PROFESSIONAL INFORMATION

WARNINGS

Cardiomyopathy: Herceptin SC 600 mg 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 SC 600 mg. Discontinuation of Herceptin SC 600 mg 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 SC 600 mg in combination with anthracyclines and cyclophosphamide. (See WARNINGS AND SPECIAL PRECAUTIONS.)

Hypersensitivity reactions including anaphylaxis, administration reactions, pulmonary events:

Herceptin SC 600 mg administration can result in severe hypersensitivity reactions (including anaphylaxis), administration reactions and pulmonary events. These may be fatal. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin SC 600 mg. Herceptin SC 600 mg administration should be interrupted for patients experiencing

dyspnoea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Herceptin SC 600 mg should be discontinued in patients who develop anaphylaxis, angioedema, or acute respiratory distress syndrome. (See WARNINGS AND SPECIAL PRECAUTIONS.)

SCHEDULING STATUS

S4

NAME OF THE MEDICINE

Herceptin® SC 600 mg subcutaneous injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mℓ vial contains 600 mg trastuzumab.

Excipients: recombinant human hyaluronidase (rHuPH20), l-histadine, α,α-trehalose, l-methionine, polysorbate 20, water for injections

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Herceptin SC 600 mg is a sterile, colourless to yellowish, clear to opalescent liquid solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Metastatic Breast Cancer (MBC)

Herceptin SC 600 mg is indicated for the treatment of patients with metastatic adenocarcinoma of the breast 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 SC 600 mg is indicated for the treatment of patients with HER2 positive early adenocarcinoma of the breast:

- Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable);
- Following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with docetaxel;
- In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin;
- In combination with neoadjuvant chemotherapy followed by adjuvant Herceptin SC 600 mg, for locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter.

Herceptin SC 600 mg 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 SC 600 mg should only be used in patients whose tumours have HER2 overexpression at a 3+ level as determined by immunohistochemistry.

4.2 Posology and method of administration

HER2 testing is mandatory prior to initiation of Herceptin SC 600 mg therapy.
Herceptin SC 600 mg should be administered by a qualified healthcare professional.
It is important to check the product labels to ensure that the correct formulation, SC is being administered to the patient as prescribed.

Limited information is currently available on switches from one formulation to the other. The three weekly dosing interval should be followed. Switching patients from SC to IV formulation was investigated in study MO22982.

Herceptin SC 600 mg formulation is not to be used for intravenous administration and must be administered via subcutaneous route only.

No loading dose is required.

The recommended fixed dose of Herceptin SC 600 mg is 600 mg irrespective of the patient's body weight. This dose should be administered subcutaneously over 2 - 5 minutes every three weeks.

The injection site should be alternated between the left and right thigh. New injections should be given at least 2,5 cm from the previous site on healthy skin and never into areas where the skin is red, bruised, tender or hard. During the treatment course with Herceptin SC 600 mg other medications for SC administration should preferably be injected at different sites.

Duration of treatment

Patients with MBC should be treated with Herceptin SC 600 mg until progression of disease or unmanageable toxicity.

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

Delayed or Missed doses

If one dose is missed, it is recommended to administer the next Herceptin SC 600 mg dose (i.e. the missed dose) as soon as possible. The interval between subsequent Herceptin SC 600 mg doses should not be less than three weeks.

Dose modifications

No reductions in the dose of Herceptin SC 600 mg were made during clinical trials. Patients may continue Herceptin SC 600 mg 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 dosing instructions

Elderly: Data suggests that the disposition of Herceptin SC 600 mg is not altered based on age. (See Pharmacokinetics in special populations.) In clinical trials, elderly patients ≥ 65 years of age did not receive reduced doses of Herceptin SC 600 mg.

Children: Herceptin SC 600 mg is not recommended for use in children below 18 years of age because the safety and efficacy in paediatric patients have not been established.

4.3 Contraindications

Patients with known hypersensitivity to trastuzumab, murine proteins, or to any of the excipients in Herceptin SC 600 mg.

