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CANHERA

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For the use only of a Registered Medical Practitioner, Oncologist, Specialist, Hospital or Laboratory

*In vitro, preclinical and clinical studies have demonstrated similarity between **CAN**HERA® 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 (reference product)" 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 **CAN**HERA® is presented, the term "**CAN**HERA®" is used.*

Rx

NAME OF THE MEDICINAL PRODUCT
***CAN**HERA®*

GENERIC NAME
Trastuzumab lyophilized powder for injection (r-DNA origin)

COMPOSITION
150 mg single-dose, 150 mg multi-dose and 440 mg multi-dose vials containing powder for concentrate for solution for intravenous infusion. Reconstituted ***CAN**HERA®* 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, Polyethylene Glycol 3350 (Macrogol 3350), D-Sorbitol, sodium hydroxide and hydrochloric acid (for pH adjustment)

DOSAGE FORM
Powder for concentrate for solution for infusion.
***CAN**HERA®* is a sterile, off-white to pale yellow, preservative-free lyophilized powder.

Bacteriostatic water for injection (BWFI), is a sterile non pyrogenic preparation of water for injection. It is colourless transparent solution free of visible particles and is intended to use for the reconstitution of ***CAN**HERA®* drug product

> **WARNING: CARDIAC DYSFUNCTION, INFUSION REACTIONS, PULMONARY TOXICITY and EMBRYO-FOETAL 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. The incidence of such events increases when administered along 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
Trastuzumab is a humanised monoclonal IgG1 antibody 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 15 to 20% of primary breast cancers. The overall rate of HER2 positivity in advanced gastric cancers as observed during screening for study BO18255 is 15% for IHC3+and IHC2+/FISH+ or 22.1% when applying the broader definition of IHC3+ or FISH+.
Studies showed that amplification or overexpression of HER2 correlates with shorter disease-free survival compared to patients whose tumors do not have amplification or overexpression of HER2.

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
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 ***CAN**HERA®* was similar to that of trastuzumab (reference product). In addition, a multicenter, double-blind, randomized, parallel-group, phase III study showed that pharmacokinetic, efficacy, safety and immunogenicity profiles of ***CAN**HERA®* was similar to trastuzumab (reference product) in patients with HER2-positive metastatic breast cancer (MBC).

Trastuzumab IV
The pharmacokinetics of Trastuzumab were evaluated in a population pharmacokinetic model analysis using pooled data from 1,582 subjects from 18 Phase I, II and III trials receiving Trastuzumab IV. A two-compartment model with parallel linear and non-linear elimination from the central compartment described the trastuzumab concentration-time profile. Due to the non-linear elimination, total clearance increased with decreasing concentrations. Linear clearance was 0.127 L/day for breast cancer (MBC/EBC) and 0.176 L/day for AGC. The nonlinear elimination parameters were 8.81 mg/day for the maximum elimination rate (Vmax) and 8.92 mg/L for the Michaelis-Menten constant (Km). The central compartment volume was 2.62 L for patients with breast cancer and 3.63 L for patients with AGC.
The population predicted PK exposures (with 5th - 95th Percentiles) and PK parameter values at clinically relevant concentrations (Cmax and Cmin) for breast cancer and AGC patients treated with the approved q1w and q3w dosing regimens are shown in Table 1 (Cycle 1) and Table 2 (steady-state) below.

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

Regimen	Primary tumor type	N	Cmin (µg/mL)	Cmax (µg/mL)	AUC (µg.day/mL)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	29.4 (5.8 - 59.5)	178 (117 - 291)	1373 (736 - 2245)
	AGC	274	23.1 (6.1 - 50.3)	132 (84.2 - 225)	1109 (588 - 1938)
4mg/kg + 2mg/kg qw	MBC/EBC	1195	37.7 (12.3 - 70.9)	88.3 (58 - 144)	1066 (586 - 1754)

Table 2: Population Predicted Steady State PK Exposure Values (with 5th - 95th Percentiles) for Trastuzumab IV Dosing Regimens in Breast Cancer and AGC Patients

Regimen	Primary tumor type	N	Cmin,ss (µg/mL)	Cmax,ss (µg/mL)	AUCss (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8mg/kg + 6mg/kg q3w	MBC/EBC	1195	47.4 (5 - 115)	179 (107 - 309)	1794 (673-3618)	12	0.173 - 0.283
	AGC	274	32.9 (6.1 - 88.9)	131 (72.5 - 251)	1338 (557 - 2875	9	0.189 - 0.337
4mg/kg + 2mg/kg qw	MBC/EBC	1195	66.1 (14.9 - 142)	109 (51.0 - 209)	1765 (647 - 3578)	12	0.201 - 0.244

Pharmacokinetics in Special Populations
Detailed pharmacokinetic studies in the geriatric population and those with renal or hepatic impairment have not been carried out.
Renal Impairment
Detailed pharmacokinetic studies in patients with renal impairment have not been carried out. In a population pharmacokinetic analysis, renal impairment was shown not to affect trastuzumab disposition.
Geriatric Population
Age has been shown to have no effect on the disposition of trastuzumab.

CLINICAL EFFICACY
The clinical efficacy of ***CAN**HERA®* 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 ***CAN**HERA®* and trastuzumab (reference product) with regard to overall response rate, progression-free survival and overall survival at 48 weeks.

PRECLINICAL SAFETY DATA
Nonclinical studies (conventional toxicity studies) on ***CAN**HERA®* did not indicate any special hazard for humans. During conventional single- and repeat-dose toxicity studies of ***CAN**HERA®* 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 ***CAN**HERA®* was similar to that of trastuzumab (reference product).

THERAPEUTIC INDICATIONS
Metastatic Breast Cancer
***CAN**HERA®* is indicated for the treatment of MBC patients who have human epidermal growth factor receptor 2 - (HER2)-overexpressing tumours.
- as monotherapy for the treatment of those patients who have received one or more chemotherapy regimens for their metastatic disease
- in combination with paclitaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease
- in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab. This indication is based on data from one Phase III trial which studied the use of trastuzumab in combination with anastrozole (Clinical Efficacy). Experience with other aromatase inhibitors is limited.

Early Breast Cancer (EBC)
***CAN**HERA®* is indicated for the treatment of adult patients with HER2 positive EBC.
- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable) (see section pharmacodynamic properties).
- 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 trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter (see sections warning and precautions and pharmacodynamic properties).

***CAN**HERA®* should only be used in MBC or EBC patients who have tumours with either overexpression of HER2 or HER2 gene amplification as determined by an accurate and validated assay.

Metastatic Gastric Cancer (MGC)
***CAN**HERA®* in combination with capecitabine or 5-fluorouracil and cisplatin is indicated for the treatment of adult patients with HER2 positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received prior anti-cancer treatment for their metastatic disease.

***CAN**HERA®* should be used in only those MGC patients whose tumours overexpress HER2, as determined by an accurate and validated assay:
- IHC2+ plus a confirmatory fluorescence in situ hybridisation (FISH) result, OR
- IHC 3+ result.

DOSE AND METHOD OF ADMINISTRATION
General
HER2 testing is mandatory prior to initiation of **CAN**HERA® therapy.
Substitution by any other biological medicinal product requires the consent of the prescribing physician.

