of these events occur during or within 2,5 hours of the start of the first infusion, but IRRs may also occur later, see below. Should an infusion reaction occur, the infusion should be discontinued or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms (see section 4.2). These symptoms can be treated with an analgesic/antipyretic such as pethidine or paracetamol, or an antihistamine such as diphenhydramine. The majority of patients experienced resolution of symptoms and subsequently received further infusions of Herceptin. Serious

reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids. However, these reactions may have 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 4.2).

Initial improvement followed by clinical deterioration and delayed reactions with rapid clinical deterioration may occur. Fatalities have occurred within hours and up to one week following infusion. Patients have experienced the onset of infusion symptoms or 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 medical practitioner if these symptoms occur.

Pulmonary events

In the post-marketing setting severe pulmonary events have been reported with the use of Herceptin (see section 4.8).

These events may result in fatal outcome and may occur as part of an IRR or with a delayed onset. In addition, cases of interstitial lung disease (ILD), 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 (ILD) include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with ILD such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at risk of pulmonary events. Therefore, these patients should not be treated with Herceptin (see section 4.2).

Other severe events reported in the post-marketing setting include pulmonary fibrosis.

Haematotoxicity

Febrile neutropenia occurred very commonly. Commonly occurring adverse reactions included anaemia, leukopenia, thrombocytopenia and neutropenia. The frequency of occurrence of hypoprothrombinemia is not known.

Hepatic and renal toxicity

Breast cancer:

WHO Grade III or IV hepatic toxicity was observed in 12 % of patients following administration of Herceptin as single agent in the metastatic setting. This toxicity was associated with progression of disease in the liver in 60 % of these patients.

WHO Grade III or IV hepatic toxicity was less frequently observed among patients receiving Herceptin and paclitaxel than among patients receiving paclitaxel alone (7 % compared with 15 %). No WHO Grade III or IV renal toxicity was observed.

Advanced Gastric-adenocarcinoma:

In the ToGA study no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

National Cancer Institute Common Toxicity Criteria Adverse Events (NCICTCAE) (v 3.0) grade ≥ 3 renal toxicity occurred in 5 % of patients.

NCICTCAE (v 3.0) grade ≥ 3 adverse event in hepatobiliary disorders: Hyperbilirubinaemia occurred in 1 % of patients.

Diarrhoea

Breast Cancer: Of patients treated with Herceptin monotherapy in the metastatic setting, 27 % experienced diarrhoea.

Infection

An increased incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed in patients treated with Herceptin.

Benzyl alcohol

Benzyl alcohol, used as a preservative in bacteriostatic water for injection, has been associated with toxicity in neonates and children up to 3 years old. When administering Herceptin to a patient with a known hypersensitivity to benzyl alcohol, Herceptin should be reconstituted with water for injection, and only one dose per Herceptin vial should be used. Any unused portion must be discarded.

4.5 Interaction with other medicines and other forms of interaction

There have been no formal medicine interaction studies performed with Herceptin in humans.

The results of an interaction substudy evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without Herceptin suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus Herceptin. However, capecitabine itself showed higher concentrations and a longer half-life when combined with Herceptin. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus Herceptin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment with Herceptin is contraindicated during pregnancy.

Breastfeeding

Herceptin crosses the placenta and appears in the breast milk (see section 4.2).

Mothers breastfeeding their infants should not use Herceptin (see section 4.2).

Contraception

In the post-marketing setting, cases of foetal renal growth, a single kidney and/or renal function impairment often in association with oligohydramnios, some of which also had 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 7 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the foetus.

Males: Based on currently available knowledge including the elimination half-life of Herceptin in humans, male and female patients treated with Herceptin, are recommended to use highly effective contraception, including a barrier method for at least 7 months following the last dose of Herceptin.

4.7 Effects on ability to drive and use machines

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

Benzyl alcohol

Benzyl alcohol, used as a preservative in bacteriostatic water for injection, has been associated with toxicity in neonates and children up to 3 years old. When administering Herceptin to a patient with a known hypersensitivity to benzyl alcohol, Herceptin should be reconstituted with water for injection, and only one dose per Herceptin vial should be used. Any unused portion must be discarded.

