BIOCON FORMULATIONS
MASTER PROOF OF APPROVED PRINTED LEAFLET ART WORK
ZUHERA® 150 FOR COLOUR COPY
[**FOR MALAYSIA**] ANNEXURE- 4 [Ref. No. : S2/BF/QA/SOP/0018]
ARTWORK CODE: **BF1779/03**

FRONT

45 mm

42 mm

Biocon Biologics™

ZUHERA® 150

BF1779/03

ZUHERA® is a biosimilar of Herceptin
*In vitro, preclinical and clinical studies have demonstrated similarity between XM1 *H é and the reference trastuzumab product. Hence, this document includes publicly available information on the reference trastuzumab product. In this document, when data on the reference (originator) trastuzumab product is being referred to, the term "trastuzumab (Herceptin)" is used. The term "trastuzumab" is used to describe properties generally applicable to the trastuzumab molecule that are described based on observations with the reference product. Where information or instructions specific to XM1 *HAé is presented, the term "XM1 *HAé" is used.*

COMPOSITION
150 mg multi-dose vials containing powder for concentrate for solution for intravenous infusion. Reconstituted **ZUHERA®** concentrate contains approximately 21 mg/mL of trastuzumab, a humanised IgG1 monoclonal antibody expressed in Chinese hamster ovary cell suspension culture, and purified by affinity and ion-exchange chromatography including specific viral inactivation and removal procedures.

List of Excipients:
L-Histidine, L-Histidine hydrochloride, Polysorbate 20, Trehalose dihydrate

DOSAGE FORM
Powder for concentrate for solution for infusion.

ZUHERA® a white to pale yellow lyophilised powder.

WARNING: CARDIAC DYSFUNCTION, INFUSION REACTIONS, PULMONARY TOXICITY and EMBRYOFOETAL TOXICITY
For complete details refer to the section Warnings and Precautions
Cardiac Dysfunction
Sub-clinical and clinical cardiac failure may result from treatment with trastuzumab. It may manifest as congestive heart failure and decreased left ventricular ejection fraction. Such events had the highest incidence when trastuzumab was given with chemotherapy regimens containing anthracyclines.

- Before and during treatment with trastuzumab, left ventricular function must be evaluated in all patients [refer to the sections *Warnings and Precautions* and Dose and *Method of Administration* in the full package insert].

Infusion Reactions; Pulmonary Toxicity
Trastuzumab needs to be discontinued for anaphylaxis, angioedema, interstitial pneumonitis, or acute
respiratory distress syndrome [refer to the section *Warnings and Precautions* in the full package insert].

Embryo-Foetal Toxicity
Trastuzumab exposure during pregnancy can result in oligohydramnios and can be complicated by
pulmonary hypoplasia and neonatal death [refer to the section *Warnings and Precautions* in the full package insert].

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies
ATC code: L01XC03

Mechanism of Action
The humanised monoclonal IgG1 antibody trastuzumab is produced by recombinant DNA technology; and contains complementarity-determining regions from a mouse antibody (anti-p185) specific for the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2), along with human framework sequences.
The HER2 receptor becomes constitutive instead of inducible in tumour cells. This is a result of increased cell surface expression/overexpression of HER2 protein caused by HER2 gene amplification. Overexpression is seen in 25% to 30% of primary breast cancers and in 6.8% to 42.6% gastric cancers.
Studies showed that amplification or overexpression of HER2 correlates with shorter disease-free survival.
Trastuzumab binds to sub-domain IV, a juxta-membrane region of HER2's extracellular domain, with high affinity and specificity. This binding inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2.
In *in vitro* assays and in animals, trastuzumab is reported to have inhibited proliferation of human tumour cells overexpressing HER2. Trastuzumab also preferentially mediates antibody-dependent cell-mediated cytotoxicity (ADCC) on tumour cells overexpressing HER2.

Pharmacokinetic Properties
A randomised, double-blind, parallel-group, comparative clinical study in patients with HER2-positive metastatic breast cancer showed that the pharmacokinetic profile of **ZUHERA®** was similar to that of trastuzumab after single- and multi-dose intravenous infusions.
As a part of global clinical development, two phase 1 studies 1) Single-center, single-dose, 2-period, randomized, double-blind, cross-over study and 2) Single-center, randomized, double-blind, three-arm, parallel-group study were conducted in normal healthy volunteers. Both studies showed that pharmacokinetic profile of Trastuzumab of Biocon was similar to that of trastuzumab (Herceptin). In addition, a multicenter, double-blind, randomized, parallel-group, phase III study showed that pharmacokinetic, efficacy, safety and immunogenicity profiles of Trastuzumab of Biocon was similar to trastuzumab (Herceptin) in patients with HER2-positive metastatic breast cancer (MBC).

The following data for pharmacokinetics in various patient populations treated with trastuzumab is summarized from publicly available information.

<u>Breast Cancer</u>
Clinical Trials for Herceptin
A population pharmacokinetics method was used to model steady-state pharmacokinetics in metastatic breast cancer patients (given 4 mg/kg trastuzumab [loading], followed by 2 mg/kg weekly [maintenance]); in phase 1, phase 2 and pivotal phase 3 clinical trials. Table 1 shows steady-state values.

Table 1: Trastuzumab Steady-State Pharmacokinetic Parameters

Parameter	Mean Value
Terminal half-life	28.5 days (95% CI, 25.5 to 32.8 days)
Weekly AUC	578 mg × day/L
Clearance	0.225 L/day
Volume of distribution	2.95 L
Peak concentration	110 mg/L
Trough concentration	66 mg/L

Patients with early breast cancer were administered an initial loading dose of 8 mg/kg followed by a three weekly maintenance dose of 6 mg/kg for 1 year. The steady state mean maximum concentration (C_{max}) was 225 µg/mL and mean minimum concentration (C_{min}) was 68.9 µg/mL at day 21 of cycle 18, the last cycle of treatment for 1 year of treatment.
The pharmacokinetics do not appear to be affected by concomitant anthracycline/cyclophosphamide or paclitaxel chemotherapy, or concomitant anastrozole.

<u>Metastatic Gastric Cancer</u>
Clinical Trials for Herceptin
A two compartment nonlinear population pharmacokinetic model was used to estimate the steady state pharmacokinetics in Metastatic Gastric Cancer patients (given 8 mg/kg trastuzumab [loading], followed by 6 mg/kg 3-weekly [maintenance]); in a phase 3 trial. At very low serum concentrations (below 10 µg/mL), non-linear clearance is 7-fold higher than linear clearance. At high serum concentrations, linear clearance dominates and the half-life is approximately 26 days. The mean predicted steady state area under the concentration-time curve (AUC), over a period of 3 weeks at steady state, is approximately 1213 mg day/L, and the median steady-state C_{max} and C_{min} are approximately 132 mg/L and 27.6 mg/L, respectively.

