**PROPOSED PROFESSIONAL INFORMATION FOR**

**TRASTUZUMAB CIPLA**

**WARNING**

**Cardiomyopathy**

TRASTUZUMAB CIPLA 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 TRASTUZUMAB CIPLA.

Discontinuation TRASTUZUMAB CIPLA 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 TRASTUZUMAB CIPLA in combination with anthracyclines and cyclophosphamide. (See **section 4.4**)

**Hypersensitivity reactions including anaphylaxis, infusion reactions, pulmonary events:**

TRASTUZUMAB CIPLA 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 TRASTUZUMAB CIPLA.

Discontinuation of TRASTUZUMAB CIPLA 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

**TRASTUZUMAB CIPLA** 440 mg, Concentrate for Solution for Infusion.

**Bacteriostatic Water for Injection for TRASTUZUMAB CIPLA**, Diluent.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**TRASTUZUMAB CIPLA**: Each multiuse vial contains 440 mg Trastuzumab.

The reconstituted solution contains 21 mg/mL trastuzumab.

Contains sugar: Sorbitol 337,9 mg.

**Bacteriostatic water for injection for TRASTUZUMAB CIPLA**: Each vial contains 20 mL sterile bacteriostatic water for injection containing 1,1 % benzyl alcohol as a preservative.

For the full list of excipients, see **section 6.1**.

## 3. PHARMACEUTICAL FORM

Lyophilized powder for intravenous infusion.

TRASTUZUMAB CIPLA is an off white to pale yellow colour intact or largely intact cake.

Reconstituted product: colourless to pale yellow solution.

Bacteriostatic water for solution: The diluent is a colourless transparent solution free of visible particles.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**Metastatic breast cancer (MBC)**

TRASTUZUMAB CIPLA 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)**

TRASTUZUMAB CIPLA 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 neoadjuvant chemotherapy consisting of docetaxel and carboplatin.

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

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

**Metastatic gastric adenocarcinoma (MGC)**

TRASTUZUMAB CIPLA 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.

TRASTUZUMAB CIPLA 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**).

## 4.2 Posology and method of administration

**Posology**

HER2 testing is mandatory prior to initiation of TRASTUZUMAB CIPLA therapy. TRASTUZUMAB CIPLA 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 TRASTUZUMAB CIPLA administered as a 90-minute intravenous infusion. Patients

should be observed for fever and chills or other infusion-associated symptoms (see **section 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 TRASTUZUMAB CIPLA 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 **section 4.8** and **section 4.4.**)

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

Paclitaxel or docetaxel in metastatic disease may be administered the day following the first dose of TRASTUZUMAB CIPLA or immediately after the subsequent doses of TRASTUZUMAB CIPLA if the preceding dose of TRASTUZUMAB CIPLA was well tolerated.

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

Currently there is no restrictions on the relative timing of TRASTUZUMAB CIPLA and anastrozole at administration. For the anastrozole dose, refer to the anastrozole package insert.

***Three weekly schedules***

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 TRASTUZUMAB CIPLA until progression of disease. Patients with EBC should be treated with TRASTUZUMAB CIPLA for 1 year or until disease progression.

***Missed doses***

If the patient misses a dose of TRASTUZUMAB CIPLA by one week or less, then the usual maintenance dose of TRASTUZUMAB CIPLA (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 TRASTUZUMAB CIPLA maintenance doses (weekly regimen: 2 mg/kg; three- weekly regimen 6 mg/kg respectively) should then be given according to the previous schedule. If the patient misses a dose of TRASTUZUMAB CIPLA by more than one week, a re-loading dose of TRASTUZUMAB CIPLA should be given over approximately 90 minutes (weekly regimen: 4 mg/kg; three weekly regimen: 8 mg/kg). Subsequent TRASTUZUMAB CIPLA maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should then be given according to the previous schedule.

***Dose reduction***

Patients may continue TRASTUZUMAB CIPLA 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 patient populations**

**Elderly**

Data suggests that the disposition of TRASTUZUMAB CIPLA is not altered based on age. See Pharmacokinetics in special populations.

**Paediatric population**

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

**Method of administration**

***Handling and disposal***

Appropriate aseptic technique should be used.

Each vial of TRASTUZUMAB CIPLA 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 TRASTUZUMAB CIPLA, at a pH of approximately 6,0. Use of other reconstitution diluents should be avoided.

TRASTUZUMAB CIPLA should be carefully handled during reconstitution. Causing excessive foaming during reconstitution or shaking the reconstituted TRASTUZUMAB CIPLA, may result in problems with the amount of TRASTUZUMAB CIPLA 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 TRASTUZUMAB CIPLA, 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. Water for injection (not supplied) may also be used for single-dose preparation.