4.8 Undesirable effects

a. Summary of the safety profile

Amongst the most serious and/or common adverse reactions reported with Herceptin usage 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 are presented in order of decreasing seriousness.

b. Tabulated list of adverse reactions

Clinical trials

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 for EBC, MBC and MGC. All the frequency terms included are based on the highest percentage seen in pivotal clinical trials.

Table 1: Clinical trial adverse drug reactions (ADRs)

System organ class	***Frequency***	***Adverse reaction***
Infections and infestations	Very common	Nasopharyngitis, infection
	Common	Neutropenic sepsis, cystitis, herpes zoster, influenza, sinusitis, skin infection, rhinitis, upper respiratory tract infection, urinary tract infection, erysipelas, cellulitis, bronchitis
	Uncommon	Sepsis
Blood and lymphatic system disorders	Very common	Anaemia, thrombocytopenia, febrile neutropenia, decreased white blood cell count/leukopenia
	Common	Neutropenia
Immune system disorders	Common	Hypersensitivity, e.g. allergic-like reactions, (itching, lacrimation, skin rash, urticaria), anaphylaxis
Metabolism and nutrition disorders	Very common	Increased weight, decreased weight, decreased appetite

System organ class	***Frequency***	***Adverse reaction***
Psychiatric disorders	Very common	Insomnia
	Common	Anxiety, depression, abnormal thinking
Nervous system disorders	Very common	Tremor, dizziness, headache, hypoaesthesia, paraesthesia, dysgeusia
	Common	Peripheral neuropathy, hypertonia, somnolence, ataxia, lethargy
	Rare	Paresis
Eye disorders	Very common	Conjunctivitis, increased lacrimation
	Common	Dry eye
Ear and Labyrinth Disorders	Common	Vertigo
	Uncommon	Deafness
Cardiac disorders	Very common	Decreased blood pressure, increased blood pressure, irregular heart beat, palpitation, atrial flutter, decreased left ventricular ejection fraction
	Common	Cardiac failure (congestive), supraventricular tachydysrhythmia, cardiomyopathy, chest discomfort

System organ class	***Frequency***	***Adverse reaction***
	Uncommon	Pericardial effusion
Vascular disorders	Very common	Hot flush, lymphoedema
	Common	Hypotension, vasodilation, hypertension
Respiratory, thoracic and mediastinal disorders	Very common	Wheezing, dyspnoea, oropharyngeal pain, epistaxis, cough, rhinorrhoea
	Common	Asthma, lung disorder, pharyngitis, hiccups, exertional dyspnoea, pneumonia, pleural effusion
	Uncommon	Interstitial pneumonitis
Gastrointestinal disorders	Very common	Diarrhoea, vomiting, nausea, lip swelling, abdominal pain, stomatitis, dyspepsia, constipation
	Common	Pancreatitis, haemorrhoids, dry mouth, gastritis
Hepatobiliary disorders	Common	Hepatitis, liver tenderness, abnormal liver function
	Rare	Jaundice
Skin and subcutaneous disorders	Very common	Erythema, rash, swelling face, palmar-plantar erythrodysaethesia syndrome

System organ class	***Frequency***	***Adverse reaction***
		(hand-foot syndrome), alopecia, nail disorder
	Common	Acne, dry skin, ecchymosis, hyperhydrosis, maculopapular rash, pruritus, onychorrhexis, dermatitis, onychoclasis
	Uncommon	Urticaria
Musculoskeletal and connective tissue disorders	Very common	Arthralgia, rigor, myalgia
	Common	Arthritis, back pain, bone pain, muscle spasms, neck pain, pain in extremity, musculoskeletal pain
Renal and urinary conditions	Common	Renal disorder, dysuria
Reproductive system and breast disorders	Common	Breast inflammation/mastitis, breast pain
General disorders and administration site conditions	Very common	Asthenia, chest pain, chills, fatigue, influenza-like symptoms, infusion related reaction, pain, pyrexia, peripheral oedema, mucosal inflammation
	Common	Oedema, malaise
Injury, poisoning and procedural complications	Very common	Nail toxicity
	Common	Contusion

Post Marketing

Table 2: Adverse reactions reported in the post-marketing setting:

System organ class	Adverse Event
Infections and infestations	Meningitis
Neoplasms benign and malignant (including cysts and polyps)	Progression of malignant neoplasm, progression of neoplasia
Blood and lymphatic system disorders	Anaemia, hypoprothrombinaemia, leukaemia, neutropenia, immune thrombocytopenia
Immune system disorders	Anaphylactoid reaction, angioedema
Psychiatric disorders	Abnormal thinking
Nervous system disorders	Cerebral oedema
Eye disorders	Papilloedema, abnormal lacrimation, retinal haemorrhage, madarosis
Ear and labyrinth disorders	Deafness
Cardiac disorders	Cardiomyopathy, deterioration in congestive heart failure, hypotension, cerebrovascular disorder, cardiac failure, cardiogenic shock, pericarditis, hypertension, gallop rhythm, tachycardia
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease, lung infiltration, bronchospasm, +respiratory distress, +respiratory failure, acute pulmonary oedema, respiratory insufficiency, acute respiratory distress syndrome, Cheyne-Stokes breathing, pneumonia, pneumonitis, +pulmonary fibrosis, dyspnoea, hypoxia, +laryngeal oedema, pleural effusion, decreased oxygen saturation, orthopnoea

Gastrointestinal system disorders	Diarrhoea, nausea, vomiting
Hepatobiliary disorders	Hepatocellular damage, liver tenderness, pancreatitis, hepatic failure, jaundice
Skin and subcutaneous tissue disorders	Rash, dermatitis, urticaria, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Myalgia, bone pain
Renal and urinary conditions	Membranous glomerulonephritis, glomerulonephropathy, renal failure
Pregnancy, puerperium and perinatal disorders	Oligohydramnios, pulmonary hypoplasia, renal hypoplasia
General disorders and administration site conditions	Infusion-related symptoms, peripheral oedema, coma, paraneoplastic cerebellar degeneration

+ Denotes adverse reactions that have been reported in association with a fatal outcome.

c. Description of selected adverse reactions from clinical trials

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Immunogenicity

In the neoadjuvant-adjuvant EBC treatment setting, 8,1 % (24/296) of patients treated with Herceptin developed antibodies against trastuzumab (regardless of antibody presence at baseline. Neutralising anti-trastuzumab antibodies were detected in post-baseline samples in 2 of 24 Herceptin patients.

The clinical relevance of these antibodies is not known; nevertheless, the pharmacokinetics, efficacy [determined by pathological complete response (pCR)] or safety determined by occurrence of administration related reactions (ARRs) of Herceptin did not appear to be adversely affected by these antibodies.

Infusion-related reactions (IRRs) and hypersensitivity

IRRs such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress were seen in all Herceptin clinical trials (see section 4.4).
IRRs may be clinically difficult to distinguish from hypersensitivity reactions.
The rate of IRRs of all grades varied between studies depending on the indication, whether Herceptin was given concurrently with chemotherapy or as monotherapy and data collection methodology.

In MBC, the rate of IRRs ranged from 49 % to 54 % in the Herceptin containing arm compared to 36 % to 58 % in the comparator arm (which may have contained other chemotherapy). Severe (grade 3 and above) ranged from 5 % to 7 % in the Herceptin containing arm compared to 5 to 6 % in the comparator arm.
In EBC, the rate of IRRs ranged from 18 % to 54 % in the Herceptin containing arm compared to 6 % to 50 % in the comparator arm (which may have contained other chemotherapy). Severe (grade 3 and above) ranged from 0,5 % to 6 % in the Herceptin containing arm compared to 0,3 to 5 % in the comparator arm.
In the neoadjuvant-adjuvant EBC treatment setting, the rates of IRRs were in line with the above and were 37,2 % in the Herceptin arm. Severe (grade 3) IRRs were 2,0 % in the Herceptin arm during the treatment phase. There were no grade 4 or 5 IRRs. Anaphylactoid reactions were observed in isolated cases.

Cardiac dysfunction

Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to Herceptin. It has been associated with fatal outcome. Signs and symptoms of cardiac dysfunction such as dyspnoea,

orthopnoea, increased cough, pulmonary oedema, S_3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin (see section 4.4).