CANHERA® is a biosimilar and the safety and efficacy of alternating or switching between products that are biosimilar but not deemed interchangeable has not been established. Therefore, the benefit/risk of alternating or switching need to be carefully considered.

CANHERA® should be administered by a qualified health care professional.

In order to prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is **CAN**HERA® (trastuzumab) and not trastuzumab emtansine.

CANHERA® (see Pharmaceutical Particulars):
CANHERA® is not to be used for subcutaneous administration and should be administered as intravenous infusion.

Do not administer as an intravenous push or bolus.

Metastatic Breast Cancer
Weekly schedule:
Loading dose: The recommended initial loading dose is 4 mg/kg body weight **CAN**HERA® administered as a 90-minute intravenous infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable effects). Interruption of the infusion may help control such symptoms. The infusion may be resumed when symptoms abate.

Subsequent doses: The recommended weekly dose of **CAN**HERA® is 2 mg/kg body weight. If the prior dose was well tolerated, the dose can be administered as a 30-minute infusion. Patients should be observed for fever and chills or other infusion-associated symptoms (see Undesirable effects).

Administration in combination with an aromatase inhibitor
In the pivotal trial trastuzumab IV and anastrozole were administered from day 1. There were no restrictions on the relative timing of trastuzumab IV and anastrozole at administration (for dose, see the Product Information for anastrozole or other aromatase inhibitors).

3-weekly schedule:
Alternatively, the following loading and subsequent doses are recommended for monotherapy and in combination with paclitaxel or an aromatase inhibitor.
Initial **CAN**HERA® 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 initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

Early Breast Cancer
3-weekly schedule:
As a three-weekly regimen the recommended initial loading dose of **CAN**HERA® is 8 mg/kg body weight. The recommended maintenance dose of **CAN**HERA® at three-weekly intervals is 6 mg/kg body weight, beginning three weeks after the loading dose.

Alternative weekly schedule:
As a weekly regimen (initial loading dose of 4 mg/kg followed by 2 mg/kg every week) concomitantly with paclitaxel following chemotherapy with doxorubicin and cyclophosphamide.

Metastatic Gastric Cancer
3-weekly schedule:
CANHERA® is administered at an 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 initial loading dose is well tolerated, the subsequent doses can be administered as a 30-minute infusion (See pharmacodynamic properties for chemotherapy combination dosing).

Duration of treatment
In clinical studies, patients with metastatic breast cancer or metastatic gastric cancer were treated with trastuzumab until progression of disease or unmanageable toxicity. Patients with early breast cancer should be treated for 1 year or until disease recurrence or unmanageable toxicity, whichever occurs first. Extending treatment in EBC beyond one year is not recommended (see Clinical Efficacy).
See incompatibilities for instructions for use and handling.

Dose modification
If the patient develops an infusion-related reaction (IRR), the infusion rate of **CAN**HERA® may be slowed or interrupted (see Warnings and Precautions).

No reductions in the dose of **CAN**HERA® were made during clinical trials. Patients may continue **CAN**HERA® 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 hold the dose of chemotherapy should be followed.

Missed doses
If the patient has missed a dose of **CAN**HERA® by one week or less, then the usual maintenance dose (weekly regimen: 2 mg/kg; three-weekly regimen: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent **CAN**HERA® maintenance doses be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of **CAN**HERA® by more than one week, a re-loading dose of **CAN**HERA® should be administered over approximately 90 minutes (weekly regimen: 4 mg/kg; 3-weekly regimen: 8 mg/kg) as soon as possible. Subsequent **CAN**HERA® maintenance doses (weekly regimen: 2 mg/kg; three-weekly regimen 6 mg/kg respectively) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules respectively.

Special Dosage Instructions
Geriatric use
Data suggest that the disposition of **CAN**HERA® is not altered based on age or serum creatinine (see Pharmacokinetics in special populations). In clinical trials, patients ≥ 65 years of age did not receive reduced doses of **CAN**HERA®. Dedicated pharmacokinetic studies in the elderly and those with renal or hepatic impairment have not been carried out. However, in a population pharmacokinetic analysis, age and renal impairment were not shown to affect **CAN**HERA® disposition.

Paediatric use
The safety and efficacy of **CAN**HERA® in pediatric patients < 18 years of age have not been established.

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

See section **Composition** for a list of components of ***CAN**HERA®*.

Data in the following section (**Warnings and Precautions**) has been taken from publicly available data on trastuzumab (reference product).

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.

Currently no data from clinical trials are available on trastuzumab re-treatment of patients with previous exposure to trastuzumab in the adjuvant setting.

Initiate trastuzumab therapy under the supervision of a physician experienced in cancer treatment.

Exacerbation of chemotherapy-induced neutropenia
Incidences of neutropenia, including febrile neutropenia, were reported in clinical trials in patients receiving trastuzumab (reference product) in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab (reference product) and those who did not. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy.

Infusion-related reactions
Serious infusion-related reactions to trastuzumab (reference product) infusion have been reported; and include dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, hypertension, supraventricular tachyarrhythmia, anaphylaxis, urticaria, angioedema and respiratory distress. Patients may be at increased risk of a fatal infusion reaction if they are experiencing dyspnoea at rest, arising from complications of advanced malignancy or comorbidities. Therefore, these patients should not be treated with trastuzumab. Should infusion reactions occur, discontinue trastuzumab infusion or slow the rate of infusion, and observe the patient until the symptoms resolve. Rarely, such reactions culminate in death. Most patients experienced resolution of symptoms and were given further infusions of trastuzumab (reference product). Supportive therapy, such as oxygen, epinephrine, antihistamine, bronchodilators, beta-agonists and corticosteroids, has been successfully used to treat serious reactions (see **Undesirable Effects**).

There have also been reports of initial improvement followed by delayed reactions with rapid clinical deterioration. Within hours and up to one week following infusion, deaths have occurred. Very rarely, the onset of infusion symptoms and pulmonary symptoms have occurred more than 6 hours after the start of the infusion. Warn patients of the possibility of such a late onset and instruct them to contact the physician if these symptoms occur. Prior to resumption of trastuzumab (reference product) infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated trastuzumab (reference product) infusions, others had recurrent severe infusion reactions despite pre-medications.

Pulmonary toxicity
Severe pulmonary events have been reported with trastuzumab (reference product), occasionally resulting in death. Cases of interstitial lung diseases including lung infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported; these events may occur as part of an infusion-related reaction or with a delayed onset. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies such as taxanes, gemcitabine, vinorelbine and radiation therapy. Patients may be at greater risk of severe reactions if they have symptomatic intrinsic lung disease; or extensive tumour involvement of the lungs, resulting in dyspnoea at rest. Therefore, such patients should not be treated with trastuzumab (see **Contraindication**). Exercise caution for pneumonitis, especially in patients being treated concomitantly with taxanes.

Cardiac dysfunction
Trastuzumab therapy increases the risk of CHF (New York Heart Association [NYHA] class II - IV) or asymptomatic cardiac dysfunction. These events have been observed in patients receiving trastuzumab (reference product) alone or in combination with paclitaxel following anthracycline (doxorubicin or epirubicin). These events can be moderate to severe and may be associated with death. Caution should be taken when treating patients with increased cardiac risk (e.g., hypertension, documented coronary artery disease, CHF, LVEF <55%, older age).