Pharmacokinetics in Special Populations
Clinical Trials for Herceptin

The pharmacokinetics of trastuzumab have not been studied specifically in elderly patients, patients with renal impairment, or patients with hepatic impairment. However, in the trials conducted with trastuzumab, distribution and elimination were not noted to be affected by age and renal impairment (see **Dose and Method of Administration**).

CLINICAL EFFICACY
The clinical efficacy of **ZUHERA®** plus docetaxel was assessed in a randomised, double-blind, comparative phase 3 study in patients with HER2-positive metastatic breast cancer (MBC) without prior chemotherapy. There were no relevant differences between **ZUHERA®** and trastuzumab with regard to overall response rate, clinical benefit rate and progression-free survival rate (at 24 weeks) in MBC.

As a part of global clinical development, the clinical efficacy of Trastuzumab of Biocon plus docetaxel/paclitaxel was assessed in a multicenter, double-blind, randomized, parallel-group, phase III study in MBC patients. There were no relevant differences between Trastuzumab of Biocon and trastuzumab (Herceptin) with regard to overall response rate, progression-free survival and overall survival at 48 weeks.

The following data for clinical efficacy in various patient populations treated with trastuzumab is summarized from publicly available information.

CLINICAL TRIALS FOR HERCEPTIN
Metastatic Breast Cancer (MBC)
The following regimens were evaluated in clinical studies with trastuzumab (Herceptin).
- Trastuzumab (Herceptin) monotherapy (in MBC patients with tumours overexpressing HER2 who had failed 1 chemotherapy regimens for metastatic disease).
- First-line combination therapy:
  - Trastuzumab (Herceptin) with paclitaxel (in MBC patients with tumours overexpressing HER2 who had previously received anthracycline-based adjuvant chemotherapy)
  - Trastuzumab (Herceptin) with an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC; in MBC patients with tumours overexpressing HER2 who had never received an anthracycline)
  - Trastuzumab (Herceptin) with docetaxel (in HER2-positive MBC patients)
  - Trastuzumab (Herceptin) with anastrozole (in hormone-receptor-positive MBC patients with tumours overexpressing HER2).

The following results were obtained in trials conducted with trastuzumab:
- Trastuzumab (Herceptin) monotherapy (second-or-third-line) produced an objective response rate of 15%, and a median duration of survival of 13 months ; in women with MBC overexpressing HER2.

First-line combination therapy:
- Trastuzumab (Herceptin) and paclitaxel in women with HER2-overexpressing MBC tumours prolonged the median time to disease progression significantly (compared with paclitaxel alone); and increased the tumour response and one-year survival rate. There was an increase of 3.9 months in median time to disease progression relative to paclitaxel alone (6.9 months for combination treatment vs. 3.0 months).
- Trastuzumab (Herceptin) plus anthracycline plus cyclophosphamide prolonged median time to disease progression, compared to that in the patients treated with only an anthracycline and cyclophosphamide (7.8 months, versus 6.1 months; p<0.001).
- Trastuzumab (Herceptin) and docetaxel in HER2-positive MBC patients significantly increased overall response rate (61%, versus 34% for docetaxel alone); and prolonged median time to disease progression by 5.6 months; and median overall survival was significantly increased (31.2 months, versus 22.7 months for docetaxel alone).
- Trastuzumab (Herceptin) and anastrozole in HER2-overexpressing, hormone-receptor- (i.e., oestrogen-receptor and/or progesterone-receptor)-positive MBC patients. In the trastuzumab (Herceptin) plus anastrozole arm, progression-free survival was double; 4.8 months versus 2.4 months for anastrozole alone. In addition, partial response (20.3% versus 6.8%), clinical benefit rate (42.7% versus 27.9%), time to progression (4.8 months versus 2.4 months), and median overall survival (extended by 4.6 months in the combination arm) were also improved. Time to response and duration of response were not different for the groups. After disease progression 70% of the patients in the anastrozole-alone arm crossed over to a trastuzumab (Herceptin)-containing regimen. Though there was no statistically significant difference; 52% of trastuzumab (Herceptin) plus anastrozole patients survived for at least 2 years; versus 45% of the anastrozole-alone patients.

Early Breast Cancer (EBC)
Neoadjuvant and adjuvant trastuzumab (Herceptin) were evaluated in patients with HER2-positive locally advanced or inflammatory breast cancer. In this phase 3, multicentre, open-label, randomized trial, patients were randomly assigned (1:1) to receive neoadjuvant trastuzumab (Herceptin) plus chemotherapy followed by adjuvant trastuzumab (Herceptin) for 1 year or the same neoadjuvant chemotherapy alone. 5- year event-free survival was achieved by more patients in the trastuzumab (Herceptin) plus chemotherapy group than the patients in the chemotherapy alone group (58% versus 43%; hazard ratio=0.64, 95% confidence interval [CI] 0.44-0.93; p=0.016).

A separate trial compared 2-year adjuvant trastuzumab (Herceptin) treatment with 1-year adjuvant trastuzumab (Herceptin) treatment in patients with HER2-positive early breast cancer. In this multicentre, randomised, open-label, phase 3 trial, patients were randomly assigned (1:1:1) to three groups: 2-year trastuzumab (Herceptin), 1-year trastuzumab (Herceptin) and observation. Patients received trastuzumab (Herceptin) following surgery and adjuvant and/or neoadjuvant chemotherapy, with or without radiation therapy. There was no significant difference in the primary endpoint, disease-free survival, between 1-year and 2-year trastuzumab (Herceptin) groups (hazard ratio=0.99, 95% CI 0.85–1.14; p=0.86). Despite crossover of 52% patients from the observation group to trastuzumab (Herceptin) therapy, 1-year trastuzumab (Herceptin) treatment was more beneficial than the observation group with respect to disease-free survival (hazard ratio=0.76, 95% CI 0.67–0.86, p<0.0001) and overall survival (hazard ratio=0.76, 95% CI 0.65–0.88; p=0.0005).

Long-term implications of adjuvant trastuzumab (Herceptin) treatment in patients with HER2-positive invasive breast cancer were evaluated in a joint analysis of two phase 3, randomised trials. In both trials, patients were randomly assigned to doxorubicin plus cyclophosphamide followed by paclitaxel with or without trastuzumab (Herceptin). At a median follow-up of 3.9 years, there was more statistically significant reduction in disease-free survival event rate in the trastuzumab (Herceptin) group compared to the control group (p<0.001).