Metastatic Breast Cancer

Depending on the criteria used to define cardiac dysfunction, the incidence in the pivotal metastatic trials varied between 9 % and 12 % in the Herceptin + paclitaxel group, compared with 1 % - 4 % in the paclitaxel-alone group. For Herceptin monotherapy, the rate was 6 % - 9 %. The highest rate of cardiac dysfunction was seen in patients receiving concurrent Herceptin + anthracycline/cyclophosphamide (27 %), and was significantly higher than in the anthracycline/cyclophosphamide-alone group (7 % - 10 %). Most of the patients (79 %) who developed cardiac dysfunction in trials experienced an improvement after receiving standard treatment for CHF.

Early Breast Cancer (adjuvant setting)

In three pivotal clinical trials of adjuvant Herceptin given in combination with chemotherapy, the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in patients who were administered Herceptin sequentially after a taxane (0,3 - 0,4 %). No increase in the cumulative incidence of cardiac events was seen with further follow-up at 5 years.

At 5,5 years, the rates of symptomatic cardiac or LVEF events were 1,0 % - 2,3 %. For symptomatic CHF (NCI-CTC Grade 3-4), the 5-year rates were 0,6 % - 1,9 %.

When Herceptin was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0,6 % of patients in the one-year arm after a median follow-up of 12 months. After a median follow-up of 3,6 years the incidence of severe CHF and left ventricular dysfunction after 1 year Herceptin therapy was 0,8 % and 9,8 %, respectively.

After a median follow-up of 8 years the incidence of severe CHF (NYHA Class III-IV) in the Herceptin ONE year treatment arm was 0,8 %, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4,6 %.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values $\geq$ 50 % after the event) was evident for 71,4 % of Herceptin-treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79,5 % of patients. Approximately 17 % of cardiac-dysfunction related events occurred after completion of Herceptin.

Early Breast Cancer (EBC) (neoadjuvant-adjuvant setting)

In a pivotal trial, Herceptin was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m^2). The incidence of symptomatic cardiac dysfunction was 1,7 % in the Herceptin arm.

In a pivotal trial, Herceptin was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m^2); at a median follow-up of 40 months, the incidence of congestive cardiac failure was 0 % in the Herceptin arm.

Advanced Gastric Cancer

The majority of the LVEF decreases noted in the clinical study were asymptomatic, with the exception of one patient in the Herceptin-containing arm whose LVEF decrease coincided with cardiac failure.

Switching treatment from Herceptin 21 mg/mL IV to SC trastuzumab

Patients with EBC may be switched to a SC formulation of trastuzumab.

4.9 Overdose

Symptoms of overdose may be exacerbated and/or exaggerated to those reported in side effects. There is no experience with overdosage in human clinical trials. Single doses higher than 10 mg/kg have not been tested.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Trastuzumab is a recombinant DNA-derived humanised monoclonal antibody that selectively targets the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). The antibody is an IgG_1 isotype that contains human framework regions with the complementarity-determining regions of a murine anti-p185 HER2 antibody that binds to HER2.

The HER2 proto-oncogene or c-erbB2 encodes for a single transmembrane spanning, receptor-like protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Overexpression of HER2 is observed in 15 - 20 % of primary breast cancers and 6,8 - 42,6 % advanced gastric-adenocarcinoma.

Trastuzumab has been shown, both in *in vitro* assays and in animals, to inhibit the proliferation of human tumour cells that overexpress HER2. *In vitro*, trastuzumab-mediated, antibody-dependent, cell-mediated cytotoxicity (ADCC) has been shown to be preferentially exerted on HER2 overexpressing cancer cells, compared with cancer cells that do not overexpress HER2.

Immunogenicity: Human anti-trastuzumab antibodies were detected in 1 of 903 patients, who had no allergic manifestations.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1 582 subjects from 18 Phase I, II and III trials receiving trastuzumab. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to the non-linear elimination, total clearance increased with decreasing concentrations. Linear clearance was 0,127 L/day for metastatic and early breast cancer (MBC/EBC) and 0,176 L/day for metastatic gastric-adenocarcinoma (MGC). The nonlinear elimination parameter values were 8,81 mg/day for the maximum elimination rate (Vmax) and 8,92 mg/L for the Michaelis-Menten constant (Km). The central compartment volume was 2,62 L for patients with breast cancer and 3,63 L for patients with MGC.

