



## Lyophilized Powder for IV Infusion

### COMPOSITION

**Trastunix Injection** : Each vial contains Trastuzumab INN 440 mg as lyophilized powder.  
**Diluent for Trastunix Injection** : Each vial contains Bacteriostatic Water for Injection 20 ml (Benzyl Alcohol BP 1.1%).

### DESCRIPTION

Trastuzumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (Kd=5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2.

### PHARMACOLOGICAL INFORMATION

#### 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 AND USAGE

#### Adjuvant Breast Cancer

Trastunix 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
- with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

#### Metastatic Breast Cancer

Trastunix 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

Trastunix 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 Trastunix (Trastuzumab) with other drugs.

#### Adjuvant Treatment, Breast Cancer

Administer according to one of the following doses and schedules for a total of 52 weeks Trastunix (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 Trastunix (Trastuzumab), administers Trastunix (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.

#### Metastatic Treatment, Breast Cancer

Administer Trastunix (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 Trastunix (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 [see Dose Modifications].

### Dose Modifications

#### 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 Trastunix (Trastuzumab) for severe or life-threatening infusion reactions.

#### Cardiomyopathy

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

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

Trastunix (Trastuzumab) may be resumed if, within 4-8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is  $\leq 15\%$ .

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

#### Preparation for Administration

##### Reconstitution

Reconstitute each 440 mg vial of Trastunix (Trastuzumab) with 20 ml of Bacteriostatic Water for Injection (BWFI), BP, 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 Sterile 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 cake of Trastunix (Trastuzumab). 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 Trastunix (Trastuzumab) at 2° C-8° C; discard unused Trastunix (Trastuzumab) after 28 days. If Trastunix (Trastuzumab) is reconstituted with Sterile Water for Injection (SWFI) without preservative, use immediately and discard any unused portion.

#### Dilution

Determine the dose (mg) of Trastunix (Trastuzumab). Calculate the volume of the 21 mg/mL reconstituted Trastunix (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.

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

#### Cardiomyopathy

Trastuzumab can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab can also cause a symptomatic 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 Trastuzumab is administered with an anthracycline.

Withhold Trastuzumab for  $\geq 16\%$  absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and  $\geq 10\%$  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 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.

In postmarketing reports, 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. 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. Advise women of the potential hazard to the fetus resulting from Trastuzumab exposure during pregnancy and provide contraception counseling to women of childbearing potential.

#### 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 Trastunix and those who did not.

#### HER2 Testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Trastuzumab therapy because these are the only patients studied and for whom benefit has been shown. Due to differences in tumor histopathology, use FDA-approved tests for the specific tumor type (breast or gastric/gastroesophageal adenocarcinoma) to assess HER2 protein overexpression and HER2 gene amplification. Tests should be performed by laboratories with demonstrated proficiency in the specific tissue type being utilized. 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.

### Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility. Trastuzumab has not been tested for carcinogenic potential.

No evidence of mutagenic activity was observed when Trastuzumab was tested in the standard Ames bacterial and human peripheral blood lymphocyte mutagenicity assays, at concentrations of up to 5000 mcg/mL. In an in vivo micronucleus assay, no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg Trastuzumab.

A fertility study conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg Trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels. Studies to evaluate the effects of trastuzumab on male fertility have not been conducted.

### ADVERSE REACTIONS

The most serious adverse reactions caused by Trastuzumab include cardiomyopathy, hypersensitivity reactions including anaphylaxis, infusion reactions, pulmonary events, and exacerbation of chemotherapy-induced neutropenia.

The most common adverse reactions associated with Trastuzumab use are fever, diarrhea, infections, chills, increased cough, headache, rash, and insomnia.

#### Cardiac Failure/Dysfunction

Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, 53 gallop, or reduced ejection fraction, have been observed in patients treated with Trastuzumab. Congestive heart failure associated with Trastuzumab therapy may be severe and has been associated with disabling cardiac failure, death, and mural thrombosis leading to stroke.