Patients with severe dyspnoea at rest due to complications of advanced malignancy or the requirement for supplementary oxygen therapy. (see Pregnancy and Lactation (see section 4.6).

4.4 Special warnings and precautions for use

General

In order to improve traceability of biological medicinal products, the trade name of the administered product should be clearly recorded (or stated) in the patient file. HER2 testing must be performed in a specialised laboratory which can ensure adequate validation of the testing procedures (see INDICATIONS section 4.1).

Herceptin SC 600 mg 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 SC 600 mg in the adjuvant or neo-adjuvant setting.

Cardiotoxicity

General considerations

Patients treated with Herceptin SC 600 mg 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 SC 600 mg 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 SIDE EFFECTS). 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 SC 600 mg treatment (see Pharmacokinetic properties). Patients who receive anthracycline after stopping Herceptin SC 600 mg 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 SC 600 mg. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Candidates for treatment with Herceptin SC 600 mg, 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 SC 600 mg.

If LVEF percentage drops 10 points from baseline and to below 50 %, Herceptin SC 600 mg 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 SC 600 mg 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 unless the benefits for the individual patient are deemed to outweigh the risks.

The safety of continuation or resumption of Herceptin SC 600 mg in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during Herceptin SC 600 mg therapy, it should be stopped and the patient treated with standard medications 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 SC 600 mg treatment continued with Herceptin SC 600 mg without additional clinical cardiac events.

Metastatic breast cancer (MBC)

Herceptin SC 600 mg 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 SC 600 mg. 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 SC 600 mg, 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 SC 600 mg.

Adjuvant treatment

Herceptin SC 600 mg 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 IV 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 IV 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 SC 600 mg treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving Herceptin SC 600 mg 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 SC 600 mg and a high body mass index (BMI >25 kg/m^2).

Neoadjuvant-adjuvant treatment

In patients with EBC eligible for neoadjuvant-adjuvant treatment, Herceptin SC 600 mg 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 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.

Administration-related reactions (ARRs), and hypersensitivity

Serious adverse reactions to Herceptin SC 600 mg administration 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 SIDE EFFECTS). These symptoms can be treated with an analgesic/antipyretic such as pethidine or paracetamol, or an antihistamine such as diphenhydramine.

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 administration reaction. Therefore, these patients should not be treated with Herceptin SC 600 mg, (see Section 4.2 Special warnings and precautions).

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 SC 600 mg administration. 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.
Administration related adverse events (ARRs) may be clinically difficult to distinguish from hypersensitivity reactions.

The rate of ARRs of all grades varied between studies depending on the indication, whether Herceptin SC 600 mg was given concurrently with chemotherapy or as monotherapy and data collection methodology.
In MBC, the rate 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 ARRs 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 setting, the rate of ARRs was in line with the above and was 47,8 % and severe grade 3 events was 1,7 % in the Herceptin SC 600 mg arm. There were no grade 4 or 5 ARRs.

Pulmonary events

Caution is advised with Herceptin SC 600 mg formulation, as severe pulmonary events leading to death have been reported with the use of Herceptin SC 600 mg, (see SIDE EFFECTS). These events may result in fatal outcome and may occur as part of an ARR or with 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. Therefore, these patients should not be treated with Herceptin SC 600 mg, (see CONTRAINDICATIONS). 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. Other severe events reported in the post-marketing setting include pulmonary fibrosis.

4.5 Interaction with other medicines and other forms of interaction

There have been no formal medicine interaction studies performed with Herceptin SC 600 mg in humans.

4.6 Fertility, pregnancy and lactation

Pregnancy

Treatment with Herceptin SC 600 mg is contraindicated during pregnancy.

Herceptin SC 600 mg crosses the placenta and appears in the breast milk. (See CONTRAINDICATIONS.)

Breastfeeding

Mothers breastfeeding their infants should not use Herceptin SC 600 mg. (See CONTRAINDICATIONS.)