***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)

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 below. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral medicine 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 °C to 8 °C.

## 4.3 Contraindications

TRASTUZUMAB CIPLA is contraindicated in:

- Patients with known hypersensitivity to trastuzumab, murine proteins, or to any of the excipients in TRASTUZUMAB CIPLA (see **section 6.1**).
- 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

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

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

***Cardiotoxicity***

Signs and symptoms of cardiac dysfunction, such as dyspnoea, increased cough, paroxysmal nocturnal dyspnoea, peripheral oedema, S3 gallop, or reduced ejection fraction, may occur in patients treated with TRASTUZUMAB CIPLA. Congestive heart failure associated with TRASTUZUMAB CIPLA therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke.

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

All candidates for treatment with TRASTUZUMAB CIPLA, but especially those with prior anthracycline and cyclophosphamide (AC) exposure, should undergo thorough baseline cardiac assessment including history and physical examination and one or more of the following: ECG, echocardiogram, and MUGA scan or magnetic resonance imaging. There are no data regarding the most appropriate method of evaluation for the identification of patients at risk for developing cardiotoxicity. Monitoring may help to identify but may not identify all patients who will develop cardiac dysfunction. A careful risk-benefit assessment should be made before deciding to treat with TRASTUZUMAB CIPLA. The use of TRASTUZUMAB CIPLA and anthracyclines in combination has been associated with a high risk of cardiotoxicity. TRASTUZUMAB CIPLA and anthracyclines should not be used concurrently in combination except in a well-controlled clinical trial setting with cardiac monitoring. Patients who have previously received anthracyclines are also at risk of cardiotoxicity with TRASTUZUMAB CIPLA treatment, although the risk is lower than with concurrent use of TRASTUZUMAB CIPLA and anthracyclines. Because the mean terminal half- life of TRASTUZUMAB CIPLA is approximately 3 weeks TRASTUZUMAB CIPLA may persist in the circulation for up to 15 weeks after stopping TRASTUZUMAB CIPLA treatment. Patients who receive anthracyclines after stopping TRASTUZUMAB CIPLA may possibly be at increased risk of cardiotoxicity. Anthracycline-based therapy should be avoided for up to 25 weeks after stopping TRASTUZUMAB CIPLA. If anthracyclines are used, the patient’s cardiac function should be monitored carefully (see below).

The following patients were excluded from the trial in early breast cancer:

- History of documented congestive heart failure (CHF)

- High-risk uncontrolled dysrhythmias
- Angina pectoris requiring medication
- Clinically significant valvular disease
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension

There are no data regarding the benefit / risk balance in early breast cancer and therefore treatment cannot be recommended in the above patients.

Formal cardiological assessment should be considered in

- Patients in whom there are cardiovascular concerns following baseline screening
- Cardiac function should be further monitored during treatment (e.g. every 12 weeks).
- Monitoring may help to identify patients who develop cardiac dysfunction.
- For early breast cancer patients, cardiac assessment, as performed at baseline, should be repeated every 3 months during treatment and at 6, 12, and 24 months following cessation of treatment.
- 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 TRASTUZUMAB CIPLA therapy has been seen.

Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction, such as symptomatic heart failure, a history of hypertension or documented

coronary artery disease, and in EBC (early breast cancer), in those patients with a left ventricular ejection fraction (LVEF) of 55 % or less. If LVEF drops 10 ejection points from baseline AND to below 50 %, TRASTUZUMAB CIPLA should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, TRASTUZUMAB CIPLA should be discontinued. All such patients should be referred for assessment by a cardiologist and followed up.

If symptomatic cardiac failure develops during TRASTUZUMAB CIPLA therapy, it should be treated with the standard medications for this purpose. TRASTUZUMAB CIPLA therapy should be discontinued in patients who develop clinically significant heart failure. The safety of continuation or resumption of TRASTUZUMAB CIPLA in patients who experience cardiac toxicity has not been prospectively studied. However, most patients who developed heart failure in the pivotal trials improved with standard medical treatment.

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

Serious adverse reactions to TRASTUZUMAB CIPLA 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. Should an infusion reaction occur, the infusion should be discontinued, or the rate of infusion slowed and the patient should be monitored until resolution of all observed symptoms, (see **section 4.2**). The majority of patients experienced resolution of symptoms and subsequently received further infusions of

TRASTUZUMAB CIPLA. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists, and corticosteroids.