Population pharmacokinetic model simulations indicate that trastuzumab may persist in the circulation for up to 7 months after stopping trastuzumab IV. Patients who receive anthracyclines after stopping trastuzumab may possibly be at increased risk of cardiotoxicity. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping treatment, and monitor cardiac function carefully if anthracyclines are used. Trastuzumab and anthracycline should not be given concurrently in the adjuvant treatment setting (EBC) or MBC setting. In patients with EBC eligible for neoadjuvant-adjuvant chemotherapy, trastuzumab should only be used concurrently with anthracyclines in chemotherapy-naive patients and only with low-dose anthracycline regimens (maximum cumulative doses of doxorubicin 180 mg/m² or epirubicin 360 mg/m²). In patients being concurrently treated with full course of low-dose anthracyclines and trastuzumab in the neoadjuvant setting, additional cytotoxic chemotherapy should not be given after surgery.

Patients who are going to start trastuzumab, especially those with prior exposure to anthracycline and cyclophosphamide, should undergo baseline cardiac assessment, including history and physical examination, ECG, echocardiogram and/or multigated acquisition (MUGA) scan. Repeat cardiac assessments every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab.

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

No prospective study has been done on the safety of continuing or resuming trastuzumab (reference product) in patients who experience cardiotoxicity. In the pivotal trials, most patients who developed heart failure improved with standard treatments (including diuretics, cardiac glycosides, beta blockers and/or angiotensin converting enzyme inhibitors). In these trials, most patients with cardiac symptoms who also had evidence of a clinical benefit from trastuzumab (reference product) treatment continued on therapy with trastuzumab (reference product) without further clinical cardiac events.

In a global early breast cancer trial with trastuzumab (reference product), patients with the following conditions were excluded:
- Angina pectoris requiring medical treatment
- Clinically significant cardiac valvular disease
- History of documented congestive heart failure.
- High-risk uncontrolled arrhythmias
- Evidence of transmural infarction on ECG
- Poorly controlled hypertension

Therefore, the benefit-risk balance for such patients is unknown, and treatment is not recommended.

Metastatic breast cancer (MBC)
Trastuzumab and anthracyclines should not be given concurrently in the metastatic breast cancer setting.

Early breast cancer (EBC)
For patients with EBC, cardiac assessments, as performed at baseline, should be repeated every 3 months during treatment and every 6 months following discontinuation of treatment until 24 months from the last administration of 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.

Adjuvant treatment
Trastuzumab and anthracyclines should not be given concurrently in the adjuvant treatment setting.
In patients with EBC an increase in the incidence of symptomatic and asymptomatic cardiac events was observed when trastuzumab was administered after anthracycline-containing chemotherapy compared to administration with a nonanthracycline 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/m2).

Neoadjuvant-adjuvant treatment
In patients with EBC eligible for neoadjuvant-adjuvant treatment, Trastuzumab concurrently with anthracyclines should be used with caution and only in chemotherapy-naive patients. The maximum cumulative doses of the low-dose anthracycline regimens should not exceed 180 mg/m2 (doxorubicin) or 360 mg/m2 (epirubicin).

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.

CANHERA®.contains sorbitol. Patients with hereditary problems with fructose intolerance should not take this medicine.

Benzyl alcohol
Benzyl alcohol (1.1%) is used as a preservative in bacteriostatic water for injection in the 150 mg and 440 mg ***CAN**HERA®* multi-dose vials. If a patient is known to be hypersensitive to benzyl alcohol, reconstitute ***CAN**HERA®* with water for injection, and use only one dose per ***CAN**HERA®* vial. Discard any unused portion.

Pregnancy and Lactation
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 (reference product) revealed no evidence of impaired fertility or harm to the foetus.

Avoid administering trastuzumab 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 (reference product).

Advise women of childbearing potential to use effective contraception during treatment with trastuzumab; 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 trastuzumab 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 (reference product).

Embryonic death was seen in mutant mice lacking HER2 receptor. In cynomolgus monkeys, placental transfer of trastuzumab (reference product) 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 trastuzumab 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 trastuzumab therapy and for 7 months after the last dose.

In cynomolgus monkeys, trastuzumab (reference product) 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 (reference product) in the serum of infant monkeys.

Effects on Ability to Drive and Use Machines
Trastuzumab has a minor influence on the ability to drive and use machines. Dizziness and somnolence may occur during treatment with trastuzumab. Patients experiencing administration-related symptoms should be advised not to drive or use machines until symptoms resolve completely.

DRUG INTERACTIONS
Formal drug interaction studies with trastuzumab (reference product) have not been performed in humans. In clinical trials of trastuzumab (reference product), no clinically significant interactions with the concomitant medications used were observed (see **Pharmacokinetic Properties**). The results of a small sub-study suggested that the exposure to the bioactive metabolites (e.g., 5-fluorouracil) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab (reference product). However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab (reference product). In studies where Trastuzumab was administered in combination with docetaxel, carboplatin, or anastrozole, the 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. Trastuzumab can increase the overall exposure of 7-deoxy-13 dihydro-doxorubicinone (D7D), a doxorubicin metabolite. The bioactivity of D7D and the clinical impact of the increase of this metabolite is not clear. No changes were observed in trastuzumab concentrations in the presence of paclitaxel and doxorubicin. Trastuzumab can increase the overall exposure of 7-deoxy-13 dihydro-doxorubicinone (D7D), a doxorubicin metabolite. The bioactivity of D7D and the clinical impact of the increase of this metabolite is not clear.

UNDESIRABLE EFFECTS
Table 3 Summary of adverse drug reactions occurring in patients treated with Trastuzumab in clinical trials Undesirable effects reported with intravenous trastuzumab monotherapy or in combination with chemotherapy in pivotal clinical trials and in post-marketing.

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

Amongst the most serious and/or common adverse reactions reported in trastuzumab usage (intravenous and subcutaneous formulations) to date are cardiac dysfunction, administration-related reactions, haematotoxicity (in particular neutropenia), infections and pulmonary adverse reactions.

The safety profile of trastuzumab subcutaneous formulation (evaluated in 298 and 297 patients treated with the intravenous and subcutaneous formulations respectively) from the pivotal trial in EBC was overall similar to the known safety profile of the intravenous formulation.

Severe adverse events (defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE grade ≥3) version 3.0) were equally distributed between both Trastuzumab formulations (52.3 % versus 53.5 % in the intravenous formulation versus subcutaneous formulation respectively).
Some adverse events / reactions were reported with a higher frequency for the subcutaneous formulation:

- Serious adverse events (most of which were identified because of in-patient hospitalisation or prolongation of existing hospitalisation): 14.1 % for the intravenous formulation versus 21.5 % for the subcutaneous formulation. The difference in SAE rates between formulations was mainly due to infections with or without neutropenia (4.4 % versus 8.1 %) and cardiac disorders (0.7 % versus 1.7 %);
- Post-operative wound infections (severe and/or serious): 1.7 % versus 3.0 % for the intravenous formulation versus subcutaneous formulation, respectively;
- Administration-related reactions: 37.2 % versus 47.8 % for the intravenous formulation versus subcutaneous formulation, respectively;
- Hypertension: 4.7 % versus 9.8 % for the intravenous formulation versus subcutaneous formulation respectively.