The population predicted PK exposures (with 5^{th} - 95^{th} percentiles) and PK parameter values at clinically relevant concentrations (C_{max} and C_{min}) for breast cancer and MGC patients treated with the approved once weekly and three weekly dosing regimens are shown in Table 3 (Cycle 1) and Table 4 (steady-state) below.

Table 3: Population Predicted Cycle 1 PK Exposure Values (with 5^{th} - 95^{th} Percentiles) for IV Regimens in Breast Cancer and MGC Patients

Regimen	Primary tumour type	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC (µg.day/mL)
8mg/kg + 6mg/kg three weekly	MBC/ EBC	1 195	29,4 (5,8 - 59,5)	178 (117 - 291)	1373 (736 - 2 245)
	MGC	274	23,1 (6,1 - 50,3)	132 (84,2 - 225)	1 109 (588 - 1 938)

4mg/kg + 2mg/kg weekly	MBC/ EBC	1 195	37,7 (12,3 - 70,9)	88,3 (58 - 144)	1 066 (586 - 1 754)

Table 4: Population Predicted Steady State PK Exposure Values (with 5th - 95th Percentiles) for Herceptin Dosing Regimens in Breast Cancer and MGC Patients

Regimen	Primary tumour type	N	Cmin,ss (µg/mL)	Cmax,ss (µg/mL)	AUCss (µg.day/ mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8mg/kg + 6mg/kg three weekly	MBC/ EBC	1 195	47,4 (5 - 115)	179 (107 - 309)	1 794 (673 - 3 618)	12	0,173 - 0,283
	MGC	274	32,9 (6,1 - 88,9)	131 (72,5 - 251)	1 338 (557 - 2 875)	9	0,189 - 0,337
4mg/kg + 2mg/kg weekly	MBC/ EBC	1 195	66,1 (14,9 - 142)	109 (51,0 - 209)	1 765 (647 - 3 578)	12	0,201 - 0,244

Trastuzumab washout

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

Pharmacokinetics in special populations

Detailed pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out.

Renal impairment

Detailed pharmacokinetic studies in patients with renal impairment have not been carried out. In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition.

Elderly

Age has been shown to have no effect on the disposition of trastuzumab, (see section 4.2)

Pregnancy and lactation:

In animal studies trastuzumab has been demonstrated to cross the placenta and to appear in breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

α,α-trehalose

l-histidine

polysorbate 20

water for injection

6.2 Incompatibilities

Herceptin must not be mixed with other medicinal products except those mentioned in section 6.6.

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

Dextrose solution should not be used since it causes aggregation of the protein.

6.3 Shelf life

Unopened vial:

48 months.

***440 mg multidose vial reconstituted solution**:*

A multidose vial of Herceptin 21 mg/mL IV, reconstituted with bacteriostatic water for injection as supplied, is stable for 28 days when stored refrigerated at 2 - 8 °C. The reconstituted solution contains a preservative and is therefore suitable for multiple use. Any remaining reconstituted solution should be discarded after 28 days. If sterile water is used to reconstitute the 21 mg/mL vial, the solution is stable for only 24 hours, and must be discarded thereafter.

Solution for infusion: Solutions of Herceptin for infusion are stable in polyvinylchloride or polyethylene bags containing 0,9 % sodium chloride at 2 - 8 °C for 24 hours. The product is not intended to be stored after dilution, unless the dilution has taken place under controlled and validated aseptic conditions.

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

***150 mg single-dose vial reconstituted solution**:*

A single-dose vial of Herceptin, reconstituted with sterile water for injection, is physically and chemically stable for 48 hours when stored refrigerated at 2 - 8 °C.

Solution for infusion: Solutions of Herceptin for infusion are physically and chemically stable in polyvinylchloride or polyethylene bags containing 0,9 % sodium chloride for up to 7 days at 2 - 8 °C and subsequently 24 hours at room temperature (≤ 30 °C).

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

This medicine should not be used after the expiry date shown on the pack.

6.4 Special precautions for storage

Vials with lyophilised powder: Store vials at 2 - 8 °C.