However, these reactions have been associated with a clinical course culminating in a fatal outcome. Patients experiencing dyspnoea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should not be treated with TRASTUZUMAB CIPLA, (see **section 4.3**).

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 TRASTUZUMAB CIPLA 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 studies severe pulmonary events leading to death have been reported with the use of Trastuzumab, (see **sections 4.8**). The manifestations include, but are not limited to, dyspnoea, interstitial lung disease including pulmonary infiltrates, pneumonia, pneumonitis, pleural effusions, non-cardiogenic pulmonary oedema, pulmonary insufficiency and hypoxia, and the acute respiratory distress syndrome. These events may or may not occur as sequelae of infusion reactions or with a delayed onset. (See above for Infusion reactions, allergic-like reactions and hypersensitivity reactions.) Patients with intrinsic lung disease or with extensive tumour involvement of the lungs, resulting in dyspnoea at rest, are at greater risk of severe reactions.

Therefore, these patients should not be treated with TRASTUZUMAB CIPLA, (see **section 4.3**).

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

**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 TRASTUZUMAB CIPLA to a patient with a known sensitivity to benzyl alcohol, TRASTUZUMAB CIPLA should be reconstituted with water for injection, and only one dose per TRASTUZUMAB CIPLA vial should be used. Any unused portion must be discarded.

**Sorbitol**

Contains sorbitol and may have a laxative effect. Patients with a rare hereditary condition of sorbitol intolerance should not take TRASTUZUMAB CIPLA

**Special Precautions**

***Haematotoxicity***

Febrile neutropenia occurred very frequently. Frequently 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 the innovator product 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 the innovator product 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*

National Cancer Institute Frequent Toxicity Criteria Adverse Events (NCICTCAE) (v 3.0) grade ≥ 3 renal toxicity occurred in 5 % of patients, during treatment with Trastuzumab. NCICTCAE (v 3.0) grade ≥ 3 adverse events in hepatobiliary disorders: Hyperbilirubinaemia occurred in 1 % of patients.

***Diarrhoea***

Breast Cancer

Of patients treated with TRASTUZUMAB CIPLA 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 the Trastuzumab.

## 4.5 Interaction with other medicines and other forms of interaction

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

## 4.6 Fertility, pregnancy and lactation

Treatment with TRASTUZUMAB CIPLA is contra-indicated during pregnancy. TRASTUZUMAB CIPLA crosses the placenta and appears in the breast milk. (See **section 4.3**.)

Mothers breast-feeding their infants should not use TRASTUZUMAB CIPLA. (See **section 4.3**.)

Post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, have been reported in pregnant women receiving TRASTUZUMAB CIPLA.

Women of childbearing potential should be advised to use effective contraception during treatment with TRASTUZUMAB CIPLA 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 TRASTUZUMAB CIPLA in humans, male and female patients treated with TRASTUZUMAB CIPLA, are recommended to use highly effective contraception, including a barrier method for at least 7 months following the last dose of TRASTUZUMAB CIPLA.

## 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 such as sleepiness, nausea, dizziness should be advised not to drive or use machines until symptoms abate.

## 4.8 Undesirable effects

Amongst the most serious and/or frequent adverse reactions reported with TRASTUZUMAB CIPLA usage are cardiotoxicity, infusion-related reactions, haematotoxicity (in particular neutropenia) and pulmonary adverse events. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Tabulated list of adverse reactions**

| **MedDRA system organ class** | **Frequency** | **Side effects** |
|---|---|---|
| **Infections and infestations** | *Frequent* | Pneumonia, neutropenic sepsis, cystitis, herpes zoster, infection, influenza, nasopharyngitis, sinusitis, skin infection, rhinitis, upper respiratory tract infection, urinary tract infection, erysipelas, cellulitis, bronchitis |
| | *Less Frequent* | Sepsis |
| **Blood and lymphatic system disorders** | *Frequent* | Febrile neutropenia, anaemia, neutropenia, thrombocytopenia, leukopenia |

| | | |
|---|---|---|
| **Immune system disorders** | *Frequent* | Hypersensitivity |
| **Metabolism and nutrition Disorders** | *Frequent* | Increased weight, decrease weight (in gastric cancer), anorexia |
| **Psychiatric disorders** | *Frequent* | Anxiety, depression, insomnia, abnormal thinking |
| **Nervous system disorders** | *Frequent* | Tremor, dizziness, headache, hypoaesthesia, peripheral neuropathy, paraesthesia, hypertonia, somnolence, dysgeusia, ataxia, lethargy |
| | *Less frequent* | Paresis |
| **Eye disorders** | *Frequent* | Conjunctivitis, dry eye, increased lacrimation |
| **Ear and Labyrinth Disorders** | *Frequent* | Vertigo, deafness |
| **Cardiac disorders** | *Frequent* | Decreased blood pressure, increased blood pressure, irregular heartbeat, palpitation, atrial flutter, cardiac failure (congestive), supraventricular tachydysrhythmia, cardiomyopathy, decreased ejection fraction, chest discomfort |
| | *Less frequent* | Pericardial effusion |
| **Vascular disorders** | *Frequent* | Hot flush, lymphoedema, hypotension, vasodilatation, hypertension |