Tabulated list of adverse reactions with the intravenous formulation
The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions should be presented in order of decreasing seriousness.

Table 3 Summary of adverse drug reactions occurring in patients treated with Trastuzumab in clinical trials
Undesirable effects reported with intravenous trastuzumab monotherapy or in combination with chemotherapy in pivotal clinical trials and in post-marketing

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

+ Denotes adverse reactions that have been reported in association with a fatal outcome.
1 Denotes adverse reactions that are reported largely in association with Infusion-related reactions. Specific percentages for these are not available.
* Observed with combination therapy following anthracyclines and combined with taxanes
**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 (SOC) category and are presented in a single table according to the highest incidence seen in any of the major clinical trials.

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

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

Additional information for selected adverse drug reactions
Infusion/Administration-related reactions (IRRs/ARRs) and Hypersensitivity
IRRs/ARRs such as chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, achycardia, reduced oxygen saturation and respiratory distress were seen in all Trastuzumab clinical trials (see section 2.4 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 (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 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 (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.

Anaphylactoid reactions were observed in isolated cases.

Serious Pulmonary Events
Single cases of pulmonary infiltrates, pneumonia, pulmonary fibrosis, pleural effusion, respiratory distress, acute pulmonary oedema, acute respiratory distress syndrome (ARDS) and respiratory insufficiency have been reported rarely. These events have been reported rarely with fatal outcome.

Cardiac Dysfunction
Congestive heart failure (NYHA Class II-IV) is a common adverse reaction to trastuzumab. It has been associated with fatal outcome. Signs and symptoms of cardiac dysfunction such as dyspnoea, orthopnoea, increased cough, pulmonary oedema, S_3 gallop, or reduced ventricular ejection fraction, have been observed in patients treated with trastuzumab (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 trastuzumab + paclitaxel group, compared with 1% – 4% in the paclitaxel alone group. For trastuzumab monotherapy, the rate was 6% – 9%. The highest rate of cardiac dysfunction was seen in patients receiving concurrent trastuzumab + anthracycline/cyclophosphamide (27%) and was significantly higher than in the anthracycline/ cyclophosphamide alone group (7% – 10%). In a subsequent trial with prospective monitoring of cardiac function, the incidence of symptomatic heart failure was 2.2% in patients receiving trastuzumab 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 three pivotal clinical trials of adjuvant trastuzumab given in combination with chemotherapy the incidence of grade 3/4 cardiac dysfunction (symptomatic CHF) was similar in patients who were administered chemotherapy alone and in patients who were administered trastuzumab sequentially after a taxane (0.3 - 0.4%). The rate was highest in patients who were administered trastuzumab 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 (NCI-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 the 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 discernable 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 trastuzumab was administered after completion of adjuvant chemotherapy NYHA Class III-IV heart failure was observed in 0.6% of patients in the one-year arm after a median follow-up of 12 months. After a median follow-up of 3.6 years the incidence of severe CHF and left ventricular dysfunction after 1 year trastuzumab 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 trastuzumab 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 trastuzumab -treated patients. Reversibility of mild symptomatic and asymptomatic left ventricular dysfunction was demonstrated for 79.5% of trastuzumab - treated patients. Approximately 17% of cardiac dysfunction related events occurred after completion of trastuzumab.

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, trastuzumab was administered concurrently with neoadjuvant chemotherapy containing three cycles of doxorubicin (cumulative dose 180 mg/m2). The incidence of symptomatic cardiac dysfunction was 1.7 % in the Trastuzumab arm.

Metastatic Gastric Cancer
In BO18255 study, at screening, the median LVEF value was 64% (range 48 %-90 %) in the Fluoropyrimidine/Cisplatin arm (FP) and 65 % (range 50 %-86 %) in the trastuzumab IV plus Fluoropyrimidine/Cisplatin arm (FP+H).
The majority of the LVEF decreases noted in BO18255 study were asymptomatic, with the exception of one patient in the trastuzumab -containing arm whose LVEF decrease coincided with cardiac failure.

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Table 4 Summary of LVEF Change from baseline (BO18255 study)

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

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

Table 5 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 cardiac dysfunction between the treatment arm and the comparator arm.

Haematological toxicity
Breast Cancer
Haematological toxicity was infrequent following the administration of trastuzumab as a single agent 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 trastuzumab and paclitaxel compared with patients receiving paclitaxel alone (34 % versus 21 %). Haematological toxicity was also increased in patients receiving trastuzumab and docetaxel, compared with docetaxel alone (32 % grade 3/4 neutropenia versus 22 %, using NCI-CTC criteria). Note that this is likely to be an underestimate since docetaxel alone at a dose of 100mg/m2 is known to result in neutropenia in 97 % of patients, 76% grade 4, based on nadir blood counts. The incidence of febrile neutropenia/neutropenic sepsis was also increased in patients treated with trastuzumab plus docetaxel (23 % versus 17 % for patients treated with docetaxel alone).

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

Advanced Gastric Cancer
The most frequently reported AEs, of Grade ≥ 3 occurring with an incidence rate of at least 1% by trial treatment, that were categorised under the Blood and Lymphatic System Disorders SOC are shown below:

Table 6 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 AE of ≥ grade 3 NCI-CTCAE v3.0 that has been 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.

Hepatic and renal toxicity
Breast Cancer
WHO Grade 3 or 4 hepatic toxicity was observed in 12 % of patients following administration of Trastuzumab 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 Trastuzumab 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 BO18255 study no significant differences in hepatic and renal toxicity were observed between the two treatment arms.

NCI-CTCAE (version 3.0) grade ≥3 renal toxicity was not significantly higher in patients receiving Trastuzumab IV + FP than those in the FP arm (3% and 2% respectively).

NCI-CTCAE (version 3.0) grade ≥3 adverse event in the Hepatobiliary Disorders SOC: Hyperbilirubinaemia was the only reported AE and was not significantly higher in patients receiving Trastuzumab IV + FP than those in the FP arm (1% and < 1% respectively).

Diarrhoea
Breast Cancer
Of patients treated with Trastuzumab IV as a single agent in the metastatic setting, 27 % experienced diarrhoea. An increase in the incidence of diarrhoea, primarily mild to moderate in severity, has also been observed in patients receiving trastuzumab in combination with paclitaxel compared with patients receiving paclitaxel alone.

In the BO16348 study trial, 8 % of trastuzumab -treated patients experienced diarrhoea during the first year of treatment.

Metastatic Gastric Cancer
In BO18255 study, 109 patients (37 %) participating in the trastuzumab -containing treatment arm versus 80 patients (28 %) in the comparator arm experienced any grade diarrhoea. Using NCI CTCAE severity criteria, the percentage of patients experiencing grade ≥ 3 diarrhoea was 4 % in the FP arm vs 9 % in the FP+H arm.

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 trastuzumab.

Laboratory Abnormalities
Febrile neutropenia occurs very commonly. Commonly occurring adverse reactions include anaemia, leukopenia, thrombocytopenia and neutropenia. The frequency of occurrence of hypoprothrombinemia is not known.

