**WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, AND PULMONARY TOXICITY**

See full prescribing information for complete boxed warning.

Cardiomyopathy: Trastuzumab products can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue HERZUMA for cardiomyopathy. (2.3, 5.1)

Infusion Reactions, Pulmonary Toxicity: Discontinue HERZUMA for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to trastuzumab products during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

**RECENT MAJOR CHANGES**

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<thead>
<tr>
<th>Indications and Usage, Adjuvant Breast Cancer (1.1)</th>
<th>05/2019</th>
</tr>
</thead>
<tbody>
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<td>Indications and Usage, Metastatic Gastric Cancer (1.3)</td>
<td>05/2019</td>
</tr>
<tr>
<td>Warnings and Precautions, Cardiomyopathy (5.1)</td>
<td>05/2019</td>
</tr>
</tbody>
</table>

**INDICATIONS AND USAGE**

HERZUMA is a HER2/neu receptor antagonist indicated for:

- the treatment of HER2-overexpressing breast cancer. (1.1, 1.2)
- the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. (1.3)

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product. (1.2, 1.3)

**DOSE AND ADMINISTRATION**

For intravenous (IV) infusion only. Do not administer as an IV push or bolus. (2.2)

Do not substitute HERZUMA (trastuzumab-pkrb) for or with ado-trastuzumab emtansine. (2.2)

Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1.2, 1.3)

**ADJUVANT TREATMENT OF HER2-OVEREXPRESSING BREAST CANCER (2.2)**

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel and carboplatin). One week after the last weekly dose of HERZUMA, administer 6 mg/kg as an IV infusion over 30–90 minutes every three weeks to complete a total of 52 weeks of therapy.
- Initial dose of 8 mg/kg over 90 minute IV infusion, then 6 mg/kg every 30–90 minute IV infusion every three weeks for 52 weeks.

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HERZUMA® (trastuzumab-pkrb) for injection

FULL PRESCRIBING INFORMATION

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, AND PULMONARY TOXICITY

Cardiomyopathy

Administration of trastuzumab products 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 HERZUMA. Discontinue HERZUMA treatment in patients receiving adjuvant therapy who have a LVEF below institutional limits of normal and for either of the following:

- LVEF below institutional limits of normal and ≥10% absolute decrease in LVEF from pretreatment values
- LVEF below institutional limits of normal and ≥15% absolute decrease in LVEF from pretreatment values

HERZUMA may be resumed if, within 4–8 weeks, the LVEF returns to normal levels and the ≥10% absolute decrease in LVEF resolves. Permanently discontinue HERZUMA for a persistent (> 8 weeks) LVEF decline or for suspension of HERZUMA dosing on more than 3 occasions for cardiomyopathy.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product [see Dosage and Administration (2.1, 2.2)].

2.3 Important Dosing Considerations

If the patient has missed a dose of HERZUMA by one week or less, then the usual treatment cycle continues. For one or two missed doses, the next dose should be administered according to the weekly or three-weekly schedules, respectively. If the patient has missed a dose of HERZUMA by more than one week, a re-loading dose of HERZUMA should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) as soon as possible. Subsequent HERZUMA maintenance doses (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

2.4 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 HERZUMA (trastuzumab-pkrb) and not ado-trastuzumab emtansine.

420 mg Multiple-dose vial

Reconstitution

Reconstitute each 420 mg vial of HERZUMA with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multiple-dose solution containing 21 mg/mL trastuzumab-pkrb that delivers 20 mL (420 mg trastuzumab-pkrb). 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 powder of HERZUMA, 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-pkrb.
- 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 HERZUMA in the refrigerator at 2°C to 8°C (36°F to 46°F); discard unused HERZUMA after 28 days.
- If HERZUMA is reconstituted with SWFI without preservative, use immediately and discard any unused portion.

Dilution

- Determine the dose (mg) of HERZUMA [see Dosage and Administration (2.2)]. Calculate the volume of the 21 mg/mL reconstituted HERZUMA solution needed, subtract 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.

