4279

Rx

Trastuzumab for Injection (r-DNA Origin)

Biocon

CANMAb™ कैनमैब 150 mg / 440 mg

*In vitro, preclinical and clinical studies have demonstrated similarity between **CANMAb™** and the reference trastuzumab product. Hence, publicly available information on the reference trastuzumab product is included here. In this document, when data on the reference trastuzumab product is being referred to, the term "trastuzumab" is used. Where information or instructions specific to **CANMAb™** is presented, the term "**CANMAb™**" is used.*

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 **CANMAb™** concentrate contains 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.
CANMAb™ a white to pale yellow lyophilised powder.

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. 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[1]
ATC code: L01XC03[2]

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[3].
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[3].
Studies showed that amplification or overexpression of HER2 correlates with shorter disease-free survival[3].
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[1].
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[1].

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 **CANMAb™** was similar to that of trastuzumab after single- and multi–dose intravenous infusions.
The following data for pharmacokinetics in various patient populations treated with trastuzumab is summarized from publicly available information.

<u>Breast Cancer</u>
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[4].

Table 1: Trastuzumab Steady-State Pharmacokinetic Parameters[4]

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[1].
The pharmacokinetics do not appear to be affected by concomitant anthracycline/cyclophosphamide or paclitaxel chemotherapy, or concomitant anastrozole[1].

<u>Advanced Gastric Cancer</u>
A two compartment nonlinear population pharmacokinetic model was used to estimate the steady state pharmacokinetics in advanced 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[1].

Pharmacokinetics in Special Populations

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[1,3,4] (see **Dose and Method of Administration**).

CLINICAL EFFICACY

The clinical efficacy of **CANMAb™** 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 **CANMAb™** and trastuzumab with regard to overall response rate, clinical benefit rate and progression-free survival rate (at 24 weeks) in MBC.
The following data for clinical efficacy in various patient populations treated with trastuzumab is summarized from publicly available information.

Metastatic Breast Cancer (MBC)

The following regimens were evaluated in clinical studies with trastuzumab.

- Trastuzumab monotherapy (in MBC patients with tumours overexpressing HER2 who had failed ≥1 chemotherapy regimens for metastatic disease).
- First-line combination therapy:
  - Trastuzumab with paclitaxel (in MBC patients with tumours overexpressing HER2 who had previously received anthracycline-based adjuvant chemotherapy)
  - Trastuzumab with an anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC; in MBC patients with tumours overexpressing HER2 who had never received an anthracycline)
  - Trastuzumab with docetaxel (in HER2-positive MBC patients)
  - Trastuzumab with anastrozole (in hormone-receptor-positive MBC patients with tumours overexpressing HER2).

The following results were obtained in trials conducted with trastuzumab:

- Trastuzumab monotherapy (second- or third-line) produced an objective response rate of 15%, and a median duration of survival of 13 months[5]; in women with MBC overexpressing HER2.

First-line combination therapy:

- Trastuzumab 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)[6].
- Trastuzumab 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)[6].
- Trastuzumab 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)[7].
- Trastuzumab and anastrozole in HER2-overexpressing, hormone-receptor- (i.e., oestrogen-receptor and/or progesterone-receptor)-positive MBC patients. In the trastuzumab 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-containing regimen. Though there was no statistically significant difference; 52% of trastuzumab plus anastrozole patients survived for at least 2 years; versus 45% of the anastrozole-alone patients[8].

Early Breast Cancer (EBC)

Neoadjuvant and adjuvant trastuzumab 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 plus chemotherapy followed by adjuvant trastuzumab for 1 year or the same neoadjuvant chemotherapy alone. 5-year event-free survival was achieved by more patients in the trastuzumab 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)[9].

A separate trial compared 2-year adjuvant trastuzumab treatment with 1-year adjuvant trastuzumab 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, 1-year trastuzumab and observation. Patients received trastuzumab 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 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 therapy, 1-year trastuzumab 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)[10].

Long-term implications of adjuvant trastuzumab 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. At a median follow-up of 3.9 years, there was more statistically significant reduction in disease-free survival event rate in the trastuzumab group compared to the control group (p<0.001)[11].

A randomized, multicentre, phase 3 study assessed the efficacy and safety of a new non-anthracycline regimen with trastuzumab 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 (AC-T plus trastuzumab) or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). The estimated disease-free survival rate at 5 years was better in the trastuzumab groups (84% in AC-T plus trastuzumab, 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 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)[12].

Advanced Gastric Cancer

A randomised, open-label, multicentre, phase 3 study assessed the effect of first-line trastuzumab 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 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 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[13].