| | | |
|---|---|---|
| **Respiratory, thoracic and mediastinal disorder** | *Frequent* | Wheezing, dyspnoea, oropharyngeal pain, asthma, cough, epistaxis, lung disorder, pharyngitis, rhinorrhoea, hiccups, exertional dyspnoea |
| | *Less frequent* | Pleural effusion, pneumonitis |
| **Gastrointestinal disorders** | *Frequent* | Diarrhoea, vomiting, nausea, lip swelling, abdominal pain, stomatitis, pancreatitis, dyspepsia, haemorrhoids, constipation, dry mouth, gastritis |
| **Hepatobiliary disorders** | *Frequent* | Hepatitis, liver tenderness |
| | *Less frequent* | Jaundice |
| **Skin and subcutaneous disorders** | *Frequent* | Erythema, rash, swelling face, palmar-plantar erythrodysaethesia syndrome (hand-foot syndrome), acne, alopecia, dry skin, ecchymosis, hyperhidrosis, maculopapular rash, nail disorder, pruritus, onychorrhexis |
| **Musculoskeletal and connective tissue disorders** | *Frequent* | Arthralgia, rigor, myalgia, arthritis, back pain, bone pain, muscle spasms, neck pain, pain in extremity, musculoskeletal pain |
| **Renal and urinary conditions** | *Frequent* | Renal disorder, dysuria |

| | | |
|---|---|---|
| **Reproductive system and breast disorders** | *Frequent* | Breast inflammation/mastitis, breast pain |
| **General disorders and administration site conditions** | *Frequent* | Asthenia, chest pain, chills, fatigue, peripheral oedema, mucosal inflammation, malaise, influenza-like symptoms, infusion related reaction, pain, pyrexia, oedema |
| **Injury, poisoning and procedural complications** | *Frequent* | Nail toxicity, contusion |

**Post-marketing reports**

The following additional serious adverse reactions have occurred during post- marketing experience:

| **MedDRA system organ class** | **Side effects** |
|---|---|
| **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 |
| **Psychiatric disorders** | Abnormal thinking |
| **Nervous system disorders** | Cerebral oedema |
| **Eye disorders** | Papilloedema, abnormal lacrimation, retinal haemorrhage |
| **Ear and labyrinth disorders** | Deafness |
| **Cardiac disorders** | Cardiomyopathy, deterioration in congestive |

| | |
|---|---|
| | heart failure, hypotension, cerebrovascular disorder, cardiac failure, cardiogenic shock, pericarditis, hypertension, gallop rhythm |
| **Respiratory, thoracic and mediastinal disorders** | Interstitial lung disease including pulmonary infiltrates, bronchospasm, respiratory distress, respiratory failure, acute pulmonary oedema, respiratory insufficiency, acute respiratory distress, 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, angioedema |
| **Musculoskeletal and connective tissue disorders** | Myalgia, bone pain |
| **Renal and urinary conditions** | Membranous glomerulonephritis, glomerulonephropathy, renal failure |
| **Pregnancy, puerperium and perinatal disorders** | Oligohydramnios |
| **General disorders and administration site conditions** | Infusion-related symptoms, peripheral oedema, coma, paraneoplastic cerebellar degeneration |

**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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

## 4.9 Overdose

There is no experience with overdosage in human clinical trials.

Single doses higher than 10 mg/kg have not been tested.

In overdose side effects can be precipitated and / or of increased severity (see **section 4.8**).

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacological classification:

**TRASTUZUMAB CIPLA**: A 26 Cytostatic agents

**BACTERIOSTATIC WATER FOR INJECTION FOR TRASTUZUMAB CIPLA**: A 32.4 Water for Injection.

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals,

ATC code: J05AX12

**Pharmacodynamic effects**

Trastuzumab is a recombinant DNA-derived humanised monoclonal antibody which discerningly targets the extracellular domain of the human epidermal growth factor

receptor2 protein (HER2). The antibody is an IgG1 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 20 - 30 % of primary breast cancers and 6,8 - 42,6 % advanced gastric- adenocarcinoma

In both *in-vitro* assays and in animals Trastuzumab has been shown both, to inhibit the proliferation of human tumour cells that over-express 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 have been detected in some patients, without significant clinical manifestation.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of Trastuzumab has been studied in patients with metastatic breast cancer and early breast cancer. Studies showed that Trastuzumab once weekly in patients demonstrated dose dependent pharmacokinetics. Mean half-life increase and clearance decrease with increased dose level.

