Trastuget®

(Trastuzumab)

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440mg/vial

Multi-use Vial, For IV Infusion, Lyophilized Powder

DESCRIPTION

Trastuget (Trastuzumab) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Trastuget (Trastuzumab) is available for administration as:

Trastuget for IV Infusion 440mg
Each vial contains:
Trastuzumab (rDNA origin)…440mg

CLINICAL PHARMACOLOGY

Mechanism of Action

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Trastuzumab products have been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Trastuzumab products are mediators of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, trastuzumab product-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Pharmacodynamics

Cardiac Electrophysiology

The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors.

Pharmacokinetics

The pharmacokinetics of trastuzumab were evaluated in a pooled population pharmacokinetic (PK) model analysis of 1,582 subjects with primarily breast cancer and metastatic gastric cancer (MGC) receiving intravenous trastuzumab. Total trastuzumab clearance increases with decreasing concentrations due to parallel linear and non-linear elimination pathways.

Although the average trastuzumab exposure was higher following the first cycle in breast cancer patients receiving the three-weekly schedule compared to the weekly schedule of trastuzumab, the average steady-state exposure was essentially the same at both dosages. The average trastuzumab exposure following the first cycle and at steady state as well as the time to steady state was higher in breast cancer patients compared to MGC patients at the same dosage; however, the reason for this exposure difference is unknown. Additional predicted trastuzumab exposure and PK parameters following the first trastuzumab cycle and at steady state exposure are described in Tables below, respectively.

Population PK based simulations indicate that following discontinuation of trastuzumab, concentrations in at least 95% of breast cancer patients and MGC patients will decrease to approximately 3% of the population predicted steady-state trough serum concentration (approximately 97% washout) by 7 months.

Population Predicted Cycle 1 PK Exposures (Median with 5th to 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	C_{min} (µg/mL)	C_{max} (µg/mL)	$AUC_{0\text{-}21days}$ (µg.day/mL)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	29.4 (5.8 to 59.5)	178 (117 to 291)	1373 (736 to 2245)
	MGC	274	23.1 (6.1 to 50.3)	132 (84.2 to 225)	1109 (588 to 1938)
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	37.7 (12.3 to 70.9)	88.3 (58 to 144)	1066 (586 to 1754)

Population Predicted Steady State PK Exposures (Median with 5th to 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	$C_{min,ss}$[a] (µg/mL)	$C_{max,ss}$[b] (µg/mL)	AUCss, 0-21days (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	47.4 (5 to 115)	179 (107 to 309)	1794 (673 to 3618)	12	0.173 to 0.283
	MGC	274	32.9 (6.1 to 88.9)	131 (72.5 to 251)	1338 (557 to 2875)	9	0.189 to 0.337
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	66.1 (14.9 to 142)	109 (51.0 to 209)	1765 (647 to 3578)	12	0.201 to 0.244

a) Steady-state trough serum concentration of Trastuzumab
b) Maximum steady-state serum concentration of Trastuzumab

Special Population

Based on a population pharmacokinetic analysis, no clinically significant differences were observed in the pharmacokinetics of trastuzumab based on age (<65 (n = 1294); ≥65 (n = 288)), race (Asian (n = 264); non-Asian (n = 1324)) and renal impairment (mild (creatinine clearance [CLcr] 60 to 90 mL/min) (n = 636) or moderate (CLcr 30 to 60 mL/min) (n = 133)). The pharmacokinetics of trastuzumab products in patients with severe renal impairment, end-stage renal disease with or without hemodialysis, or hepatic impairment is unknown.

THERAPEUTIC INDICATIONS

Adjuvant Breast Cancer

Trastuget (Trastuzumab) is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature) breast cancer:

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel.
- as part of a treatment regimen with docetaxel and carboplatin.
- as a single agent following multi-modality anthracycline based therapy.

Metastatic Breast Cancer

Trastuget (Trastuzumab) is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Metastatic Gastric Cancer

Trastuget (Trastuzumab) is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

DOSAGE & ADMINISTRATION

Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency.

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

Recommended Doses and Schedules

- Before starting Trastuget (Trastuzumab) treatment, HER2 testing is mandatory.
- Administer Trastuget (Trastuzumab) as intravenous infusion.
- Do not administer as an intravenous push or bolus. Do not mix Trastuget (Trastuzumab) with other drugs.
- Do not substitute Trastuget (Trastuzumab) for or with ado-trastuzumab emtansine.
- 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 Trastuget (Trastuzumab) 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. 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.