HERZUMA® (trastuzumab-pkrb) for injection

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

HERZUMA is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [see Clinical Studies (14.1)]) 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

1.2 Metastatic Breast Cancer

HERZUMA 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. Select patients for therapy based on an FDA-approved diagnostic test for HER2 protein overexpression and HER2 gene amplification.
- In combination with other drugs, for the treatment of patients with HER2 overexpressing metastatic breast cancer
- As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:
  - Initial dose at 6 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 [see Dosage and Administration (2.3)]
  - Extending adjuvant treatment beyond one year is not recommended [see Adverse Reactions (6.1)].

2 DOSE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification as determined by a laboratory with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification should be available at: http://www.fda.gov/CompanionDiagnoses

2.2 Recommended Doses and Schedules

- Do not administer as an intravenous push or bolus. Do not mix HERZUMA with other drugs.
- Do not substitute HERZUMA (trastuzumab-pkrb) for or with ado-trastuzumab emtansine.

Adjuvant Treatment, Breast Cancer:

- Administer according to one of the following doses and schedules for a total of 52 weeks of HERZUMA therapy:
- 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).
HERZUMA® (trastuzumab-pkrb) for injection

- Gently invert the bag to mix the solution.
- The solution of HERZUMA 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. Do not freeze.

150 mg Single-dose vial

Reconstitution

Reconstitute each 150 mg vial of HERZUMA with 7.4 mL of Sterile Water for Injection (SWFI) (not supplied) to yield a single-dose solution containing 21 mg/mL trastuzumab-pkrb that delivers 7.15 mL (150 mg trastuzumab-pkrb).

Use appropriate aseptic technique when performing the following reconstitution step:
- Using a sterile syringe, slowly inject the 7.4 mL of SWFI (not supplied) into the vial containing the lyophilized powder of HERZUMA, which has a cake-like appearance.
- The stream of diluent should be directed into the cake. The reconstituted vial yields a solution for single-dose use, containing 21 mg/mL trastuzumab-pkrb.
- 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 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.
- Use the HERZUMA solution immediately following reconstitution with SWFI, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted HERZUMA solution for up to 24 hours at 2°C to 8°C (36°F to 46°F); discard any unused HERZUMA after 24 hours. Do not freeze.

Dilution

- Determine the dose (mg) of HERZUMA [see Dosage and Administration (2.2)].
- Calculate the volume of the 21 mg/mL reconstituted HERZUMA 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.
- The solution of HERZUMA 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.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 150 mg of HERZUMA as a white to pale yellow lyophilized powder in a single-dose vial.
- For injection: 420 mg of HERZUMA as a white to pale yellow lyophilized powder in a multiple-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Trastuzumab products may cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [see Boxed Warning: Cardiomyopathy]. Trastuzumab products 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 products as a single agent or in combination therapy compared with control products. The highest absolute incidence occurs when a trastuzumab product is administered with an anthracycline.

Withhold HERZUMA 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 [see Dosage and Administration (2.3)]. The safety of continuation or resumption of HERZUMA in patients with trastuzumab product-induced left ventricular cardiac dysfunction has not been studied.

Patients who receive anthracycline after stopping HERZUMA may also be at increased risk of cardiac dysfunction [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

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 HERZUMA
- LVEF measurements every 3 months during and upon completion of HERZUMA
- Repeat LVEF measurement at 4 week intervals if HERZUMA is withheld for significant left ventricular cardiac dysfunction [see Dosage and Administration (2.3)]
- LVEF measurements every 6 months for at least 2 years following completion of HERZUMA as a component of adjuvant therapy

In Study 1 (158/1031) of patients discontinued trastuzumab due to clinical evidence of myocardial dysfunction or significant decline in LVEF after a median follow-up duration of 8.7 years in the AC-TH (anthracycline, cyclophosphamide, paclitaxel, and trastuzumab) arm. In Study 3 (one-year trastuzumab treatment), the number of patients who discontinued trastuzumab due to cardiac toxicity at 12.6 months median duration of follow-up was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) of patients in the TCH (docetaxel, carboplatin, trastuzumab) arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) of patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued trastuzumab due to cardiac toxicity.

Among 64 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy, one patient died suddenly without documented etiology and 33 patients were receiving cardiac medication at last follow-up. Approximately 24% of the surviving patients had recovery to a normal LVEF (defined as ≥ 50%) and no symptoms on continuing medical management at the time of last follow-up. Incidence of congestive heart failure (CHF) is presented in Table 1. There were no data regarding the most appropriate method of identification or resolution of HERZUMA in patients with trastuzumab product-induced left ventricular cardiac dysfunction has not been studied.