A randomized, multicentre, phase 3 study assessed the efficacy and safety of a new non-anthracycline regimen with trastuzumab (Herceptin) in patients with HER2-positive early breast cancer. Patients were randomly assigned to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (Herceptin) (AC-T plus trastuzumab (Herceptin)) or docetaxel and carboplatin plus 52 weeks of trastuzumab (Herceptin) (TCH). The estimated disease-free survival rate at 5 years was better in the trastuzumab (Herceptin) groups (84% in AC-T plus trastuzumab (Herceptin), 81% in TCH) compared to the AC-T group (75%).
The rates of congestive heart failure (CHF) and cardiac dysfunction were significantly higher in the AC-T plus trastuzumab (Herceptin) group than in the TCH group (CHF, 2.0% vs. 0.4% for the two groups, respectively; >10% relative loss of left ventricular ejection fraction (LVEF), 18.6% vs. 9.4%; both comparisons, p<0.001).

Metastatic Gastric Cancer
A randomised, open-label, multicentre, phase 3 study assessed the effect of first-line trastuzumab (Herceptin) in combination with chemotherapy (fluoropyrimidine and cisplatin) versus chemotherapy alone in patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer. Patients were randomly assigned (1:1) to receive trastuzumab (Herceptin) in combination with chemotherapy (capecitabine or 5-fluorouracil [5-FU] plus cisplatin) or chemotherapy alone. The median overall survival, the primary endpoint, was longer in the trastuzumab (Herceptin) plus chemotherapy group compared to the chemotherapy alone group (13.8 [95%CI: 12-16] versus 11.1 months [95%CI: 10-13]; hazard ratio=0.74, 95%CI 0.60-0.91; p=0.0046). Rates of overall grade 3 or 4 adverse events (201 [68%] vs 198 [68%]) and cardiac adverse events (17 [6%] vs 18 [6%]) did not differ between groups.

Immunogenicity
Out of 903 patients that were evaluated, 1 patient was reported to have developed detectable anti-trastuzumab (Herceptin) antibodies; but had no allergic symptoms.

PRECLINICAL SAFETY DATA
Nonclinical studies (conventional toxicity studies) on **ZUHERA®** did not indicate any special hazard for humans. During conventional single- and repeat-dose toxicity studies of **ZUHERA®** in mice and rabbits, no clinically relevant adverse events were observed at the highest dose levels tested. Local tolerance was also evaluated in these toxicity studies, and no clinically relevant effects were observed.
As a part of global non-clinical development, nonclinical studies (conventional toxicity studies) on Trastuzumab of Biocon did not indicate any special hazard for humans. During conventional single- and repeat-dose toxicity studies of Trastuzumab of Biocon in mice and rabbits, no clinically relevant adverse events were observed at the highest dose levels tested. Local tolerance was also evaluated in these toxicity studies, and no clinically relevant effects were observed. Two comparative nonclinical studies undertaken in cynomolgus monkeys showed that the pharmacokinetic and toxicokinetic profile of Trastuzumab of Biocon was similar to that of trastuzumab (Herceptin).

INDICATIONS
Breast Cancer
Metastatic Breast Cancer (MBC)
ZUHERA® is indicated for the treatment of patients with metastatic breast cancer who have tumors that overexpress HER2:
a) As monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease.
b) In combination with paclitaxel or docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease.
c) In combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer.

Early Breast Cancer (EBC)
ZUHERA® is indicated for the treatment of patients with HER2-positive early breast cancer:
- Following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- Following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- In combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- In combination with neoadjuvant chemotherapy followed by adjuvant **ZUHERA®,** for locally advanced (including inflammatory) breast cancer or tumors >2 cm in diameter.

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

ZUHERA® should only be used in patients with metastatic gastric cancer whose tumour have HER2 overexpression as defined by immunohistochemistry (IHC2+) and a confirmatory SISH or FISH (fluorescence in situ hybridization) result, or by an IHC 3+ result. Accurate and validated assay method should be used.

DOSE AND METHOD OF ADMINISTRATION
Before starting **ZUHERA®** treatment, HER2 testing is mandatory.
- Administer **ZUHERA®** as intravenous infusion.
- **ZUHERA®** is not to be administered as an intravenous push or bolus.
- Do not mix with other drugs.
- Patients with MBC and MGC should be treated until disease progression.
- Only a physician experienced in the administration of cytotoxic chemotherapy treatment should initiate treatment. Only a healthcare professional should administer **ZUHERA®** and it should be administered by a healthcare professional prepared to manage anaphylaxis and an emergency kit should be available to manage any unexpected complications.
- Loading dose should be administered as a 90-minute intravenous infusion. If the initial loading dose is well tolerated, subsequent doses can be administered as a 30-minute infusion. Observe patients for at least six hours after the start of the first infusion and for two hours after the start of subsequent infusions for symptoms like fever and chills or other infusion-related symptoms (see **Undesirable Effects**). If a patient displays infusion-associated symptoms, the infusion may be interrupted to help control the symptoms; and may be resumed once the symptoms have abated.

Metastatic Breast Cancer (MBC)
3-weekly dosing
- An initial loading dose of 8 mg/kg is recommended; a maintenance dose of 6 mg/kg at 3-weekly intervals is recommended, beginning 3 weeks after the loading dose.
- The loading dose should be administered as an intravenous infusion over approximately 90 minutes. The subsequent doses can be administered as a 30-minute infusion, if the initial loading dose was well tolerated.

Weekly dosing
- An initial loading dose of 4 mg/kg is recommended; a maintenance dose of 2 mg/kg at weekly intervals is recommended, beginning one week after the loading dose.
- The loading dose should be administered as an intravenous infusion over approximately 90 minutes. The subsequent doses can be administered as a 30-minute infusion, if the initial loading dose was well tolerated.

Trastuzumab is indicated as monotherapy in patients who have already had two or more chemotherapy regimens for metastatic disease. Prior chemotherapy must have been an anthracycline and a taxane (at least), unless patients are unsuitable for these treatments. Hormonal therapy must also have been tried, and have failed, in hormone receptor-positive patients (unless patients are unsuitable for hormonal therapy).

Trastuzumab is indicated in combination with paclitaxel in patients who have not received chemotherapy for their metastatic disease and for whom an anthracycline is not suitable; in combination with docetaxel in patients who have not received chemotherapy for their metastatic disease; and in combination with an aromatase inhibitor in postmenopausal patients with hormone-receptor positive MBC, who have not previously been treated with trastuzumab.

