Tazumab

Trastuzumab INN Injection

DRUG INTERNATIONAL LTD.

COMPOSITION

Tazumab Injection: Each vial contains Trastuzumab INN 440mg lyophilized powder for IV infusion.

Diluent for Tazumab Injection: Each vial contains Bacteriostatic Water for Injection 20ml (Benzyl Alcohol USP 1.1%).

DESCRIPTION

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.

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 has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC). In vitro, Trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

INDICATIONS

Adjuvant Breast Cancer: 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: 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 patient who have received one or more chemotherapy regimens for metastatic disease.overexpressing breast cancer in patient

Metastatic Gastric Cancer: 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 AND ADMINISTRATION

Recommended Doses and Schedules: Do not administer as an intravenous push or bolus. Do not mix Trastuzumab with other drugs.

Adjuvant Treatment, Breast Cancer: Administer according to one of the following doses and schedules for a total of 52 weeks of Trastuzumab therapy:

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

• Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/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 Trastuzumab, administer Trastuzumab at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

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

• Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes

• Subsequent doses at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

• Extending adjuvant treatment beyond one year is not recommended

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

Metastatic Gastric Cancer: Administer Trastuzumab at an initial dose of 8 mg/kg as a 90-minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks until disease progression. Or, as directed by the registered physician.

Important Dosing Considerations:

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 Trastuzumab for severe or life-threatening infusion reactions.

Cardiomyopathy: Assess left ventricular ejection fraction (LVEF) prior to initiation of Trastuzumab and at regular intervals during treatment. Withhold 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.

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

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

PREPARATION FOR ADMINISTRATION

Reconstitution: Reconstitute each 440 mg vial of Trastuzumab with 20 ml of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21 mg/ml Trastuzumab. In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 ml of Sterille Water for Injection (SWFI) without preservative to yield a single use solution.

Use appropriate aseptic technique when performing the following reconstitution steps:

• Using a sterile syringe, slowly inject the 20 ml of diluent into the vial containing the lyophilized powder of Trastuzumab, which has a cake-like appearance. The stream of diluent should be directed into the cake. The reconstituted vial yields a solution for multiple-dose use, containing 21 mg/ml Trastuzumab.

• 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 Trastuzumab in the refrigerator at 2°C to 8°C, discard unused Trastuzumab after 28 days. If Tazumab is reconstituted with SWFI without preservative, use immediately and discard any unused portion.

Dilution: Determine the dose (mg) of Trastuzumab. Calculate the volume of the 21 mg/ml reconstituted Trastuzumab solution needed, withdraw this amount from the vial and add it to an infusion bag containing 250 ml of 0.9% Sodium Chloride Injection, USP. DO NOT USE DEXTROSE (5%) SOLUTION.

• Gently invert the bag to mix the solution.

ADVERSE EFFECTS

The most serious adverse reactions caused by Trastuzumab includes 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.

CONTRAINDICATIONS

None.

DRUG INTERACTIONS

Patients who receive anthracycline after stopping Trastuzumab 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. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

PRECAUTIONS

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 4–6 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 Trastuzumab is administered with an anthracycline.

Withhold Trastuzumab for ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values. The safety of continuation or resumption of Trastuzumab in patients with Trastuzumab-induced left ventricular cardiac dysfunction has not been studied.

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 Tazumab 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.

Serious and fatal infusion reactions have been reported. Severe reactions, which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable, including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

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.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Trastuzumab after experiencing a severe infusion reaction. 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.

Embryo-Fetal Toxicity: Trastuzumab can cause fetal harm when administered to a pregnant woman. Use of Trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. 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, non-cardiogenic 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 3–4 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.

Pediatric Use: The safety and effectiveness in pediatric patients have not been established.

Use in Pregnancy: It can cause fetal harm when administered to a pregnant woman. 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.

Use in Lactation: There is no information regarding the presence of Trastuzumab in human milk, the effects on the breastfed infant, or the effects on milk production.

OVERDOSE

There is no experience with overdosage in human clinical trials.

PHARMACEUTICAL INFORMATION

Storage: Store the vial in original carton at 2^{o}-8^{o} C. Protect from light. Keep out of the reach of children.

Store reconstituted Trastuzumab in the refrigerator at 2°C to 8°C, discard unused Trastuzumab after 28 days. If Trastuzumab is reconstituted with SWFI without preservative, use immediately and discard any unused portion. Do not freeze.

The solution of Trastuzumab for infusion diluted in 0.9% Sodium Chloride Injection, USP, should be stored at 2°C to 8°C for no more than 24 hours prior to use. Do not freeze.

Packing: Each combipack contains 1 vial of Tazumab Injection and 1 vial of Diluent for Tazumab Injection.