Adjuvant Treatment, Breast Cancer

Administer according to one of the following doses and schedules for a total of 52 weeks of Trastuget (Trastuzumab) therapy:

During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

- Initial dose of 4mg/kg as an intravenous infusion over 90 minutes then at 2mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Trastuget (Trastuzumab), administer Trastuget (Trastuzumab) at 6mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline based chemotherapy regimens:

- Initial dose at 8mg/kg as an intravenous infusion over 90 minutes.
- Subsequent doses at 6mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks.
- Extending adjuvant treatment.

Metastatic Treatment, Breast Cancer

- Administer Trastuget (Trastuzumab), alone or in combination with paclitaxel, at an initial dose of 4mg/kg as a 90-minute intravenous infusion followed by subsequent once weekly doses of 2mg/kg as 30-minute intravenous infusions until disease progression.

Metastatic Gastric Cancer

- Administer Trastuget (Trastuzumab) at an initial dose of 8mg/kg as a 90 minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks until disease progression.

Important Dosing Considerations

If the patient has missed a dose of Trastuget (Trastuzumab) by one week or less, then the usual maintenance dose (weekly schedule: 2mg/kg; three-weekly schedule: 6mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent Trastuget (Trastuzumab) maintenance doses should 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 Trastuget (Trastuzumab) by more than one week, a re-loading dose of Trastuget (Trastuzumab) should be administered over approximately 90 minutes (weekly schedule: 4mg/kg; three-weekly schedule: 8mg/kg) as soon as possible. Subsequent Trastuget (Trastuzumab) maintenance doses (weekly schedule: 2mg/kg; three-weekly schedule 6mg/kg) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

Infusion Reactions

- Decrease the rate of infusion for mild or moderate infusion reactions.
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension.
- Discontinue Trastuget (Trastuzumab) for severe or life-threatening infusion reactions.

Cardiomyopathy

Assess left ventricular ejection fraction (LVEF) prior to initiation of Trastuget (Trastuzumab) and at regular intervals during treatment. Withhold Trastuget (Trastuzumab) dosing for at least 4 weeks for either of the following:

- ≥16% absolute decrease in LVEF from pre-treatment values.
- LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.

Trastuget (Trastuzumab) may be resumed if, within 4 to 8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%.

Permanently discontinue Trastuget (Trastuzumab) for a persistent (>8 weeks) LVEF decline or for suspension of Trastuget (Trastuzumab) dosing on more than 3 occasions for cardiomyopathy.

Preparation for Administration

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Trastuget (Trastuzumab).

<u>440mg multiple-dose vial</u>

Reconstitution

Reconstitute each 440mg vial of Trastuget with 20mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21mg/mL trastuzumab.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20mL of BWFI into the vial containing the lyophilized Trastuget. The stream of diluent should be directed into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. DO NOT SHAKE.
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.

- Store reconstituted Trastuget at 2°C−8°C; discard unused Trastuget after 28 days. If Trastuget is reconstituted with Sterile Water for Injection without preservative, use immediately and discard any unused portion.

Dilution
- Determine the dose (mg) of Trastuget.
- Calculate the volume of the 21mg/mL reconstituted Trastuget solution needed.
- Withdraw this amount from the vial and add it to an infusion bag containing 250mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.
- The solution of Trastuget for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. Discard after 24 hours. This storage time is additional to the time allowed for the reconstituted vials. Do not freeze.

ADVERSE REACTIONS
The following adverse reactions have been report with the use of Trastuzumab:
Cardiomyopathy, infusion reactions, embryo-fetal toxicity, pulmonary toxicity, exacerbation of chemotherapy-induced neutropenia.

The most common adverse reactions in patients receiving trastuzumab in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of trastuzumab treatment include congestive heart failure (CHF), significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity.
In the metastatic gastric cancer setting, the most common adverse reactions arm were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common adverse reactions which resulted in discontinuation of treatment on the trastuzumab containing arm in the absence of disease progression were infection, diarrhea, and febrile neutropenia.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Trastuzumab is contraindicated in:
- Patients with hypersensitivity to trastuzumab, murine proteins and to any excipient of the product.
- Severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

PRECAUTIONS

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, AND PULMONARY TOXICITY
Cardiomyopathy
Trastuzumab administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens. Evaluate left ventricular function in all patients prior to and during treatment with trastuzumab. Discontinue trastuzumab treatment in patients receiving adjuvant therapy and withhold trastuzumab in patients with metastatic disease for clinically significant decrease in left ventricular function.