In the post-marketing setting, cases of foetal renal growth 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 SC

600 mg 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 SC 600 mg in humans, male and female patients treated with Herceptin SC 600 mg, are recommended to use highly effective contraception, including a barrier method for at least 7 months following the last dose of Herceptin SC 600 mg.

4.7 Effects on ability to drive and use machines

Herceptin has a minor influence on the ability to drive and use machines. (see section 4.8). Dizziness and somnolence may occur during treatment with Herceptin (see section 4.8). Patients experiencing infusion-related symptoms ~~reactions~~ (see section 4.4) 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 (ADRs) reported with Herceptin SC 600 mg usage are cardiotoxicity, administration-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.

Clinical trials

Presented in the following table, Table 1 are adverse reactions that have been reported in association with the use of Herceptin alone or in combination with chemotherapy.

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

Table 1 : Clinical trial ADRs

System organ class	***Frequency***	***Adverse reaction***
Infections and infestations	Very common	Nasopharanygitis, infection
	Common	Neutropenic sepsis, cystitis, herpes zoster, influenza, sinusitis, skin infection, rhinitis, upper respiratory tract infection, urinary tract infection.
Blood and lymphatic system disorders	Very common	Anaemia, thrombocytopenia, febrile neutropenia, leukopenia
	Common	neutropenia,
Immune system disorders	Common	Hypersensitivity, e.g. allergic-like reactions, (itching, lacrimation, skin rash, urticaria),
	Rare	analphalytic shock
Metabolism and nutrition disorders	Very common	Increased weight, decreased weight, decreased appetite, anorexia

System organ class	*Frequency*	*Adverse reaction*
Psychiatric disorders	Very common	Insomnia
	Common	Anxiety, depression,
Nervous system disorders	Very common	Tremor, dizziness, headache, hypoaesthesia, paraesthesia, dysgeusia
	Common	Peripheral neuropathy, hypertonia, somnolence
Eye disorders	Very common	Conjunctivitis, increased lacrimation
	Common	Dry eye
	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
	Uncommon	Pericardial effusion
Vascular disorders	Very common	Hot flushes, lymphoedema

System organ class	*Frequency*	*Adverse reaction*
	Common	Hypotension, vasodilatation, hypertension
Respiratory, thoracic and mediastinal disorders	Very common	Wheezing, dyspnoea, oropharyngeal pain, epistaxis, cough, rhinorrhoea
	Common	Asthma, cough,lung disorder, pharyngitis, hiccups, exertional dyspnoea, pleural effusion, pneumonia
	Uncommon	Interstitial pneumonitis
Gastrointestinal disorders	Very common	Diarrhoea, vomiting, nausea, lip swelling, abdominal pain, stomatitis, dyspepsia, constipation
	Common	Pancreatitis, haemorrhoids, dry mouth, gastritis, Hepatocellular injury
Hepatobiliary disorders	Common	Hepatitis, liver tendernerss
	Rare	Jaundice
	Very common	Erythema
Skin and subcutaneous tissue disorders	Very common	rash, swelling face, palmar-plantar erythrodysaethesia syndrome (hand-foot syndrome), alopecia, nail disorder

System organ class	*Frequency*	*Adverse reaction*
	Common	Acne, dry skin, ecchymosis, hyperhidrosis, maculopapular rash, pruritus, onychoclasis, injection site pain, dermatitis
	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, administration related reaction, pain, pyrexia, peripheral oedema, mucosal inflammation
	Common	Malaise, oedema, injection site pain**
Injury, poisoning and procedural complications	Very common	Nail changes including brittle nail, nail loss, splitting nails

** Injection site pain was identified as an ADR in the SC arm in the phase 3 study. ADRs were added to the appropriate system organ class (SOC) category and are presented in a single table according to the highest incidence seen in any of the major 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

Cardiac dysfunction

Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to Herceptin SC 600 mg. It has been associated with fatal outcome. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin SC 600 mg (see WARNINGS AND SPECIAL PRECAUTIONS).