Do not freeze the reconstituted solution.

For storage conditions of the unopened medicine, see sections 6.3 and 6.6

Disposal of unused/expired medicines:

The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established collection systems, if available in your location.

6.5 Nature and contents of container

Herceptin 21 mg/mL: Vials with lyophilised powder. Herceptin is a white, to pale yellow, lyophilised powder.

Reconstituted product: The reconstituted product is a colourless to pale yellow, clear to slightly opalescent, solution.

Diluted product: The diluted product is a clear, colourless to pale yellow, transparent solution.

Bacteriostatic Water for Injection for Herceptin: The diluent is a clear, colourless liquid. Each vial contains sterile bacteriostatic water for injection.

Multidose vial pack:

Each carton contains one multidose vial of Herceptin in a 50 mL clear, colourless glass type I vial, with a grey siliconised butyl rubber stopper, for use with lyophilised formulations. The stoppered vial is sealed with a silver aluminium cap, fitted with a green flip-off disk and one vial of bacteriostatic water for injection in a 20 mL, clear glass type I vial, with a grey butyl rubber stopper. The stoppered vial is sealed with a silver aluminium cap, fitted with a white flip-off disk.

Single-dose vial pack: Each carton contains one single-dose vial of Herceptin in a 15 mL clear, colourless glass type I vial, with a grey siliconised butyl rubber stopper, for use with lyophilised formulations. The stoppered vial is sealed with a silver aluminium cap, fitted with a red flip-off disk

For storage conditions of the diluted product see section 6.3.

Store all medicines out of reach of children.

Any unused product or waste material should be disposed of.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Appropriate aseptic technique should be used.

Reconstitution of 440 mg multidose vials

Each vial of Herceptin is reconstituted with 20 mL of bacteriostatic water for injection, containing 1,1 % m/v benzyl alcohol, as supplied. This yields a solution for multiple use, containing 21 mg/mL Herceptin, at a pH of approximately 6,0. Use of other reconstitution diluents should be avoided.

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 the vial.

Instructions for reconstitution

1. Using a sterile syringe, slowly inject 20 mL of bacteriostatic water for injection 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 preparation results in a colourless to pale yellow transparent solution, free of visible particles.

When administering Herceptin to a patient with a known hypersensitivity to benzyl alcohol (see section 4.4), Herceptin should be reconstituted with water for injection (not supplied), which may also be used for single-dose preparation.

Reconstitution of 150 mg single-dose vials

Each vial of Herceptin is reconstituted with 7,2 mL of sterile water for injection (not supplied). Use of other reconstitution solvents should be avoided.

This yields a 7,4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab, at a pH of approximately 6.0. A volume overage of 4 % ensures that the labelled dose of 150 mg can be withdrawn from each vial.

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

The reconstituted solution should not be frozen.

Instructions for aseptic reconstitution

1) Using a sterile syringe, slowly inject 7,2 mL of sterile water for injection in the vial containing the lyophilised Herceptin, directing the stream into the lyophilised cake.

2) Swirl the vial gently to aid reconstitution. DO NOT SHAKE!

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

Instructions for dilution

Determine the volume of the solution required

- based on a loading dose of 4 mg trastuzumab per kilogram body weight, or a maintenance dose of 2 mg trastuzumab per kilogram body weight:

Volume (mL) = **Body weight** (kg) x **dose** (**4** mg/kg loading or **2** mg/kg maintenance) / **21** (mg/mL, concentration of reconstituted solution).

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

Volume (mL) = **Body weight** (kg) x **dose** (**8** mg/kg loading or **6** mg/kg maintenance) / **21** (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. Dextrose solution should not be used, see *Incompatibilities*, section 6.2. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral medicinal products should be inspected visually for particulates and discolouration prior to administration. Once the infusion is prepared, it should be administered immediately. If diluted aseptically, it may be stored for 24 hours when refrigerated at 2 to 8 °C.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road

Hertford Office Park

Building E

Vorna Valley

Midrand, Johannesburg

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

Herceptin 21 mg/mL IV: 34/26/0419

Bacteriostatic Water for Injection for Herceptin: 34/32.4/0420

9. DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

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