Postmarketing Experience
The following adverse drug reactions have been identified from postmarketing experience with trastuzumab (Table 7).

Table 7 Adverse Reactions reported in the post marketing setting

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

OVERDOSE
There is no information on overdose from human clinical trials. Single doses greater than 10 mg/kg of trastuzumab (reference product) alone have not been administered in the clinical trials. Doses up to this level were well tolerated

Efficacy
MBC
Trastuzumab monotherapy has been used in clinical trials for patients with metastatic breast cancer who have tumors that overexpress HER2 and who have failed one or more chemotherapy regimens for their metastatic disease.
Trastuzumab has also been used in clinical trials in combination with paclitaxel or an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC) as first line therapy for patients with metastatic breast cancer who have tumors that overexpress HER2.
Patients who had previously received anthracycline-based adjuvant chemotherapy were treated with paclitaxel (175 mg/m2 infused over 3 hours) with or without trastuzumab. Patients could be treated with trastuzumab until progression of disease.
Trastuzumab monotherapy, when used as second- or third-line treatment of women with metastatic breast cancer which overexpresses HER-2, results in an overall tumor response rate of 15% and a median survival of 13 months.
The use of trastuzumab in combination with paclitaxel as first-line treatment of women with metastatic breast cancer that overexpresses HER-2 significantly prolongs the median time to disease progression, compared with patients treated with paclitaxel alone. The increase in median time to disease progression for patients treated with Trastuzumab and paclitaxel is 3.9 months (6.9 months vs. 3.0 months). Tumor response and one year survival rate are also increased for trastuzumab in combination with paclitaxel versus paclitaxel alone.

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

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

Table 8 Efficacy results from the non-comparative monotherapy and combination therapy studies

Parameter	Monotherapy		Combination Therapy
	Trastuzumab1 N=105	Trastuzumab2 N=72	Trastuzumab plus paclitaxel3 N=32
Response rate (95%CI)	24% (15 - 35)	27% (14 - 43)	59% (41-76)
Median duration of response (months) (range)	10.1 (2.8-35.6)	7.9 (2.1-18.8)	10.5 (1.8-21)
Median TTP (months) (95%CI)	3.4 (2.8-4.1)	7.7 (4.2-8.3)	12.2 (6.2-ne)
Median Survival (months) (95%CI)	ne	ne	ne

TTP = time to progression; "ne" indicates that it could not be estimated or it was not yet reached.
1. Study WO16229: loading dose 8 mg/kg, followed by 6 mg/kg 3 weekly schedule
2. Study MO16982: loading dose 6mg/kg weekly x 3; followed by 6mg/kg 3-weekly schedule
3. Bo15935

EBC
In the adjuvant treatment setting, Trastuzumab was investigated in 4 large multicentre, randomised, phase 3 trials:

- Study BO16348 study was designed to compare one year and two years of three-weekly Trastuzumab treatment versus observation in patients with HER2 positive early breast cancer following surgery, established chemotherapy and radiotherapy (if applicable). In addition, a comparison of two years of Trastuzumab treatment versus one year of Trastuzumab treatment was performed. Patients assigned to receive Trastuzumab were given an initial loading dose of 8 mg/kg, followed by 6 mg/kg every three weeks for either one or two years.
- Studies NSABP B-31 and NCCTG N9831 that comprise the joint analysis were designed to investigate the clinical utility of combining Trastuzumab IV treatment with paclitaxel following AC chemotherapy; additionally the NCCTG N9831 study investigated adding Trastuzumab sequentially to AC-paclitaxel chemotherapy in patients with HER2 positive early breast cancer following surgery.
- Study BCIRG 006 study was designed to investigate combining Trastuzumab IV treatment with docetaxel either following AC chemotherapy or in combination with docetaxel and carboplatin in patients with HER2 positive early breast cancer following surgery.

Early breast cancer in the Study BO16348 was limited to operable, primary, invasive adenocarcinoma of the breast, with axillary nodes positive or axillary nodes negative tumours of at least 1 cm in diameter.

The efficacy results from the BO16348 study are summarized in the following table:

Table 9 Efficacy Results BO16348 study: Results at 12months* and 8 years of median follow-up**

Parameter	Median follow-up 12 months		Median follow-up 8 years	
	Observation N=1693	Trastuzumab 1 Year N = 1693	Observation N= 1697***	Trastuzumab 1 Year N = 1702***
Disease-free survival - No. patients with event	219 (12.9%)	127 (7.5%)	570 (33.6%)	471 (27.7%)
- No. patients without event	1474 (87.1%)	1566 (92.5%)	1127 (66.4%)	1231 (72.3%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.54		0.76	
Recurrence-free survival - No. patients with event	208 (12.3%)	113 (6.7%)	506 (29.8%)	399 (23.4%)
- No. patients without event	1485 (87.7%)	1580 (93.3%)	1191 (70.2%)	1303 (76.6%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.51		0.73	
Distant disease -free survival - No. patients with event	184 (10.9%)	99 (5.8%)	488 (28.8%)	399 (23.4%)
- No. patients without event	1508 (89.1%)	1594 (94.6%)	1209 (71.2%)	1303 (76.6%)
P-value versus Observation	< 0.0001		< 0.0001	
Hazard Ratio versus Observation	0.50		0.76	
Overall survival (death) - No. patients with event	40 (2.4%)	31 (1.8%)	350 (20.6%)	278 (16.3%)
- No. patients without event	1653 (97.6%)	1662 (98.2%)	1347 (79.4%)	1424 (83.7%)
P-value versus Observation	0.24		0.0005	
Hazard Ratio versus Observation	0.75		0.76	

*Co-primary endpoint of DFS of 1 year vs observation met the pre-defined statistical boundary
**Final analysis (including crossover of 52% of patients from the observation arm to Trastuzumab)
*** There is a discrepancy in the overall sample size due to a small number of patients who were randomized after the cut-off date for the 12-month median follow-up analysis

The efficacy results from the interim efficacy analysis crossed the protocol pre-specified statistical boundary for the comparison of 1-year of trastuzumab vs. observation. After a median follow-up of 12 months, the hazard ratio (HR) for disease free survival (DFS) was 0.54 (95% CI 0.44, 0.67) which translates into an absolute benefit, in terms of a 2-year disease-free survival rate, of 7.6 percentage points (85.8% versus 78.2%) in favour of the Trastuzumab arm.
A final analysis was performed after a median follow-up of 8 years, which showed that 1 year Trastuzumab treatment is associated with a 24% risk reduction compared to observation only (HR=0.76, 95% CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8 year disease free survival rate of 6.4 percentage points in favour of 1 year trastuzumab treatment.

In this final analysis, extending trastuzumab treatment for a duration of two years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years vs 1 year=0.99 (95% CI: 0.87, 1.13), p-value=0.90 and OS HR=0.98 (0.83, 1.15); p-value= 0.78]. The rate of asymptomatic cardiac dysfunction was increased in the 2-year treatment arm (8.1% versus 4.6% in the 1-year treatment arm). More patients experienced at least one grade 3 or 4 adverse event in the 2-year treatment arm (20.4%) compared with the 1-year treatment arm (16.3%).