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 IV + paclitaxel group, compared with 1 % - 4 % in the paclitaxel-alone group. For Herceptin IV monotherapy, the rate was 6 % - 9 %. The highest rate of cardiac dysfunction was seen in patients receiving concurrent Herceptin 21 mg/ml IV + 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 1 year treatment arm was 0,8 %, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4,6 %.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values 50 % after the event) was evident for 71,4 % of Herceptin-treated patients

.Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79,5 % of patients. Approximately 17 % of cardiac-dysfunction related events occurred after completion of Herceptin.

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/m2). The incidence of symptomatic cardiac dysfunction was 1,7 % in the Herceptin arm.

In a pivotal trial, Herceptin SC 600 mg was administered concurrently with neoadjuvant chemotherapy that contained four cycles of epirubicin (cumulative dose 300 mg/m2); at a median

follow-up of 40 months, the incidence of congestive cardiac failure was 0 % in the Herceptin SC 600 mg arm

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

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.

Diarrhoea

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.

Immunogenicity:

In the neoadjuvant-adjuvant EBC study (BO22227), at a median follow-up exceeding 70 months, 10.1 % (30/296) of patients treated with Herceptin intravenous developed antibodies against

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

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

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

Switching treatment from Herceptin 600 mg SC to trastuzumab 440 mg IV

Patients with breast cancer may be switched from Herceptin SC 600 mg to an IV formulation of trastuzumab.

Herceptin SC safety and tolerability in EBC patients

Study MO28048 investigating the safety and tolerability of Herceptin SC 600 mg as adjuvant therapy in HER2 positive EBC patients who were enrolled in either a Herceptin SC 600 mg cohort

(N=1 868 patients, including 20 patients receiving neoadjuvant therapy) or a Herceptin SC single injection device (SID) cohort (N=710 patients, including 21 patients receiving neoadjuvant therapy) .The primary analysis included patients with a median follow-up of up to 23.7 months.~~resulted in n~~No new safety signals were observed and ~~R~~results were consistent with the known safety profile for Herceptin SC 600 mg. In addition, treatment of lower body weight patients with Herceptin SC 600 mg fixed dose in adjuvant EBC was not associated with increased safety risk, AEs and SAEs, compared to the higher body weight patients.

The final results of study BO22227 at a median follow-up exceeding 70 months (see section 3.1.2 Clinical /Efficacy Studies) were also consistent with the known safety profile for Herceptin IV and Herceptin SC, and no new safety signals were observed.

Post marketing Experience

The following adverse drug reactions have been identified from postmarketing experience with Herceptin (Table 2).

System organ class	Adverse reaction
Blood and lymphatic system disorders	Hypoprothrombinaemia, immune thrombocytopenia
Immune system disorders	Anaphylactoid reaction Anaphylactic reaction
Metabolism and nutrition disorders	Tumour lysis syndrome
Eye disorders	Madarosis
Cardiac disorders	Cardiogenic shock, tachycardia
Respiratory, thoracic and mediastinal disorders	Bronchospasm, decreased oxygen saturation, respiratory failure, interstitial lung disease, lung infiltration, acute respiratory distress syndrome, respiratory distress, pulmonary fibrosis, hypoxia, laryngeal oedema
Skin and subcutaneous tissue disorders	Angioedema
Renal and urinary disorders	Glomerulonephropathy, renal failure
Pregnancy, puerperium and perinatal conditions	Pulmonary hypoplasia, renal hypoplasia, oligohydramnios

Historical Adverse Events

Table 3 below indicates additional adverse events that historically have been reported in patients who have received Herceptin. As no evidence of a causal association has been found between

Herceptin and these events, these events are not considered expected for the purposes of regulatory reporting.