Administration in combination with paclitaxel or docetaxel
In clinical trials, paclitaxel or docetaxel was administered the day following the first dose of trastuzumab. If the dose was well tolerated, paclitaxel/docetaxel was administered immediately after the subsequent doses of trastuzumab.

Administration in combination with an aromatase inhibitor
In a clinical trial, trastuzumab and anastrozole were administered from day 1; without restrictions on the relative timing of administration of trastuzumab and anastrozole.

Early Breast Cancer (EBC)
Weekly dosing
Initial loading dose of 4 mg/kg followed by 2 mg/kg every week concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

Three-weekly dosing
An initial loading dose of 8 mg/kg is recommended; a maintenance dose of 6 mg/kg at 3-weekly intervals is recommended, beginning 3 weeks after the loading dose.
Trastuzumab is indicated after surgery, neoadjuvant or adjuvant chemotherapy, and (if applicable) radiotherapy. Trastuzumab should be used after adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
Trastuzumab should be used in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
Trastuzumab should be used in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced disease (including inflammatory disease) or tumours of diameter >2 cm.

Metastatic Gastric Cancer (MGC)
Three-weekly dosing
An initial loading dose of 8 mg/kg is recommended; a maintenance dose of 6 mg/kg at 3-weekly intervals is recommended, beginning 3 weeks after the loading dose.

Duration of Treatment
Patients with metastatic breast cancer or metastatic gastric cancer should be treated with trastuzumab until disease progression. Patients with early breast cancer should be treated with trastuzumab for 1 year or until disease recurrence, whichever occurs first; it is not recommended to extend treatment in early breast cancer beyond one year.

Dose Reduction
During periods of reversible chemotherapy-induced myelosuppression, Trastuzumab may be continued; but observe the patient carefully for complications of neutropenia. Chemotherapy doses should be reduced or maintained as per the instructions for the specific regimen.

If LVEF drops 10 ejection fraction (EF) points from baseline and to below 50%, treatment should be stopped and a repeat LVEF assessment should be performed within approximately 3 weeks. Discontinuation of trastuzumab should be strongly considered if LVEF does not improve, or declines further, or symptomatic congestive heart failure (CHF) develops; unless the benefits outweigh the risks for the individual patient. All such patients should be referred for assessment by a cardiologist and followed up.

Missed Doses
For a dose missed by 1 week, administer the usual maintenance dose of trastuzumab (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg), as soon as possible, without waiting till the next planned cycle. Subsequent maintenance doses should then be given according to the previous schedule.
For a dose missed by >1 week, administer a re-loading dose of trastuzumab (weekly regimen: 4 mg/kg; three-weekly regimen: 8 mg/kg) over approximately 90 minutes; subsequent maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should then be given (weekly regimen: every week; three-weekly regimen: every 3 weeks) from that point.

Interchangeability and Automatic Substitution:
ZUHERA® has been developed as a Biosimilar Product to Herceptin and is similar in quality, safety and efficacy to Herceptin. **ZUHERA®** is approved for all indications of Herceptin. **ZUHERA®** is not automatically substitutable or interchangeable with the reference product.

USE IN SPECIAL POPULATIONS
From available data, disposition of trastuzumab is not altered with increasing age, renal impairment or serum creatinine levels. Elderly patients in reported clinical trials did not receive reduced doses.

Children
The safety and efficacy of trastuzumab has not been established in paediatric patients (below 18 years of age). **ZUHERA®** should not be used in these patients.

Pregnancy
It is not known whether trastuzumab can harm the foetus when administered to a pregnant woman or whether it can affect reproductive capacity. Animal reproduction studies done with trastuzumab revealed no evidence of impaired fertility or harm to the foetus.Avoid administering **ZUHERA®** to pregnant women, unless the potential benefit for the mother outweighs the potential risk to the foetus. Oligohydramnios, and cases of impaired foetal renal growth and/or function in association with oligohydramnios (some associated with fatal pulmonary hypoplasia of the foetus), skeletal abnormalities and neonatal death have been reported in pregnant women receiving trastuzumab.Advise women of childbearing potential to use effective contraception during treatment with **ZUHERA®**, and for at least 7 months thereafter. Women who become pregnant should be informed that harm to the foetus is possible. If a pregnant woman is treated with **ZUHERA®**, close monitoring by a multidisciplinary team is desirable. Monitor women exposed to trastuzumab during pregnancy for oligohydramnios.At doses up to 25 times the weekly human maintenance dose of 2 mg/kg, no evidence of impaired fertility or harm to the foetus was seen in cynomolgus monkey reproductive studies with trastuzumab.Embryonic death was seen in mutant mice lacking HER2 receptor. In cynomolgus monkeys, placental transfer of trastuzumab during the early (days 20-50 of gestation) and late (days 120-150 of gestation) foetal development was observed.

Lactation
Breast-feeding should be avoided during **ZUHERA®** therapy. Human IgG is secreted into human milk; and the potential for harm to the infant is unknown. There is no information on whether trastuzumab is secreted in human milk. Women should not breast-feed during **ZUHERA®** therapy and for 7 months after the last dose.In cynomolgus monkeys, trastuzumab was found to be secreted in milk at doses up to 25 times that of the weekly human maintenance dose of 2 mg/kg. However, no adverse effects on their growth or development from birth to 1 month were associated with the presence of trastuzumab in the serum of infant monkeys.

CONTRAINDICATIONS
- Hypersensitivity to trastuzumab, murine proteins or to any other component of **ZUHERA®**
- Severe dyspnoea at rest due to complications of advanced malignancy
- Requiring supplementary oxygen therapy

See section **Composition** for a list of components of **ZUHERA®.**
Data in the following section (**Warnings and Precautions**) has been taken from publicly available data on trastuzumab.

WARNINGS AND PRECAUTIONS
General
In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.
Initiate **ZUHERA®** therapy under the supervision of a physician experienced in cancer treatment.

Clinical Trials and post-marketing data of Herceptin
Infusion/Administration-related reactions (IRRs/ARRs)
IRRs/ARRs are known to occur with the administration of trastuzumab (see Undesirable Effects).
IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions.
Pre-medication may be used to reduce the risk of occurrence of IRRs.
Serious IRRs/ARRs to trastuzumab including dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, supraventricular tachyarrhythmia and urticaria have been reported (see Undesirable Effects). Patients should be observed for IRRs/ARRs. Interruption of an IV infusion may help control such symptoms and the infusion may be resumed when symptoms abate. These symptoms can be treated with an analgesic/antipyretic such as paracetamol and an antihistamine. Serious reactions have been treated successfully with supportive therapy such as oxygen, beta-agonists and corticosteroids. In rare cases, these reactions are associated with a clinical course culminating in a fatal outcome.
Patients who are experiencing dyspnea at rest due to complications of advanced malignancy or co-morbidities may be at increased risk of a fatal infusion reaction. Therefore, these patients should be treated with extreme caution and the risk versus benefit should be considered for each patient.