In the joint analysis of the NSABP B-31 and NCCTG N9831 studies, early breast cancer was limited to women with operable breast cancer at high risk, defined as HER2-positive and axillary lymph node positive or HER2 positive and lymph node negative with high risk features (tumour size > 1 cm and ER negative or tumour size > 2 cm, regardless of hormonal status). Trastuzumab was administered in combination with paclitaxel, following AC chemotherapy. Paclitaxel was administered as follows:

- intravenous paclitaxel - 80 mg/m2 as a continuous IV infusion, given every week for 12 weeks, or
- intravenous paclitaxel - 175 mg/m2 as a continuous IV infusion, given every 3 weeks for 4 cycles (day 1 of each cycle).

Table 10 Summary of Efficacy results from the joint analysis studies NSABP B-31 and NCCTG N9831 at the time of the definitive DFS analysis*

Parameter	AC® ¨P (n=1679)	AC® ¨PH (n=1672)	p-value versus AC® ¨P	Hazard Ratio versus AC® ¨P (95% CI)
Disease-free survival No. patients with event (%) Distant	261 (15.5)	133 (8.0)	< 0.0001	0.48 (0.39, 0.59)
Recurrence No. patients with event (%)	193 (11.5)	96 (5.7)	< 0.0001	0.47 (0.37, 0.60)
Death (OS event): No. patients with event (%)	92 (5.5)	62 (3.7)	0.014	0.67 (0.48, 0.92)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: Trastuzumab
* at median duration of follow up of 1.8 years for the patients in the AC® P arm and 2.0 years for patients in the AC® PH arm
** p value for OS did not cross the pre-specified statistical boundary for comparison of AC® PH vs. AC® P
Source: Table 15 Clinical Study Report: Joint Analysis of B-31 and N9831, 04 February 2006, Genentech, Inc.

For the primary endpoint, DFS, the addition of trastuzumab to paclitaxel chemotherapy resulted in a 52% decrease in the risk of disease recurrence. The hazard ratio translates into an absolute benefit, in terms of a 3-year disease-free survival rate, of 11.8 percentage points (87.2% versus 75.4%) in favour of the AC® PH (trastuzumab) arm.

The pre-planned final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831 was performed when 707 deaths had occurred (median follow-up 8.3 years in the AC® P H group). Treatment with AC® P H resulted in a statistically significant improvement in OS compared with AC® P (stratified HR=0.64; 95% CI [0.55, 0.74]; log-rank p-value® 0.0001). At 8 years, the survival rate was estimated to be 86.9% in the AC® P H arm and 79.4% in the AC® P arm, an absolute benefit of 7.4% (95% CI 4.9%, 10.0%).

The final OS results from the joint analysis of studies NSABP B-31 and NCCTG N9831 are summarized in the following table:

Table 11 Final Overall Survival Analysis from the joint analysis of trials NSABP B-31 and NCCTG N9831

Parameter	AC® P (N=2032)	AC® PH (N=2031)	p-value versus AC® P	Hazard Ratio versus AC® P (95% CI)
Death (OS event): No. patients with event (%)	418 (20.6%)	289 (14.2%)	< 0.0001	0.64 (0.55, 0.74)

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; H: Trastuzumab
In the BCIRG 006 study, HER-2 positive, early breast cancer was limited to either lymph node positive or high risk node negative patients, defined as negative (pN0) lymph node involvement, and at least 1 of the following factors: tumour size greater than 2 cm, estrogen receptor and progesterone receptor negative, histologic and/or nuclear grade 2-3, or age < 35 years. Trastuzumab was administered either in combination with docetaxel, following AC chemotherapy (AC-DH) or in combination with docetaxel and carboplatin (DCarbH).

Docetaxel was administered as follows:

- intravenously (100 mg/m2 as an IV infusion over 1 hour) given every 3 weeks for 4 cycles (day 2 of first docetaxel cycle, then day 1 of each subsequent cycle), or
- intravenously (75 mg/m2 as an IV infusion over 1 hour) given every 3 weeks for 6 cycles (day 2 of cycle 1, then day 1 of each cycle).

Docetaxel therapy was followed by carboplatin (at target AUC = 6 mg/mL/min) administered by IV infusion over 30-60 minutes repeated every 3 weeks for a total of 6 cycles.
The efficacy results from the BCIRG 006 study are summarized in the following tables:

Table 12 Overview of Efficacy Analyses AC® D versus AC® DH (BCIRG 006 study)

Parameter	AC→D (N=1073)	AC→DH (N=1074)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival No. patients with event	195	134	< 0.0001	0.61 (0.49, 0.77)
Distant recurrence No. patients with event	144	95	< 0.0001	0.59 (0.46, 0.77)
Overall Survival (Death) No. patients with event	80	49	0.0024	0.58 (0.40, 0.83)

AC® D = doxorubicin plus cyclophosphamide, followed by docetaxel; AC® DH = doxorubicin plus cyclophosphamide, followed by docetaxel plus Trastuzumab; CI = confidence interval

Table 13 Overview of Efficacy Analyses AC® D versus DCarbH (BCIRG 006 study)

Parameter	AC→D (N=1073)	DCarbH (N=1075)	p-value versus AC→D (log-rank)	Hazard Ratio versus AC→D (95% CI)
Disease-free survival No. patients with event	195	145	0.0003	0.67 (0.54, 0.83)
Distant recurrence No. patients with event	144	103	0.0008	0.65 (0.50, 0.84)
Death (OS event) No. patients with event	80	56	0.0182	0.66 (0.47, 0.93)

AC® D = doxorubicin plus cyclophosphamide, followed by docetaxel; DCarbH = docetaxel, carboplatin and Trastuzumab; CI = confidence interval

In the BCIRG 006 study for the primary endpoint, DFS, the hazard ratio translates into an absolute benefit, in terms of a 3-year disease-free survival rate, of 5.8 percentage points (86.7% versus 80.9%) in favour of the AC® DH (trastuzumab) arm and 4.6 percentage points (85.5% versus 80.9%) in favour of the DCarbH (trastuzumab) arm compared to AC® D.
For the secondary endpoint overall survival, treatment with AC® DH reduced the risk of death by 42% when compared to AC® D (hazard ratio 0.58 [95% CI: 0.40, 0.83] p = 0.0024, log-rank test) and the risk of death was reduced by 34% for patients treated with DCarbH compared to patients treated with AC® D (hazard ratio 0.66 [95% CI: 0.47, 0.93], p = 0.0182). In the BCIRG 006 study at the second interim analysis, 185 randomized patients had died: 80 patients (7.5%) in the AC® D arm, 49 patients (4.6%) in the AC® DH arm, and 56 patients (5.2%) in the DCarbH arm. The median duration of follow-up was 2.9 years in the AC® D arm and 3.0 years in both the AC® DH and DCarbH arms.

In the neoadjuvant-adjuvant treatment setting, Trastuzumab was evaluated in two phase 3 trials.