***Breast cancer***

**Steady state pharmacokinetics:**

*Steady state pharmacokinetics in patients with metastatic disease:*

Trastuzumab administered at a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/ resulted in the typical clearance of Trastuzumab is 0,241 litres/day (for a body weight of 68 kg) and the typical volume of distribution of the central compartment Vc is 3,02 litres, with a corresponding elimination half-life of approximately 3 weeks. Most recent population PK describes the clearance as 0,231 litres/day and the volume of distribution of 2,79 litres with a corresponding elimination half-life of approximately 3 weeks.

Steady state pharmacokinetics therefore should be reached by approximately 15 weeks (105 days or 5 elimination half-lives). The same time interval would be predicted for Trastuzumab elimination after discontinuation of TRASTUZUMAB CIPLA therapy.

**Assessment in early breast cancer patients:**

The administration of concomitant chemotherapy (either anthracycline/ cyclophosphamide, paclitaxel or docetaxel) do not appear to influence the pharmacokinetics of Trastuzumab.

***Gastric adenocarcinoma***

*Steady state pharmacokinetics in advanced gastric- adenocarcinoma*

The steady state pharmacokinetics in patients with advanced gastric-adenocarcinoma were assessed by administering Trastuzumab 3-weekly at a loading dose of 8 mg/kg followed by a 3-weekly maintenance dose of 6 mg/kg. The distribution in the central compartment was 3,91 litres with a corresponding median elimination half-life of 14,5 days.

The typical clearance of Trastuzumab is 0,378 litres/day and the typical volume of Steady state concentrations should be reached within 72 days, (five elimination half-lives) or approximately 10 weeks.

***Pharmacokinetics in special populations***

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

*Elderly:*

Age has been shown to have no effect on the disposition of Trastuzumab. (See **section 4.2**.)

*Pregnancy and lactation:*

Trastuzumab has been demonstrated to cross the placenta and to appear in breast milk.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

D-sorbitol

L-histidine

L-Histidine hydrochloride monohydrate

Polyethylene glycol

Water for injection.

### 6.2 Incompatibilities

No incompatibilities between TRASTUZUMAB CIPLA and polyvinylchloride, polyethylene bags or polypropylene bags have been observed. Dextrose solution should

not be used since it causes aggregation of the protein. TRASTUZUMAB CIPLA should not be mixed or diluted with other medicines.

### 6.3 Shelf life

48 months.

### 6.4 Special precautions for storage

*Vials with lyophilised powder*: Must be stored in a refrigerator at 2 °C to 8 °C).

Keep the vials in the outer carton until required for use.

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

*Reconstituted solution:* A vial of TRASTUZUMAB CIPLA, reconstituted with Bacteriostatic Water for Injection as supplied, is stable for 28 days when stored refrigerated at 2 °C to 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 TRASTUZUMAB CIPLA vial, the solution is stable for only 24 hours and must be discarded thereafter. Do not freeze the reconstituted solution.

*Solution for infusion:*

Solutions of TRASTUZUMAB CIPLA for infusion are stable in polyvinylchloride or polyethylene bags containing 0,9 % sodium chloride at 2 °C to 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.

This medicine should not be used after the expiry date shown on the label or outer carton.

*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.

KEEP OUT OF REACH OF CHILDREN

### 6.5 Nature and contents of container

TRASTUZUMAB CIPLA (Concentrate for Solution for Infusion) is packed in a clear colourless 50 mL glass vial and covered with a lavender colour flip-off seal.

**Bacteriostatic Water for Injection for TRASTUZUMAB CIPLA:**

is packed in a clear colourless 20 mL glass vial, with grey bromobutyl rubber stopper, and covered with a red colour flip-off seal.

Both the 50 mL vial for TRASTUZUMAB CIPLA and 20 mL vial for Bacteriostatic Water for Injection (diluent) are co-packed in one carton.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

**Cipla Medpro (Pty) Ltd.**

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

## 8. REGISTRATION NUMBER(S)

53/26/0051

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

First authorisation: 07 April 2020

Latest renewal: Not applicable.

## 10. DATE OF REVISION OF THE TEXT

26 August 2026.