Infusion Reactions; Pulmonary Toxicity
Trastuzumab administration can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of trastuzumab administration. Interrupt trastuzumab infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue trastuzumab for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Embryo-Fetal Toxicity
Exposure to trastuzumab during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception.

Cardiomyopathy
Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).
There is a 4 to 6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving trastuzumab as a single agent or in combination therapy compared with those not receiving trastuzumab. The highest absolute incidence occurs when a trastuzumab is administered with an anthracycline.
Patients who receive anthracycline after stopping trastuzumab may also be at increased risk of cardiac dysfunction.

Cardiac Monitoring
Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:
- Baseline LVEF measurement immediately prior to initiation of trastuzumab.
- LVEF measurements every 3 months during and upon completion of trastuzumab.
- Repeat LVEF measurement at 4 week intervals if trastuzumab is withheld for significant left ventricular cardiac dysfunction.
- LVEF measurements every 6 months for at least 2 years following completion of trastuzumab as a component of adjuvant therapy.

Infusion Reactions
Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia.
Interrupt trastuzumab infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered (which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen). Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions.

Embryo-Fetal Toxicity
Trastuzumab can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.
Verify the pregnancy status of females of reproductive potential prior to the initiation of trastuzumab. Advise pregnant women and females of reproductive potential that exposure to trastuzumab during pregnancy or within 7 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of trastuzumab.

Pulmonary Toxicity
Trastuzumab use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, noncardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

Exacerbation of Chemotherapy-Induced Neutropenia
In randomized, controlled clinical trials, the per-patient incidences of NCI-CTC Grade 3 to 4 neutropenia and of febrile neutropenia were higher 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.

Benzyl alcohol
Benzyl alcohol is used as preservative in Bacteriostatic Water for Injection (BWFI) in the 440mg multidose vials. If a patient is known to be hypersensitive to benzyl alcohol, reconstitute Trastuget with water for injection and use only one dose per Trastuget vial. Discard any used portion.

Effects on ability to drive and use machines
Trastuzumab may have a minor influence on the ability to drive or use machines. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

Pregnancy
Verify the pregnancy status of females of reproductive potential prior to the initiation of trastuzumab. Trastuzumab can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment with trastuzumab and for 7 months following the last dose of trastuzumab.

Nursing Mother
There is no information regarding the presence of trastuzumab in human milk, the effects on the breastfed infant, or the effects on milk production. Published data suggest human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. As human IgG1 is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during trastuzumab therapy and for 7 months after the last dose.

DRUG INTERACTIONS
Anthracyclines
Patients who receive anthracycline after stopping trastuzumab products may be at increased risk of cardiac dysfunction because of trastuzumab's long washout period based on population PK analysis. If possible, physicians should avoid anthracycline based therapy for up to 7 months after stopping trastuzumab products. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

Capecitabine
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.

Paclitaxel
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.

7-deoxy-13 dihydro-doxorubicinone
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.

OVERDOSAGE
There is no experience with overdose in human clinical trials. Single doses of trastuzumab alone greater than 10 mg/kg have not been administered in the clinical trials; a maintenance dose of 10 mg/kg q3w following a loading dose of 8 mg/kg has been studied in a clinical trial with metastatic gastric cancer patients. Doses up to this level were well tolerated.

STORAGE
Store at 2°C - 8°C in a refrigerator prior to reconstitution.
Protect from light.
Reconstituted solution (only with BWFI) can be used within 28 days when stored at 2°C - 8°C.
Do not freeze the reconstituted solution.
Discard any remaining multi-dose reconstituted solution after 28 days.
Infusion solution (0.9% sodium chloride) containing the reconstituted drug product is physically and chemically stable for 24 hours at 2°C - 8°C. From the perspective of microbiological safety, the Trastuget (Trastuzumab) 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.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Trastuget (Trastuzumab) for IV Infusion 440mg, as multiple use vial, is available in pack of 1 vial of Trastuget with 2 x 10mL Bacteriostatic Water for Injection (BWFI).

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Biocon Biologics India Limited
Block No. B1, B2, Q13 of Q1 and W20 & Unit S18, 1st Floor, Block B4,
Special Economic Zone, Plot No. 2, 3, 4 & 5 Phase-IV,
Bommasandra-Jigani Link Road, Bommasandra Post,
Bengaluru 560 099, India.

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