Study MO16432, a multicenter randomised trial, was designed to investigate a total of 10 cycles of neoadjuvant chemotherapy [an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H] concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone, followed by adjuvant Trastuzumab for up to a total treatment duration of 1 year) in newly diagnosed locally advanced (Stage III) or inflammatory HER2 positive breast cancer patients. The clinical utility of concurrent administration of Trastuzumab with neoadjuvant chemotherapy including both an anthracycline and a taxane (AP+H followed by P+H, followed by CMF+H, followed by adjuvant trastuzumab, up to a total treatment duration of 1 year) as follow:

- Doxorubicin 60mg/m2 and paclitaxel 150 mg/m2, administered 3-weekly for 3 cycles, which was followed by
- Paclitaxel 175 mg/m2 administered 3-weekly for 4 cycles, which was followed by
- CMF on day 1 and 8 every 4 weeks for 3 cycles which was followed after surgery by
- additional cycles of adjuvant trastuzumab (to complete 1 year of treatment)

The study recruited patients with newly diagnosed locally advanced (Stage III) or inflammatory breast cancer. Patients with HER2+ tumours were randomised to receive either neoadjuvant chemotherapy concurrently with neoadjuvant-adjuvant trastuzumab, or neoadjuvant chemotherapy alone.

Table 14 Overview of Efficacy Analyses MO16432 study

Parameter	Chemo +Trastuzumab (n=115)	Chemo only (n=116)	
Event-free survival No. patients with event	46	59	Hazard Ratio (95% CI) 0.65 (0.44, 0.96) p=0.0275
Total pathological complete response* (95% CI)	40% (31.0, 49.6)	20.7% (13.7, 29.2)	P=0.0014
Overall survival No. patients with event	22	33	Hazard Ratio (95% CI)

* defined as absence of any invasive cancer both in the breast and axillary nodes

For the primary endpoint, EFS, the addition of trastuzumab to the neoadjuvant chemotherapy followed by adjuvant trastuzumab for a total duration of 52 weeks resulted in a 35% reduction in the risk of disease recurrence/progression. The hazard ratio translates into an absolute benefit, in terms of 3-year event-free survival rate estimates of 13 percentage points (65 % vs 52 %) in favour of the trastuzumab arm.

Metastatic Gastric Cancer
Trastuzumab has been investigated in one randomised, open-label phase III trial BO18255 in combination with chemotherapy versus chemotherapy alone.

Chemotherapy was administered as follows:

- capecitabine - 1000 mg/m2 orally twice daily for 14 days every 3 weeks for 6 cycles (evening of day 1 to morning of day 15 of each cycle)

or

- intravenous 5-fluorouracil - 800 mg/m2/day as a continuous i.v. infusion over 5 days, given every 3 weeks for 6 cycles (days 1 to 5 of each cycle)

Either of which was administered with:

- cisplatin - 80 mg/m2 every 3 weeks for 6 cycles on day 1 of each cycle.

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

Table 15 Summary of Efficacy (from study BO18255 study)

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

FP + H: Fluoropyrimidine/cisplatin + Trastuzumab
FP: Fluoropyrimidine/cisplatin
a Odds ratio

Patients were recruited to the trial who were previously untreated for HER2-positive inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-oesophageal junction not amenable to curative therapy. The primary endpoint was overall survival which was defined as the time from the date of randomization to the date of death from any cause. At the time of the analysis a total of 349 randomized patients had died: 182 patients (62.8 %) in the control arm and 167 patients (56.8 %) in the treatment arm. The majority of the deaths were due to events related to the underlying cancer.

Post-hoc subgroup analyses indicate that positive treatment effects are limited to targeting tumours with higher levels of HER2 protein (IHC 2+/FISH+ or IHC 3+). The median overall survival for the high HER2 expressing group was 11.8 months versus 16 months, HR 0.65 (95 % CI 0.51-0.83) and the median progression free survival was 5.5 months versus 7.6 months, HR 0.64 (95 % CI 0.51-0.79) for FP versus FP + H, respectively. For overall survival, the HR was 0.75 (95% CI 0.51-1.11) in the IHC 2+/FISH+ group and the HR was 0.58 (95% CI 0.41-0.81) in the IHC 3+/FISH+ group.

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

In an exploratory subgroup analysis performed in the BO18255 trial there was no apparent benefit on overall survival with the addition of trastuzumab in patients with ECOG PS 2 at baseline [HR 0.96 (95% CI 0.51-1.79)], non-measurable [HR 1.78 (95% CI 0.87-3.66)] and locally advanced disease [HR 1.20 (95% CI 0.29-4.97)].

PIVOTAL CLINICAL TRIAL
MYL-Her-3001
Efficacy
The pivotal confirmatory efficacy and safety study MYL-Her-3001 was designed to detect whether there are clinically meaningful differences between **CAN**HERA® and EU-approved Herceptin. The study included female patients with histologically confirmed diagnosis of breast cancer, and who had not received prior systemic therapy in the metastatic disease setting, and who had HER2 gene amplification as confirmed by fluorescent in situ hybridization (FISH), or HER2-overexpression by immunohistochemistry (defined as IHC3+, or IHC2+ with FISH confirmation). Enrolled patients should have had at least 1 metastatic target lesion. Before randomization, HER2 detection and tumor assessment were conducted independently at a central laboratory.

The demographic profile was similar in the **CAN**HERA® group versus the Herceptin group with respect to height, weight, race, and body surface area. With regards to age, the mean age was slightly lower in the Herceptin group compared with the **CAN**HERA® group (52.9 years vs. 54.3 years) and a slightly higher percentage of patients were <50 years of age in the Herceptin group compared with the **CAN**HERA® group (37.7% vs. 32.2%).

The results of the primary efficacy analysis are summarized in Table 6. At Week 24, the ORR in the **CAN**HERA® group was 69.6% and 64.0% in the Herceptin group. The ratio of the ORRs of **CAN**HERA®: Herceptin was 1.09 with a 90% CI of (0.974, 1.211). As this CI is entirely within the pre-defined equivalence boundaries of 0.81 and 1.24, therapeutic equivalence of **CAN**HERA® and Herceptin was statistically confirmed in this study.

Table 16: Best Overall Response Rate (ORR) at Week 24 and Ratio of Best ORR (ITT1 Population; Study MYL-Her-3001)

Response		CANHERA + Taxane (N = 230)	Herceptin + Taxane (N = 228)
Complete response (CR)	n (%)	3 (1.3)	0 (0.0)
Partial response (PR)	n (%)	157 (68.3)	146 (64.0)
Stable disease (SD)	n (%)	48 (20.9)	49 (21.5)
Progressive disease (PD)	n (%)	9 (3.9)	20 (8.8)
N/A	n (%)	13 (5.7)	13 (5.7)
Overall response rate	n (%)	160 (69.6)	146 (64.0)
90% CI		(64.57, 74.56)	(58.81, 69.26)
95% CI		(63.62, 75.51)	(57.81, 70.26)
Ratio CANHERA:Herceptin		1.09	
90% CI		(0.974, 1.211)	
95% CI		(0.954, 1.237)	

CI: confidence interval, ITT: intent-to-treat, N: number of patients in treatment arm, n: number of patients with data available, N/A: not applicable
Percentages are based on the number of patients in the ITT1 population.

Objective response was defined as confirmed CR or PR according to RECIST Version 1.1 based on central tumor evaluation. Equivalence was declared if the 90% CI of the ratio is completely within the equivalence range of (0.81, 1.24). The 90% and 95% CI was calculated on the natural log scale and back transformed using the exponential function to the original scale.