Pulmonary reactions
Severe pulmonary events leading to death have been reported with the use of trastuzumab in the post-marketing setting. These events have occasionally resulted in fatal outcome and may occur as part of an IRR or with a delayed onset. In addition, cases of interstitial lung disease including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported.

Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients with dyspnoea at rest due to complications of advanced malignancy and co-morbidities may be at increased risk of pulmonary events. Therefore, these patients should not be treated with trastuzumab.

Cardiac dysfunction
General Considerations
Patients treated with trastuzumab 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 trastuzumab 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 Undesirable Effects). In addition, caution should be exercised in treating patients with increased cardiac risk (e.g. hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age).

Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab treatment (see **Pharmacokinetics**). Patients who receive anthracycline after stopping trastuzumab may also be at increased risk of cardiac dysfunction. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Candidates for treatment with Trastuzumab, especially those with prior exposure to anthracycline, should undergo baseline cardiac assessment including history and physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scanning. 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 treatments until 24 months from the last administration of trastuzumab.

If Left Ventricular Ejection Fraction (LVEF) percentage drops 10 points from baseline and to below 50%, Trastuzumab should be withheld and a repeat LVEF assessment performed within approximately 3 weeks. If LVEF has not improved, or has declined further, or clinically significant CHF has developed, discontinuation of Trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks.

Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6 - 8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of Trastuzumab therapy has been seen.

The safety of continuation or resumption of Trastuzumab in patients who experience cardiac dysfunction has not been prospectively studied. If symptomatic cardiac failure develops during Trastuzumab therapy, it should be treated with the standard medications for heart failure. In the pivotal trials, most patients who developed heart failure or asymptomatic cardiac dysfunction improved with standard heart failure treatment consisting of 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 Trastuzumab treatment continued with Trastuzumab without additional clinical cardiac events.

Metastatic breast cancer
Trastuzumab and anthracycline should not be given concurrently in the metastatic breast cancer setting.

Early breast cancer
For patients with early breast cancer, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of Trastuzumab. In patients who receive anthracycline containing chemotherapy further monitoring is recommended, and should occur yearly up to 5 years from the last administration of Trastuzumab, 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 arrhythmia requiring medication, clinically significant cardiac valvular disease, poorly controlled hypertension (hypertension controlled by standard medication eligible), and haemodynamic effective pericardial effusion were excluded from adjuvant breast cancer clinical trials with Trastuzumab.

Adjuvant treatment
Trastuzumab and anthracyclines should not be given concurrently in the adjuvant treatment setting.
In patients with early breast cancer an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when Trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a non-anthracycline regimen of docetaxel and carboplatin. The incidence was more marked when Trastuzumab 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, Trastuzumab treatment, and prior or concurrent use of anti-hypertensive medications. In patients receiving Trastuzumab after completion of adjuvant chemotherapy the risk of cardiac dysfunction was associated with a higher cumulative dose of anthracycline given prior to initiation of Trastuzumab and a high body mass index (BMI) (> 25 kg/m^2).

Neoadjuvant-adjuvant treatment
In patients with early breast cancer eligible for neoadjuvant-adjuvant treatment, Trastuzumab should only be used concurrently with anthracyclines in chemotherapy-naive patients and only with low-dose anthracycline regimens, i.e. with maximum cumulative doses of doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2.

If patients have been treated concurrently with low-dose anthracyclines and Trastuzumab 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.

Benzyl alcohol
Benzyl alcohol, used as a preservative in Bacteriostatic Water for Injection in the 440 mg multidose vial, has been associated with toxicity in neonates and children up to 3 years old. When administering Trastuzumab to a patient with a known hypersensitivity to benzyl alcohol, Trastuzumab should be reconstituted with water for injection, and only one dose per Trastuzumab vial should be used. Any unused portion must be discarded. Sterile water for injection, used to reconstitute the 150 mg single dose vials, does not contain benzyl alcohol.

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

DRUG INTERACTIONS
Clinical Trials for Herceptin

No formal interaction studies have been performed with Herceptin in humans. Clinically significant interactions between Herceptin and the concomitant medication used in clinical trials have not been observed (see section Pharmacokinetics).
In studies where Herceptin was administered in combination with docetaxel, carboplatin, or anastrozole, pharmacokinetics of these medications was not altered nor was the pharmacokinetics of trastuzumab altered.

Concentrations of paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) were not altered in the presence of trastuzumab. However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite is unclear. No changes were observed in trastuzumab concentrations in the presence of paclitaxel and doxorubicin.

The results of the drug interaction substudy evaluating the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab 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 with trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab.

UNDESIRABLE EFFECTS
Clinical Trials for Herceptin
The following categories of frequency has been used in this section: 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.

List of adverse reactions
Presented in the following table are adverse reactions that have been reported in association with the use of Herceptin alone or in combination with chemotherapy in pivotal clinical trials. All the terms included are based on the highest percentage seen in pivotal clinical trials.

As Herceptin is commonly used along with other chemotherapeutic agents and radiotherapy it is often difficult to ascertain the causal relationship of an adverse event to a particular drug or radiotherapy