Immunogenicity

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

PRECLINICAL SAFETY DATA

Nonclinical studies (conventional toxicity studies) on **CANMAb™** did not indicate any special hazard for humans. During conventional single- and repeat-dose toxicity studies of **CANMAb™** 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.

INDICATIONS

Metastatic Breast Cancer (MBC)

CANMAb™ is indicated for the treatment of metastatic breast cancer patients who have human epidermal growth factor receptor 2- (HER2)-overexpressing tumours.

Early Breast Cancer (EBC)

CANMAb™ is indicated for the treatment of adult patients with HER2 positive early breast cancer.
CANMAb™ should only be used in MBC or EBC patients who have tumours with either overexpression of HER2, or HER2 gene amplification.

Metastatic Gastric Cancer (MGC)

CANMAb™ 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.
CANMAb™ should be used in only those MGC patients whose tumours overexpress HER2, as defined by:

- IHC2+ plus a confirmatory silver in situ hybridisation (SISH) or fluorescence in situ hybridisation (FISH) result, OR
- IHC 3+ result.

DOSE AND METHOD OF ADMINISTRATION

Before starting **CANMAb™** treatment, HER2 testing is mandatory.

- Administer **CANMAb™** as intravenous infusion.
- **CANMAb™** 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 **CANMAb™** 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 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.

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[1,3,4].
Children
The safety and efficacy of trastuzumab has not been established in paediatric patients (below 18 years of age)[1]. **CANMAb™** should not be used in these patients.

CONTRAINDICATIONS

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

See section **Composition** for a list of components of **CANMAb™.**

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

WARNINGS AND PRECAUTIONS

General
Initiate **CANMAb™** 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 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 and those who did not. The risk of neutropenia may be slightly increased when trastuzumab is administered with docetaxel following anthracycline therapy[1].

Infusion-related reactions
Serious infusion-related reactions to trastuzumab infusion have been reported; and include dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, hypertension, supraventricular tachyarrhythmia, anaphylaxis, urticaria, angioedema and respiratory distress. The majority of these events occur during or within 2.5 hours of the start of the first infusion. 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[1,3]. 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. Supportive therapy, such as oxygen, epinephrine, antihistamine, bronchodilators, beta-agonists and corticosteroids, has been successfully used to treat serious reactions[1,3] (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 infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated trastuzumab infusions, others had recurrent severe infusion reactions despite pre-medications[1,3].

Pulmonary toxicity
Severe pulmonary events have been reported with trastuzumab, 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[1,3] (see **Contraindication**). Exercise caution for pneumonitis, especially in patients being treated concomitantly with taxanes[1,3].

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 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)[1,3].
Since the half-life of trastuzumab is long, it may persist in the circulation for up to 27 weeks after stopping treatment. 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 27 weeks after stopping treatment, and monitor cardiac function carefully if anthracyclines are used. If left ventricular function continues to decrease, but patients remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of therapy has been seen. Trastuzumab and anthracycline should not be given concurrently in the adjuvant treatment setting (early breast cancer) or metastatic breast cancer setting. In patients with early breast cancer 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/m^2 or epirubicin 360 mg/m^2). 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[1,3].
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[1,3].
No prospective study has been done on the safety of continuing or resuming trastuzumab 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 treatment continued on therapy with trastuzumab without further clinical cardiac events[1,3].
In a global early breast cancer trial[1] with trastuzumab, patients with the following conditions were excluded:

- History of myocardial infarction
- Angina pectoris requiring medical treatment
- Clinically significant cardiac valvular disease
- History of existing cardiac heart failure (NYHA II –IV)
- Other cardiomyopathy, cardiac arrhythmia requiring medical treatment

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

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Rx

Trastuzumab for Injection (r-DNA Origin)

Biocon

CANMAb™ कैनमैब 150 mg / 440 mg

- Poorly controlled hypertension
- LVEF <55%
- hemodynamic effective pericardial effusion

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

Benzyl alcohol
Benzyl alcohol (1.1%) is used as a preservative in bacteriostatic water for injection in the 150 mg and 440 mg **CANMAb™** multidose vials. If a patient is known to be hypersensitive to benzyl alcohol, reconstitute **CANMAb™** with water for injection, and use only one dose per **CANMAb™** vial. Discard any unused portion[3].

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 revealed no evidence of impaired fertility or harm to the foetus[1].
Avoid administering **CANMAb™** 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[1,3].
Advise women of childbearing potential to use effective contraception during treatment with **CANMAb™** 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 **CANMAb™** 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[1].
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 **CANMAb™** 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 **CANMAb™** therapy and for 7 months after the last dose[1].
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[1].