#### Anemia and Leukopenia

In a randomized, controlled trial, the per-patient incidences of anemia (30% vs. 21%) and leukopenia (53% vs. 37%) were higher in patients receiving Trastuzumab in combination with chemotherapy as compared to those receiving chemotherapy alone. The majority of these cytopenic events were mild to moderate in intensity, reversible, and none resulted in discontinuation of therapy with Trastuzumab. In a randomized, controlled trial conducted in the post-marketing setting, there were also increased incidences of NCI-CTC Grade 3/4 neutropenia (32% [29/92] vs. 22% [21/94]) and of febrile neutropenia (23% [21/91] vs. 17% [16/94]) in patients randomized to Trastuzumab in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

Hematologic toxicity is infrequent following the administration of Trastuzumab as a single agent, with an incidence of Grade III toxicities for WBC, platelets, hemoglobin all <1%. No Grade IV toxicities were observed.

#### Diarrhea

Patients treated with trastuzumab as a single agent, 25% experienced diarrhea. An increased incidence of diarrhea, primarily mild to moderate in severity, was observed in patients receiving Trastuzumab in combination with chemotherapy.

#### Infection

In a randomized, controlled trial, the incidence of infections, primarily mild upper respiratory infections of minor clinical significance or catheter infections, was higher (46% vs. 30%) in patients receiving Trastuzumab in combination with chemotherapy as compared to those receiving chemotherapy alone.

In a randomized, controlled trial conducted in the post-marketing setting, the reported incidence of febrile neutropenia was higher (23% [21/92] vs. 17% [16/94]) in patients receiving Trastuzumab in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In the postmarketing setting there have also been reports of febrile neutropenia and infection with neutropenia culminating in death associated with the use of Trastuzumab and myelosuppressive chemotherapy.

#### Infusion Reactions

During the first infusion with Trastuzumab, a symptom complex most commonly consisting of chills and/or fever was observed in about 40% of patients in clinical trials. The symptoms were usually mild to moderate in severity and were treated with Acetaminophen, Diphenhydramine, and Meperidine (with or without reduction in the rate of Trastuzumab infusion). Trastuzumab discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. The symptoms occurred infrequently with subsequent Trastuzumab infusions. Additional adverse reactions have been identified during postmarketing use of Trastuzumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Trastuzumab exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Trastuzumab.

#### Hypersensitivity Reactions Including Anaphylaxis

##### Pulmonary Events

In the postmarketing setting, severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pulmonary adverse events have been reported: Hypersensitivity Reactions (Including Anaphylaxis). These events include anaphylaxis, angioedema, bronchospasm, hypotension, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description.

##### Glomerulopathy

In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of Trastuzumab therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

##### Other Serious Adverse Events

The following other serious adverse events occurred in at least one of the 958 patients treated with Trastuzumab in clinical studies:

*Body as a Whole:* Cellulitis, anaphylactoid reaction, ascites, hydrocephalus, radiation injury, deafness, amblyopia.

*Cardiovascular:* Vascular thrombosis, pericardial effusion, heart arrest, hypotension, syncope, hemorrhage, shock, arrhythmia.

*Digestive:* Hepatic failure, gastroenteritis, hematemesis, ileus, intestinal obstruction, colitis, esophageal ulcer, stomatitis, pancreatitis, hepatitis.

*Endocrine:* Hypothyroidism

*Hematological:* Pancytopenia, acute leukemia, coagulation disorder, lymphangitis

*Metabolic:* Hypercalcemia, hypomagnesemia, hyponatremia, hypoglycemia, growth retardation, weight loss

*Musculoskeletal:* Pathological fractures, bone necrosis, myopathy

*Nervous:* Convulsion, ataxia, confusion, manic reaction

*Respiratory:* Apnea, pneumothorax, asthma, hypoxia, laryngitis

*Skin:* Herpes zoster, skin ulceration

*Urogenital:* Hydronephrosis, kidney failure, cervical cancer, hematuria, hemorrhagic cystitis, pyelonephritis

##### Immunogenicity

Patients who have been evaluated, human anti-human antibody (HAHA) to Trastuzumab was detected in one patient, who had no allergic manifestations.