Table 2 Adverse drug reactions

System organ class	Adverse reaction*	Frequency
Infections and infestations	Nasopharyngitis	Very common
	Infection	Very common
	Influenza	Common
	Pharyngitis	Common
	Sinusitis	Common
	Rhinitis	Common
	Upper respiratory tract infection	Common
	Urinary tract infection	Common
Blood and lymphatic system disorders	Anaemia	Very common
	Thrombocytopenia	Very common
	Febrile neutropenia	Very common
	White blood cell count decreased/Leukopenia	Very common
	Neutropenia	Common
Immune system disorders	Hypersensitivity	Common
Metabolism and nutrition disorders	Weight decreased	Very common
	Wight increased	Very common
	Decreased appetite	Very common
Psychiatric disorders	Insomnia	Very common
	Depression	Common
	Anxiety	Common
Nervous system disorders	Dizziness	Very common
	Headache	Very common
	Paraesthesia	Very common
	Hypoaesthesia	Very common
	Dysgeusia	Very common
	Hypertonia	Common
	Peripheral neuropathy	Common
	Somnolence	Common
Eye disorders	Lacrimation increased	Very common
	Conjunctivitis	Very common
Cardiac disorders	Ejection fraction decreased	Very common
	[+]Cardiac failure (congestive)	Common
	Cardiomyopathy	Common
	[+1]Supraventricular tachyarrhythmia	Common
	[1]Palpitation	Common
Vascular disorders	Lymphoedema	Very common
	Hot flush	Common
	[+1]Hypotension	Common
	Hypertension	Common
	Vasodilation	Common
Respiratory, thoracic and mediastinal disorders	[+]Dyspnoea	Very common
	Epistaxis	Very common
	Oropharyngeal pain	Very common
	Cough	Very common
	Rhinorrhoea	Very common
	Asthma	Common
	Lung disorder	Common
	[+]Pleural effusion	Common
	Pneumonia	Common
	Pneumonitis	Uncommon
	Wheezing	Uncommon
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common
	Nausea	Very common
	Abdominal pain	Very common
	Dyspepsia	Very common
	Constipation	Very common
	Stomatitis	Very common
	Pancreatitis	Uncommon
Skin and subcutaneous disorders	Erythema	Very common
	Rash	Very common
	Alopecia	Very common
	Palmar - pantar erythrodysasthesia syndrome	Very common
	Nail disorder	Very common
	Acne	Common
	Dermatitis	Common
	Dry skin	Common
	Hyperhidrosis	Common
	Maculopapular rash	Common
	Pruritus	Common
	Onychoclasis	Common
	Urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Myalgia	Very common
	Arthritis	Common
	Back pain	Common
	Bone pain	Common
	Muscle spasms	Common
	Neck pain	Common
	Pain in extremity	Common
General disorders and administration site conditions	Asthenia	Very common
	Chest pain	Very common
	Chills	Very common
	Fatigue	Very common
	Influenza-like symptoms	Very common
	Infusion/Administration –related reaction	Very common
	Pain	Very common
	Pyrexia	Very common
	Peripheral oedema	Very common
	Mucosal inflammation	Very common
	Oedema	Common
	Injection site pain**	Common
	Malaise	Common
Injury, poisoning and procedural complications	Nail toxicity	Very common
Hepatobiliary disorders	Hepatocellular injury	Common
	Jaundice	Rare
Ear and labyrinth disorders	Deafness	Uncommon

*Adverse drug reactions (ADRs) were identified as events that occurred with at least a 2% difference compared to the control arm in at least one of the major randomised clinical trials.
**Injection site pain was identified as an ADR in the SC arm in the BO22227 study. ADRs were added to the appropriate system organ class category and are presented in a single table according to the highest incidence seen in any of the major clinical trials
+Denotes adverse reactions that have been reported in association with a fatal outcome.
1Denotes adverse reactions that are reported largely in association with infusion-related reactions. Specific percentages for these are not available.

Immunogenicity
In the neoadjuvant-adjuvant EBC treatment setting, 8.1% (24/296) of patients treated with Herceptin IV and 14.9% (44/295) of patients receiving Herceptin SC 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 IV and 4 of 44 Herceptin SC treated 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 ARRs) of Herceptin IV and Herceptin SC did not appear to be adversely affected by these antibodies.

Infusion/Administration-related reactions (IRRs/ARRs) and hypersensitivity
IRRs/ARRs such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress were seen in all trastuzumab clinical trials and for the IV and the SC formulation (see Warnings and Precautions)

IRRs/ARRs may be clinically difficult to distinguish from hypersensitivity reactions.

The rate of IRRs/ARRs of all grades varied between studies depending on the indication, whether trastuzumab 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 trastuzumab-containing arm compared to 36% to 58% in the comparator arm (which may have contained other chemotherapy). Severe reactions (grade 3 and above) ranged from 5 % to 7% in the trastuzumab-containing arm compared to 5% to 6% in the comparator arm.

In EBC, the rate of IRRs/ARRs ranged from 18% to 54% in the trastuzumab-containing arm compared to 6% to 50% in the comparator arm (which may have contained other chemotherapy). Severe reactions (grade 3 and above) ranged from 0.5% to 6% in the trastuzumab-containing arm compared to 0.3% to 5 % in the comparator arm.

In the neoadjuvant-adjuvant EBC treatment setting (Bo22227), the rates of IRRs/ARRs were in line with the above and were 37.2% in the Herceptin IV arm to 47.8% in the Herceptin SC arm. Severe reaction (grade 3) IRRs/ARRs were 2.0% and 1.7% in the Herceptin IV and Herceptin SC arms, respectively during the treatment phase. There were no grade 4 and 5 IRRs/ARRs.

Anaphylactoid reactions were observed in isolated cases.

<u>**Cardiac dysfunction**</u>
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, S3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with Herceptin (see Warnings and 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 + paclitaxel subgroup, compared with 1% - 4% in the paclitaxel alone subgroup. For Herceptin monotherapy, the rate was 6% - 9%. The highest rate of cardiac dysfunction was seen in patients receiving Herceptin + anthracycline/cyclophosphamide (27%), and was significantly higher than in the anthracycline/cyclophosphamide alone subgroup (7% - 10%). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving Herceptin and docetaxel, compared with 0% in patients receiving docetaxel alone. Most of the patients (79%) who developed cardiac dysfunction in these trials experienced an improvement after receiving standard treatment for CHF.

Early Breast Cancer (adjuvant setting)
In 3 pivotal clinical trials of adjuvant Herceptin given in combination with chemotherapy the incidence of NCI-CTC Grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in patients who were administered Herceptin after a taxane (0.3 - 0.4%). The rate was highest in patients who were administered Herceptin concurrently with a taxane (2.0%). At 3 years, the cardiac event rate in patients receiving AC→P (doxorubicin plus cyclophosphamide followed by paclitaxel) + H (trastuzumab) was estimated at 3.2%, compared with 0.8% in AC→P treated patients. 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%, and 1.1% in the AC→D (doxorubicin plus cyclophosphamide, followed by docetaxel), AC→DH (doxorubicin plus cyclophosphamide, followed by docetaxel plus trastuzumab), and DCarbH (docetaxel, carboplatin and trastuzumab) treatment arms, respectively. For symptomatic CHF (NCT-CTC Grade 3 - 4), the 5-year rates were 0.6%, 1.9%, and 0.4% in the AC→D, AC→DH, and DCarbH treatment arms, respectively. The overall risk of developing symptomatic cardiac events was low and similar for patients in AC→D and DCarbH arms; relative to both the AC→D and DCarbH arms there was an increased risk of developing a symptomatic cardiac event for patients in the AC→DH arm, being discernible by a continuous increase in the cumulative rate of symptomatic cardiac or LVEF events up to 2.3% compared to approximately 1% in the two comparator arms (AC→D and DCarbH).