Effects on Ability to Drive and Use Machines

Trastuzumab has no or negligible influence on the ability to drive or use machines. Patients should be advised not to drive and use machines if they are experiencing infusion-related symptoms; until the symptoms abate[3].

DRUG INTERACTIONS

Formal drug interaction studies with trastuzumab have not been performed in humans. In clinical trials of trastuzumab, 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-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The mean serum trough concentration of trastuzumab was consistently elevated approximately 1.5-fold, when administered in combination with paclitaxel as compared to trough concentrations of trastuzumab when administered in combination with an anthracycline and cyclophosphamide. 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[1].

UNDESIRABLE EFFECTS

The following undesirable effects are based on publicly available information categorized on the basis of frequency of occurrence of adverse reactions in different clinical trials and post–marketing information for trastuzumab.

Very common (≥1/10): Tremor, blood pressure decreased, blood pressure increased, heart beat irregular, palpitation, cardiac flutter, lip swelling, swelling face, muscle tightness (adverse reactions reported largely in association with infusion-related reactions); ejection fraction decreased (observed with combination therapy following anthracyclines and combined with taxanes); wheezing (adverse reactions reported in association with a fatal outcome and infusion-related reactions); dyspnoea (adverse reactions reported in association with a fatal outcome); infection, nasopharyngitis, febrile neutropenia, anaemia, neutropenia, leukopenia, thrombocytopenia, weight decreased/weight loss, anorexia, weight increased, decreased appetite, insomnia, dizziness, headache, paraesthesia, hypoaesthesia, dysgeusia, conjunctivitis, lacrimation increased, lymphoedema, hot flush, cough, epistaxis, rhinorrhoea, oropharyngeal pain, diarrhoea, vomiting, nausea, abdominal pain, dyspepsia, constipation, stomatitis, erythema, rash, alopecia, nail disorder, Palmar-plantar erythrodysaesthesia syndrome, arthralgia, myalgia, asthenia, chest pain, chills, fatigue, influenza–like symptoms, infusion-related reaction, pain, pyrexia, mucosal inflammation, peripheral oedema, nail toxicity[1,3].

Common (≥1/100 to <1/10): Cardiac failure (congestive), pneumonia, pleural effusion (adverse reactions reported in association with a fatal outcome); supraventricular tachyarrhythmia, hypotension (adverse reactions reported in association with a fatal outcome and infusion-related reactions); neutropenic sepsis, cystitis, herpes zoster, influenza, sinusitis, skin infection, rhinitis, upper respiratory tract infection, urinary tract infection, erysipelas, cellulitis, pharyngitis, hypersensitivity, anxiety, depression, thinking abnormal, peripheral neuropathy, hypertonia, somnolence, ataxia, dry eye, cardiomyopathy, hypertension, vasodilatation, asthma, lung disorder, pancreatitis, haemorrhoids, dry mouth, hepatocellular injury, hepatitis, liver tenderness, acne, dry skin, ecchymosis, hyperhydrosis, maculopapular rash, pruritus, onychoclasis, dermatitis, arthritis, back pain, bone pain, muscle spasms, neck pain, pain in extremity, renal disorder, breast inflammation/mastitis, malaise, oedema, contusion[1,3].

Uncommon (≥1/1,000 to <1/100): Sepsis, deafness, pericardial effusion, urticaria[1,3].

Rare (≥1/10,000 to <1/1,000): Paresis, pneumonitis, jaundice[1,3].

Not known (cannot be estimated from the available data): Anaphylactic reaction, anaphylactic shock, pulmonary fibrosis, respiratory distress, respiratory failure, lung infiltration, acute pulmonary oedema, acute respiratory distress syndrome, bronchospasm, hypoxia, oxygen saturation decreased (adverse reactions reported in association with a fatal outcome); malignant neoplasm progression, neoplasm progression, hypoprothrombinaemia, hyperkalaemia, brain oedema, papilledema, retinal haemorrhage, cardiogenic shock, pericarditis, bradycardia, gallop rhythm present, laryngeal oedema, pharyngolaryngeal pain, pulmonary hypertension, Herpes simplex, hypokalaemia, dysphagia, accidental injury, thrombosis/embolism, sudden death, autoimmune thyroiditis, flu syndrome, allergic reaction, orthopnoea, pulmonary oedema, interstitial lung disease, hepatic failure, angioedema, dermatitis, urticaria, glomerulonephritis membranous, glomerulonephropathy, renal failure, oligohydramnios, renal hypoplasia, pulmonary hypoplasia[1,3].