Table 3: Adverse Events

System organ class	Adverse Event
Infections and infestations	Cellulitis, erysipelas, sepsis, meningitis, bronchitis, herpes zoster, cystitis
Blood and lymphatic system disorders	Leukaemia
Immune system disorders	Anaphylaxis, anaphylactic shock
Psychiatric disorders	Abnormal thinking
Nervous system disorders	Ataxia, paresis, cerebrovascular disorder, brain oedema, lethargy, coma
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Pericardial effusion, bradycardia, pericarditis
Respiratory, thoracic and mediastinal system disorders	Hiccups, exertional dyspnoea
Gastrointestinal system disorders	Gastritis, Pancreatitis
Hepatobiliary disorders	Hepatic failure, hepatocellular damage
Musculoskeletal and connective tissue disorders	Musculoskeletal pain
Renal and urinary ~~system~~ disorders	Dysuria
Reproductive system and breast disorders	Breast pain
General disorders and administration site conditions	Chest discomfort

4.9 Overdose

Symptoms of overdose may be exacerbated and, or exaggerated to those reported in side effects. Single doses of up to 960 mg have been administered with no reported untoward effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, 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 IgG1 isotope 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. 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.

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

Immunogenicity:

In the neoadjuvant-adjuvant setting, 7,0 % of patients treated with the trastuzumab intravenous (IV) and 14,5 % in the trastuzumab subcutaneous formulation developed antibodies against trastuzumab (regardless of antibody presence at baseline). The clinical relevance of these antibodies is not known. However, the pharmacokinetics, efficacy determined by pathological complete response (pCR)] or safety of trastuzumab IV and SC did not appear to be adversely affected by these antibodies.

The pharmacokinetics (PK) of trastuzumab at a fixed dose of 600 mg administered three-weekly by the SC route was compared to the IV route (8 mg/kg loading dose, 6 mg/kg maintenance dose every three weeks) in a phase III study. The pharmacokinetic results for the co-primary end-point, pre-dose trastuzumab trough concentration cycle 8, have shown non-inferiority of the PK for the trastuzumab SC arm with a flat dosing compared to the trastuzumab IV arm with a body weight adjusted dosing.The mean observed trastuzumab concentration during the neoadjuvant treatment phase, at the pre-dose cycle 8 time point, were higher in the trastuzumab SC arm than the IV arm of the study, with mean observed values of 78,7 µg/mℓ (standard deviation (SD): 43,9 µg/mℓ) as compared to 57,8 µg/mℓ (SD: 30,3 µg/mℓ). During the adjuvant phase of the treatment, at the pre-dose cycle 13 time point, the mean observed trastuzumab trough concentration values, were 90,4 µg/mℓ (SD: 41,9 µg/mℓ) and 62,1 µg/mℓ (SD: 37,1 µg/mℓ), respectively for the SC and IV arms of the study. While approximate steady state concentrations with the IV or SC formulations are reached at approximately cycle 8, observed concentrations with the SC formulation tended to increase slightly up to cycle 13 with the SC administration. The mean observed trastuzumab trough concentration at the SC pre-dose cycle 18 was: 90,7 µg/mℓ similar to that of cycle 13, suggesting no further increase after cycle 13.

The median Tmax following SC cycle 7 administration was approximately 3 days with high variability (range 1 - 14 days). The mean Cmax was expectedly lower in the trastuzumab SC formulation (149 µg/mℓ) than in the IV arm (end of infusion value: 221 µg/mℓ).

The mean observed $AUC_{0\text{-}21\ days}$ following the cycle 7 dose was approximately 10 % higher with the trastuzumab SC formulation as compared to the IV formulation, with mean AUC values of 2 268 µg/mℓ·day and 2 056 µg/mℓ·day respectively. With IV and SC formulations, body weight had an influence on the pre-dose trastuzumab trough concentration and $AUC_{0\text{-}21\ days}$ values. In patients with body weight (BW) below 51 kg (10^{th} percentile), the mean steady state AUC of trastuzumab following the cycle 7 dose was about 80 % higher after SC than after IV treatment

whereas in the highest BW group above 90 kg (90^{th} percentile) AUC was 20 % lower after the SC than after the IV treatment. Across body weight subsets patients who received trastuzumab SC had pre-dose trastuzumab trough concentration and $AUC_{0\text{-}21\ days}$ values that were comparable or higher than observed in patients who received trastuzumab IV. Multiple logistic regression analyses showed no correlation of PK to efficacy (pCR) or safety and dose adjustment for body weight is not needed.