When Herceptin was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6% of patients in the 1-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 remained low at 0.8% and 9.8%, respectively.

In study BO16348, after a median follow-up of 8 years, the incidence of severe CHF (NYHA Class III & IV) in the Herceptin 1 year treatment arm was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Reversibility of severe CHF (defined as a sequence of at least two consecutive LVEF values ≥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 Herceptin-treated patients. Approximately 17% of cardiac dysfunction related events occurred after completion of Herceptin.

In the joint analysis of studies NSABP B-31 and NCCTG N9831, with a median follow-up of 8.1 years for the AC→PH group (doxorubicin plus cyclophosphamide, followed by paclitaxel plus trastuzumab), the per patient incidence of new onset cardiac dysfunction, as determined by LVEF, remained unchanged compared to the analysis performed at a median follow up of 2.0 years in the AC→PH group: 18.5% of AC→PH patients with an LVEF decrease of ≥10% to below 50%. Reversibility of left ventricular dysfunction was reported in 64.5% of patients who experienced a symptomatic CHF in the AC→PH group being asymptomatic at latest follow up, and 90.3% having full or partial LVEF recovery.

Early breast cancer (neoadjuvant-adjuvant setting)
In the pivotal trial MO16432 (NOAH), 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 the pivotal trial BO22227, Herceptin was administered concurrently with neoadjuvant chemotherapy that contained four cycles of of epirubicin (cumulative dose 300 mg/m2); at a median follow-up of 40 months the incidence of CHF was 0% in the Herceptin IV arm and 0.7% in the Herceptin SC arm. In patients with lower body weights (<59 kg, the lowest body weight quartile), the fixed dose used in the Herceptin SC arm was not associated with an increased risk of cardiac events or significant drop in LVEF.

Metastatic Gastric Cancer
In Study BO18255, at screening, the median LVEF value was 64% (range 48% - 90%) in the fluoropyrimidine/cisplatin arm (FP) and 65% (range 50% - 86%) in the Herceptin IV plus fluoropyrimidine/cisplatin arm (H+FP).

The majority of the LVEF decreases noted in BO18255 Study were asymptomatic, with the exception of one patient in the Herceptin-containing arm whose LVEF decrease coincided with cardiac failure.

Table 3 Summary of LVEF change from baseline (BO18255 study)

LVEF Decrease: Lowest Post-screening value	Fluoropyrimidine/Cisplatin (N=290) (% of patients in each treatment arm)	Trastuzumab/ Fluoropyrimidine/Cisplatin (N=294) (% of patients in each treatment arm)
*LVEF decrease of = 10% to a value of < 50%	1.1%	4.6%
Absolute Value < 50%	1.1%	5.9%
*LVEF decrease of = 10% to a value of = 50%	11.8%	16.5%

*Only includes patients whose method of assessment at that visit is the same as at their initial assessment (FP, N=187, and H+FP, N=237)

Table 4 Cardiac Adverse Events (BO18255 study)

	Fluoropyrimidine/Cisplatin (N=290) (% of patients in each treatment arm)	Trastuzumab/ Fluoropyrimidine/Cisplatin (N=294) (% of patients in each treatment arm)
Total Cardiac events	6%	6%
= Grade 3 NCI CTCAE v3.0	*3%	**1%

* 9 patients experienced 9 events
** 4 patients experienced 5 events

Overall, there were no significant differences in the cardiac dysfunction between the treatment arm and the comparator arm.

<u>Hematological toxicity</u>
Breast Cancer
Haematological toxicity is infrequent following the administration of Herceptin monotherapy in the metastatic setting, WHO Grade 3 leucopenia, thrombocytopenia and anaemia occurring in < 1% of patients. No WHO Grade 4 toxicities were observed. There was an increase in WHO Grade 3 or 4 haematological toxicity in patients treated with the combination of Herceptin and paclitaxel compared with patients receiving paclitaxel alone (34% vs. 21%). Haematological toxicity was also increased in patients receiving Herceptin and docetaxel, compared with docetaxel alone (32% grade 3/4 neutropenia versus 22%, using HCI-CTC criteria). The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with Herceptin + docetaxel (23% versus 17% for patients treated with docetaxel alone).

Using NCI-CTC criteria, in the BO16348 trial, 0.4% of Herceptin-treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.6% in the observation arm.

<u>Metastatic Gastric Cancer</u>
The most frequently reported AEs, of Grade ≥3 occurring with an incidence rate of at least 1% by trial treatment, that were categorized under the blood and lymphatic system disorders SOC are shown below:

Table 5 Frequently reported AEs grade ≥ 3 in blood and lymphatic system disorders SOC

	Fluoropyrimidine/Cisplatin (N=290) (% of patients in each treatment arm)	Trastuzumab/ Fluoropyrimidine/Cisplatin (N=294) (% of patients in each treatment arm)
Neutropenia	30%	27%
Anaemia	10%	12%
Febrile neutropenia	3%	5%
Thrombocytopenia	3%	5%

The total percentage of patients who experienced an adverse event of ≥ Grade 3 NCI CTCAE v3.0 categorised under this SOC were 38% in the FP arm and 40% in the FP + H arm.
Overall, there were no significant differences in haematotoxicity between the treatment arm and the comparator arm.

<u>Hepatic and renal toxicity</u>
Breast Cancer
WHO Grade 3 or 4 hepatic toxicity was observed in 12% of patients following administration of Herceptin IV 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 3 or 4 hepatic toxicity was less frequently observed among patients receiving Herceptin IV and paclitaxel than among patients receiving paclitaxel (7% compared with 15%). No WHO Grade 3 or 4 renal toxicity was observed.

Metastatic Gastric Cancer
In Study BO18255, no significant differences in hepatic and renal toxicity were observed between the two treatment arms.
NCI-CTCAE (v3.0) grade ≥3 renal toxicity was not significantly higher in patients receiving Herceptin than those in the F+P arm (3% and 2% respectively).
NCI-CTCAE (v3.0) grade ≥3 adverse events in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported adverse event and was not significantly higher in patients receiving Herceptin IV than those in the F+P arm (1% and <1% respectively).

Diarrhoea
Breast Cancer
Of patients treated with Herceptin IV monotherapy in the metastatic setting, 27% experienced diarrhoea. An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has been observed in patients receiving Herceptin in combination with paclitaxel compared with patients receiving paclitaxel alone.
In the BO16348 trial, 8% of Herceptin-treated patients experienced diarrhoea during the first year of treatment.