The most serious and/or common adverse reactions reported with trastuzumab are: cardiac dysfunction, infusion-related reactions and hypersensitivity, haematological toxicity, infections and pulmonary toxicity[1,3].

Cardiac dysfunction

Congestive heart failure (NYHA II-IV) is a common adverse reaction observed with trastuzumab and has been associated with fatal outcome. Signs and symptoms of cardiac dysfunction observed in patients treated with trastuzumab include: dyspnoea, orthopnoea, increased cough, pulmonary oedema, S3 gallop or reduced ventricular ejection fraction[1,3] (see **Warnings and Precautions**).

Infusion-related reactions (IRRs) and Hypersensitivity

The following infusion-related reactions (IRRs) were seen in all trastuzumab trials: chills and/or fever, dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress (see **Warning and Precautions)**. Majority of IRRs are mild to moderate in intensity; usually occur during first, second or third infusion and lessen in frequency in subsequent infusions. Anaphylactoid reactions have been observed with trastuzumab in isolated cases[1,3].

Haematological toxicity

Febrile neutropenia is the most common haematological toxicity observed with trastuzumab. The common haematological toxicity are: anaemia, leukopenia, thrombocytopenia and neutropenia. When trastuzumab is administered with docetaxel following anthracycline therapy, the risk of neutropenia may be slightly increased[1,3].

Infections

In the adjuvant setting, the most common sites of infections include upper respiratory tract, skin and urinary tract[1,3].

Pulmonary toxicity

The following pulmonary adverse reactions were observed with trastuzumab: pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency[1,3].

OVERDOSE

There is no information on overdose from human clinical trials. Single doses greater than 10 mg/kg of trastuzumab alone have not been administered in the clinical trials. Doses up to this level were well tolerated[1,3].

INCOMPATIBILITIES

CANMAb™ 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 2-8°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 48 hours at 2-8°C. From the perspective of microbiological safety, the **CANMAb™** 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 48 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 2: 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)	7.2 mL of BWFI (containing 1.1% benzyl alcohol)	~21	~6.0
440 mg (multi-dose)	20 mL of BWFI (containing 1.1% benzyl alcohol)	~21	~6.0

BWFI: bacteriostatic water for injection.
*Not supplied

- During reconstitution, handle **CANMAb™** carefully. Causing excessive foaming during reconstitution or shaking the reconstituted solution may result in problems with the amount of **CANMAb™** that can be withdrawn from the vial.
- Do not freeze the reconstituted solution.

<u>*Instructions for reconstitution-150 mg vial (single -dose vial)*</u>
1) Slowly inject 7.2 mL of sterile water for injection into the vial containing the lyophilised **CANMAb™**, using a sterile syringe. Direct the stream into the lyophilised cake.
2) To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.

<u>*Instructions for reconstitution-150 mg vial (multi-dose vial)*</u>
1) Slowly inject 7.2 mL of bacteriostatic water for injection into the vial containing the lyophilised **CANMAb™**, using a sterile syringe. Direct the stream into the lyophilised cake.
2) To aid reconstitution, the vial should be swirled gently. DO NOT SHAKE.

<u>*Instructions for reconstitution-440 mg vial (multi-dose vial)*</u>
1) Slowly inject 20 mL of bacteriostatic water for injection into the vial containing the lyophilised **CANMAb™**, using a sterile syringe. Direct the stream into the lyophilised 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 **CANMAb™** is a colourless to pale yellow, transparent solution. No particles should be visible.

<u>*Instructions for dilution:*</u>
Determine the volume of **CANMAb™** solution required:

- Based on a loading dose of 4 mg **CANMAb™**/kg, or a subsequent weekly dose of 2 mg **CANMAb™**/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 **CANMAb™**/kg, or a subsequent 3–weekly dose of 6 mg **CANMAb™**/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 CANMAb™ (Single-dose vial)
CANMAb™ finished product 150 mg is filled in 15 mL USP type 1 glass vial, closed with a halobutyl rubber stopper and sealed with 20 MM blue flip-off seal.

150 mg CANMAb™ (Multi-dose vial)
CANMAb™ finished product 150 mg is filled in 15 mL USP type 1 glass vial, closed with a halo butyl rubber stopper and sealed with 20 MM blue flip-off 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 CANMAb™ (Multi-dose vial)
CANMAb™ finished product 440 mg is filled in 50 mL USP type 1 glass vial closed with a halo butyl rubber stopper and sealed with 20 MM blue flip-off seal. The 440 mg pack is provided with total 20 mL bacteriostatic water for injection (containing 1.1% benzyl alcohol as preservative) for reconstitution.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com**.

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