A population PK model with parallel linear and non-linear elimination from the central compartment was constructed using pooled trastuzumab PK data from the phase III study of SC vs. IV, to describe the observed PK concentrations following trastuzumab IV or trastuzumab SC administration in early breast cancer (EBC) patients. Bioavailability of trastuzumab given as SC was estimated to be 77,1 %, and the first order absorption rate constant was estimated to be 0,4 day^{-1}.

Linear elimination clearance was 0,111 ℓ/day and the central compartment volume (V_c) was 2,91 ℓ. The non-linear elimination Michaelis-Menten parameters were 11,9 mg/day and 33,9 mg/ℓ for V_{max} and, concentration at which the non-linear clearance rate is half of V_{max} (Km), respectively. The population predicted PK exposure parameter values (with 5^{th} - 95^{th} percentiles) for the SC 600 mg three-weekly regimen in EBC patients is shown in Table 4 below.

Table 4: Population Predicted PK Exposure Values (with 5th - 95th percentiles) for trastuzumab SC 600 mg SC three-weekly regimen in EBC patients

Primary tumour type and Regimen	**Cycle**	**N**	**Cmin (µg/mℓ)**	**Cmax (µg/mℓ)**	**AUC (µg.day/mℓ)**
EBC trastuzumab SC 600 mg three-weekly	Cycle 1	297	28,2 (14,8 – 40,9)	79,3 (56,1 - 109)	1 065 (718 – 1 504)
	Cycle 7 (steady state)	297	75,0 (35,1 - 123)	149 (86,1 - 214)	2 337 (1 258 – 3 478)

Pharmacokinetics in special populations

Detailed pharmacokinetic studies in the elderly population 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 DOSAGE AND DIRECTIONS FOR USE.)

Pregnancy and lactation

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

Paediatric population

Herceptin SC 600 mg is not recommended for use in children below 18 years of age because the safety and efficacy in paediatric patients have not been established.

Trastuzumab washout

Trastuzumab washout time period was assessed following IV and SC 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

Glacial acetic acid,

l-histidine,

polysorbate 20,

sucrose,

water for injections.

6.2 Incompatibilities

No incompatibilities between Herceptin SC 600 mg and the following materials have been observed:

- propylene or polycarbonate syringe
- stainless steel transfer
- injection needles

- polyethylene luer cones stoppers

6.3 Shelf life

21 months

6.4 Special precautions for storage

Store vials between 2 °C - 8 °C. Do not freeze. Store in the original package in order to protect from light.

The vials should not be kept for more than 6 hours at ambient temperature: do not store at or above 30 °C.

Store out of reach of children.

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

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

Each carton contains one 6 mℓ colourless, type 1 glass vial, sealed with a grey rubber stopper (laminated with fluoro-resin) and crimped with an aluminium overseal, fitted with a light blue plastic flip-off disk.

6.6 Special precautions for disposal and other handling

Appropriate aseptic technique should be used.

The 600 mg/5 mℓ solution is a ready to use solution which does not need to be diluted.

Herceptin SC 600 mg should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

Herceptin SC 600 mg is for single-use only.

As Herceptin SC 600 mg does not contain any antimicrobial preservative, from a microbiological point of view, the medicine should be used immediately. If not being used immediately, preparation should take place in controlled and validated aseptic conditions. Once transferred from the vial to the syringe, the medicinal product is physically and chemically stable for 28 days ~~48 hours~~ at 2°C - 8°C and subsequently for 6 hours (cumulative time in the vial and the syringe) at ambient temperature (do not store above 30°C) in diffused daylight

After transfer of the solution to the syringe, it is recommended to replace the transfer needle by a syringe closing cap to avoid drying of the solution in the needle and not compromise the quality of the medicine. The hypodermic injection needle must be attached to the syringe immediately prior to administration followed by volume adjustment to 5 mℓ.

The appropriate amount of solution should be withdrawn from the vial using a sterile needle and syringe and added to an infusion bag containing 250 ml of 0.9% sodium chloride.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

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