The data reflect the percentage of patients whose test results were considered positive for antibodies to Trastuzumab in the HAHA assay for Trastuzumab, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Trastuzumab with the incidence of antibodies to other products may be misleading.

### DRUG INTERACTIONS

There have been no formal drug interaction studies performed with Trastuzumab in humans. Administration of Paclitaxel in combination with Trastuzumab resulted in a two-fold decrease in Trastuzumab clearance in a non-human primate study and in a 1.5-fold increase in Trastuzumab serum levels in clinical studies.

In other pharmacokinetic studies, where Trastuzumab was administered in combination with paclitaxel, docetaxel or doxorubicin, Trastuzumab did not alter the plasma concentrations of these chemotherapeutic agents, or the metabolites that were analyzed. In a drug interaction substudy, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with Trastuzumab.

### USE IN SPECIFIC POPULATIONS

#### Pregnancy: Category D

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 of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

These case reports described oligohydramnios in pregnant women who received Trastuzumab either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after Trastuzumab was stopped. In one case, Trastuzumab therapy resumed after the amniotic fluid index improved, and oligohydramnios recurred.

Monitor women exposed to Trastuzumab during pregnancy for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care. The efficacy of IV hydration in management of oligohydramnios due to Trastuzumab exposure is not known.

Advise women of the potential hazard to the fetus resulting from Trastuzumab exposure during pregnancy.

No teratogenic effects were observed in offspring from reproduction studies in cynomolgus monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg Trastuzumab. In mutant mice lacking HER2, embryos died in early gestation. Trastuzumab exposure was reported at delivery in offspring of cynomolgus monkeys treated during the early (Days 20-50 of gestation) or late (Days 120-150 of gestation) fetal development periods, at levels of 15 to 28% of the maternal blood levels.

#### Nursing Mothers

It is not known whether Trastuzumab is excreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts.

Trastuzumab was present in the breast milk of lactating cynomolgus monkeys given 12.5 times the recommended weekly human dose of 2 mg/kg of Trastunix. Infant monkeys with detectable serum levels of Trastuzumab did not have any adverse effects on growth or development from birth to 3 months of age; however, Trastuzumab levels in animal breast milk may not accurately reflect human breast milk levels.

Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from Trastuzumab, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of trastuzumab and the importance of the drug to the mother.

#### Pediatric Use

The safety and effectiveness of Trastuzumab in pediatric patients has not been established.

#### Geriatric Use

Trastuzumab has been administered to 386 patients who were 65 years of age or over (253 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease. In Study of metastatic gastric cancer, of the 294 patients treated with Trastuzumab 108 (37%) were 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or effectiveness were observed.

### OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 500 mg have not been tested.

### PHARMACEUTICAL INFORMATION

#### Storage Conditions

Store the vial in original carton at 2° C-8° C. Protect from light. Keep out of the reach of children.

A vial of Trastunix Injection reconstituted with Diluent for Trastunix Injection, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2° C-8° C, and the solution is preserved for multiple uses. Discard any remaining multi-dose reconstituted solution after 28 days. If unpreserved Sterile Water for Injection (SWFI) is used, the reconstituted Trastunix solution should be used immediately and any unused portion must be discarded. Do not freeze the reconstituted solution.

The solution of Trastunix for infusion diluted in 0.9% Sodium Chloride Injection may be stored at 2° C-8° C for up to 24 hours prior to use.

#### Presentation & Packaging

Each combipack contains 1 vial of Trastunix Injection and 1 vial of Diluent for Trastunix Injection.