Metastatic Gastric Cancer
In Study BO18255, 109 patients (37%) in the Herceptin treatment arm versus 80 patients (28%) in the comparator arm experienced any grade diarrhea. Using NCI-CTCAE v3.0 severity criteria, the percentage of patients experiencing any Grade ≥ 3 diarrhoea was 4% in the FP arm versus 9% in the FP+H arm.

<u>Infection</u>
An increases incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, has been observed in patients treated with Herceptin.

Post-marketing data
Table 6 Adverse Reactions reported in the post-marketing setting

System organ class	Adverse reaction
Blood and lymphatic system disorders	Hypothrombinemia
	Immune thrombocytopenia
Immune system disorders	Anaphylactoid reaction
Eye disorders	Madarosis
Cardiac disorders	Cardiogenic shock
	Tachycardia
Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Oxygen saturation decreased
	Respiratory failure
	Interstitial lung disease
	Lung infiltration
	Acute respiratory distress syndrome
	Respiratory distress
	Pulmonary fibrosis
	Hypoxia
	Laryngeal oedema
Renal and urinary conditions	Glomerulonephropathy
	Renal failure
Pregnancy, puerperium and perinatal disorders	Pulmonary hypoplasia
	Renal hypoplasia
	Oligohydramnios
Metabolism and nutrition disorders	Tumour lysis syndrome

Adverse Events
Table 7 below indicates 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.

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BACK

Table 7 Adverse Events

System organ class	Adverse Event
Infections and infestations	Cellulitis
	Erysipelas
	Sepsis
	Meningitis
	Bronchitis
	Herpes Zoster
	Cystitis
Blood and lymphatic system disorder	Leukaemia
Immune system disorders	Anaphylaxis
	Anaphylactic shock
Psychiatric disorders	Thinking abnormal
Nervous system disorders	Ataxia
	Paresis
	Cerebrovascular disorder
	Brain oedema
	Lethargy
	Coma
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Pericardial effusion
	Bradycardia
	Pericarditis
Respiratory, thoracic, mediastinal system disorders	Hiccups
	Dyspnoea, exertional
Gastrointestinal system disorders	Gastritis
Hepatobiliary disorders	Hepatic failure
Musculoskeletal and connective tissue disorders	Musculoskeletal pain
Renal system disorders	Dysuria
Reproductive system and breast disorders	Breast pain
General disorders and administrative site conditions	Chest discomfort

OVERDOSE
There is no experience with overdose in human clinical trials. Single doses greater than 10 mg/kg of trastuzumab have not been tested.

INCOMPATIBILITIES
ZUHERA® should not be mixed or diluted with other products except those mentioned under **Special Precautions for Disposal and Other Handling** section.
Do not dilute with glucose solutions, since these cause aggregation of the protein.

SHELF-LIFE: Refer to Carton/Label.

STORAGE AND HANDLING INFORMATION
Store vials at 2°C to 8°C prior to reconstitution.
Store away from light.
Keep out of reach of children.
Vials should not be used beyond the expiration date stamped on the vial; the reconstituted drug solution should be used as given below; and any unused portion must be discarded. DO NOT FREEZE DRUG THAT HAS BEEN RECONSTITUTED.

Shelf-life of the reconstituted solution
150 mg (Single-dose use vial)
The reconstituted product is physically and chemically stable for 48 hours at 2-8°C after dissolving in Sterile Water for Injection (not supplied). From a microbiological safety perspective, the reconstituted solution should be used immediately. Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product
Infusion solution (0.9% Sodium Chloride) containing the reconstituted drug product is physically and chemically stable for 24 hours at 2°C to 8°C. From the perspective of microbiological safety, the ZUHERA® infusion solution should be used immediately. If not used immediately, 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°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Special Precautions for Disposal and Other Handling
- Appropriate aseptic technique should be used.
- Use of other reconstitution solvents should be avoided.
- Reconstitution details are given in the table below:

Table 8: Reconstitution Details of 150 mg vial Single dose vial

Type of Vial	Reconstitution	Trastuzumab mg/mL	p H
150 mg (single-dose)	7.2 mL of sterile water for injection	~21	~6.0

Commercially available WFI should be bought by user.
- During reconstitution, handle **ZUHERA®** carefully. Causing excessive foarming during reconstitution or shaking the reconstitution solution may result in problems with the amount of **ZUHERA®** that can be withdrawn from the vial
- Do not freeze the reconstituted solution.

Instructions for reconstitution-150 mg vial (single-dose vial)
1) Slowly inject 7.2 mL of sterile water for injection into the vial containing the lyophilised **ZUHERA®**, using a sterile syringe. Direct the stream into the lyophilised cake.
2) To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.
Instructions for dilution:
Determine the volume of **ZUHERA®** solution required:
- Based on a loading dose of 4 mg **ZUHERA®**/kg, or a subsequent weekly dose of 2 mg **ZUHERA®**/kg:

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

- Based on a loading dose of 8 mg ZUHERA®/kg, or a subsequent 3-weekly dose of 6 mg ZUHERA®/kg:

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

- Withdraw the appropriate amount of solution from the vial, and add it to an infusion bag containing 250 mL of 0.9% sodium chloride solution.
- Glucose/dextrose-containing solutions should not be used.
- Mix the solution by inverting the bag gently (to avoid foaming).
- Once the infusion is prepared it should be administered immediately.
- If diluted aseptically, it may be stored for 24 hours (do not store above 30°C).

Inspect visually for particulate matter and discoloration prior to administration.
No incompatibilities have been observed between trastuzumab and polyvinylchloride, polyethylene or polypropylene bags.
Dispose of unused medicinal product in accordance with local regulations.

PACKAGING INFORMATION
150 mg ZUHERA®(Single-dose vial)
ZUHERA® finished product 150 mg is filled in 15 mL USP type 1 glass vial, closed with a chlorobutyl rubber stopper and sealed with 20 mm blue flip-off seal.

ZUHERA® has been developed as a similar biological medicinal product to Herceptin

Manufactured and released by: **Biocon Biologics Limited**
Block No B1, B2, B3, Q13 of Q1 and W20 & Unit S18, 1st Floor,
Block B4, Special Economic Zone, Plot No. 2,3,4 & 5,
Phase IV, Bommasandra -Jigani Link Road, Bommasandra Post
Bengaluru 560099, India.

Product Registration Holder: **Biocon Sdn. Bhd.**
No. 1, Jalan Bioteknologi 1,
Kawasan Perindustrian SiLC,
79200 Iskandar Puteri, Johor, Malaysia

Marketed by: **Duopharma HAPI Sdn. Bhd**.
No. 2, Jalan Saudagar U1/16,
Pusat Perindustrian Hicom Glenmarie,
Seksyen U1, 40150 Shah Alam, Selangor, Malaysia
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