The equivalence of both treatments was also evaluated using the 2-sided 95% CI for the difference in best ORRs at Week 24 being entirely within the equivalence range of (-15%, 15%). The results of Study MYL-Her-3001 showed that the difference in best ORR between both treatment arms (**CAN**HERA® minus Herceptin) was 5.5% with a 95% CI of (-3.08%, 14.04%). As this CI is entirely within the pre-defined equivalence boundaries of -15% and 15%, therapeutic equivalence of **CAN**HERA® and Herceptin was statistically confirmed. The results of these analyses are summarized in Table 17.

Table 17: Difference of Best Overall Response Rate (ORR) at Week 24 (ITT1 Population; Study MYL-Her-3001)

Response	CANHERA + Taxane (N = 230)	Herceptin + Taxane (N = 228)
Overall response rate, n (%)	160 (69.6)	146 (64.0)
90% CI	(64.57, 74.56)	(58.81, 69.26)
95% CI	(63.62, 75.51)	(57.81, 70.26)
Difference CANHERA:Herceptin (%)	5.5	
90% CI	(-1.70, 12.69)	
95% CI	(-3.08, 14.04)	

CI: confidence interval, CR: complete response, ITT: intent-to-treat, N: number of patients in treatment arm, n: number of patients with data available, PR: partial response

Percentages are based on the number of patients in the ITT1 population.

Objective response was defined as confirmed CR or PR according to RECIST Version 1.1 based on central tumor evaluation. Equivalence was declared if the 95% CI of the difference is completely within the equivalence range of (-15%, 15%).

Time to Tumor Progression
Median time to tumor progression (Kaplan-Meier estimates) was 11.1 months in both treatment arms.

Progression-Free Survival
The median time for Progression-Free Survival (Kaplan-Meier estimates) was 11.1 months in both treatment arms.
Overall Survival
Overall survival (OS) was defined as the time from randomization to date of death due to any cause. Until Week 48, 205 patients (89.1%) survived in the CANHERA group compared to 194 patients (85.1%) in the Herceptin group. According to the log-rank test, the survival curves for both treatment groups were not statistically significantly different (p = 0.131). The Kaplan-Meier estimates for OS, the median was not reached due to the relatively small number of patients in the analysis population who died prior to Week 24 and Week 48.

Adverse Events
The most frequently reported TEAEs were alopecia (56.4%), neutropenia (56.0%), and diarrhea (20.9%). The majority of TEAEs were Grade 1 or Grade 2 in severity. Overall, 324 patients (65.7%) experienced TEAEs of Grade 3 or greater intensity, and the incidence of these events was similar between treatment arms (65.6% in the MYL-1401O arm and 65.9% in the Herceptin arm). The most frequently reported TEAEs of Grade 3 or greater intensity overall were neutropenia (45.2%) and leukopenia (14.2%), which occurred in similar frequencies between treatment arms.

Immunogenicity
In the neoadjuvant-adjuvant EBC study (Bo22227), at a median follow-up exceeding 70 months, 10.1% (30/296) of patients treated with trastuzumab IV developed antibodies against trastuzumab. Neutralizing anti-trastuzumab antibodies were detected in postbaseline samples in 2 of 30 patients in the Herceptin IV arm.

INCOMPATIBILITIES
CANHERA® 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
Please refer to carton/label.

STORAGE AND HANDLING INFORMATION
Store vials at 2°C to 8°C prior to reconstitution.
Store away from light.

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 24 hours at 2°C to 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.

440 mg/150 mg (Multi-dose use vials)
Reconstituted solutions made with bacteriostatic water for injection, as supplied, are stable (physico-chemically and microbiologically) for 28 days, when refrigerated at 2°C to 8°C. The reconstituted solution is suitable for multiple uses, as it contains preservative. Discard any remaining reconstituted solution after 28 days. Do not freeze the reconstituted solution.

Shelf-life of the solution for infusion containing the reconstituted product
150 mg (single-dose and multi-dose use vials) and 440 mg (multi-dose use vials)
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 **CAN**HERA® infusion solution should be used immediately, unless reconstitution and dilution have taken place under aseptic conditions. If reconstitution and dilution have taken place under aseptic conditions, the infusion solution can be stored up to 24 hours when refrigerated at 2°C to 8°C.

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 18 Reconstitution Details of 150 mg (Single- and Multi-dose Use) and 440 mg Vials (Multi-dose Use)

Type of Vial	Reconstitution	Trastuzumab mg/mL	pH
150 mg (single-dose)	7.2 mL of sterile water for injection*	~21	~6.0
150 mg (multi-dose) (containing 1.1% benzyl alcohol)	7.2 mL of BWFI	~21	~6.0
440 mg (multi-dose) (containing 1.1% benzyl alcohol)	20 mL of BWFI	~21	~6.0

BWFI: bacteriostatic water for injection.
*Not supplied

- During reconstitution, handle **CAN**HERA® carefully. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of **CAN**HERA® 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 lyophilized **CAN**HERA®, using a sterile syringe. Direct the stream into the lyophilized cake.
2) To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.

Instructions for reconstitution-150 mg vial (multi-dose vial)
1) Slowly inject 7.2 mL of bacteriostatic water for injection into the vial containing the lyophilized **CAN**HERA®, using a sterile syringe. Direct the stream into the lyophilized cake.
2) To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.

Instructions for reconstitution-440 mg vial (multi-dose vial)
1) Slowly inject 20 mL of bacteriostatic water for injection into the vial containing the lyophilized **CAN**HERA®, using a sterile syringe. Direct the stream into the lyophilized cake.
2) To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.
Slight foaming of the product may be seen upon reconstitution; this is not unusual. The vial should be allowed to stand undisturbed for approximately 5 minutes. Reconstituted **CAN**HERA® is a colourless to pale yellow, transparent solution. No particles should be visible.

Instructions for dilution:
Determine the volume of **CAN**HERA® solution required:

- Based on a loading dose of 4 mg **CAN**HERA®/kg, or a subsequent weekly dose of 2 mg **CAN**HERA®/kg:

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

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

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

- 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 CANHERA®**(Single-dose vial)**
CANHERA® 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.

150 mg CANHERA®**(Multi-dose vial)**
CANHERA® 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.

The diluent BWFI is filled in 15 mL type I glass vial closed with a chlorobutyl rubber stopper and sealed with 20 MM aluminum seal.

The 150 mg pack is provided with total 10 mL bacteriostatic water for injection (containing 1.1% benzyl alcohol as preservative), of which 7.2 mL is to be used for reconstitution.
440 mg CANHERA® **(Multi-dose vial)**
CANHERA® finished product 440 mg is filled in 50 mL USP type 1 glass vial closed with a chlorobutyl rubber stopper and sealed with 20 MM blue flip-off seal.

The diluent BWFI is filled in 20 mL type I glass vial closed with a chlorobutyl rubber stopper and sealed with 20 MM aluminum seal.

The 440 mg pack is provided with total 20 mL bacteriostatic water for injection (containing 1.1% benzyl alcohol as preservative) for reconstitution.

Not all presentations may be available locally

Manufactured by: **Biocon Biologics India Limited**
Block No. B1, B2, Q13 of Q1 and W20 & Unit S18, 1st floor, Block B4, Special Economic Zone,
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