Table 1: Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

<table>
<thead>
<tr>
<th>Incidence of CHF</th>
<th>Study</th>
<th>Regimen</th>
<th>Trastuzumab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &amp; 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AC--Paclitaxel+Trastuzumab</td>
<td>3.2% (64/2000)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.3% (21/1565)</td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Chemo -- Trastuzumab</td>
<td>2% (30/1578)</td>
<td>0.3% (5/1708)</td>
<td></td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AC--Docetaxel+Trastuzumab</td>
<td>2% (20/1068)</td>
<td>0.3% (3/1050)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Docetaxel+Carbo+Trastuzumab</td>
<td>0.4% (4/1056)</td>
<td>0.3% (3/1050)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Median follow-up duration for studies 1 and 2 combined was 8.3 years in the AC–TH arm.
<sup>b</sup> Anthracycline (doxorubicin) and cyclophosphamide.

In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the trastuzumab containing regimens (AC-TH: 0.3% (3/1068) and TCH: 0.2% (2/1056)) as compared to none in AC-T.

5.2 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 [see Adverse Reactions (6.1)]. In post-marketing reports, serious and fatal infusion reactions have been reported. Severe reactions, which included bronchospasm, hypotension, 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 HERZUMA infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered (which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen). All patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be 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 products after experiencing a severe infusion reaction. Prior to resumption of trastuzumab infusion, the majority of patients experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated trastuzumab with severe infusion reactions. There are no data regarding the most appropriate method of identification of patients who may safely be retreated with trastuzumab products after experiencing a severe infusion reaction.

5.3 Embryo-Fetal Toxicity

Trastuzumab products 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 manifested as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Verify the pregnancy status of females of reproductive potential prior to the initiation of HERZUMA. Advise pregnant women and females of reproductive potential that exposure to HERZUMA 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 HERZUMA [see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.3)].

5.4 Pulmonary Toxicity

Trastuzumab product 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...
HERZUMA® (trastuzumab-pkrb) for injection

hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions [see Warnings and Precautions (5.2)]. 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.

5.5 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 [see Adverse Reactions (6.1)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiomyopathy [see Warnings and Precautions (5.1)]
- Infusion Reactions [see Warnings and Precautions (5.2)]
- Embryo-Fetal Toxicity [see Warnings and Precautions (5.3)]
- Pulmonary Toxicity [see Warnings and Precautions (5.5)]
- Exacerbation of Chemotherapy-induced Neutropenia [see Warnings and Precautions (5.5)]

The most common adverse reactions in patients receiving trastuzumab products 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 product treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity [see Dosage and Administration (2.3)]

In the metastatic gastric cancer setting, the most common adverse reactions (≥ 10%) that were increased (≥ 5% difference) in patients receiving trastuzumab as compared to patients receiving chemotherapy alone 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 trastuzumab treatment in the absence of disease progression were infection, diarrhea, and febrile neutropenia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Breast Cancer Studies

The data below reflect exposure to one-year trastuzumab therapy across three randomized, open label studies, Studies 1, 2, and 3 with n = 3678 or without n = 3383 trastuzumab in the adjuvant treatment of breast cancer.

The data summarized in Table 3 below, from Study 3, reflect exposure to trastuzumab in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in the observation and one-year trastuzumab arm, Study 3 at a median follow-up of 12.6 months in the trastuzumab arm, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

Table 3: Adverse Reactions for Study 3, All Grades

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>One Year Trastuzumab (n = 1678)</th>
<th>Observation (n = 1708)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>64 (4%)</td>
<td>35 (2%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>60 (4%)</td>
<td>29 (2%)</td>
</tr>
<tr>
<td>Ejection Fraction Decreased</td>
<td>58 (3.5%)</td>
<td>11 (0.6%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>48 (3%)</td>
<td>12 (0.7%)</td>
</tr>
<tr>
<td>Cardiac Arrhythmias</td>
<td>40 (3%)</td>
<td>17 (1%)</td>
</tr>
<tr>
<td>Cardiac Failure Congestive</td>
<td>30 (2%)</td>
<td>5 (0.3%)</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>9 (0.5%)</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>Cardiac Disorder</td>
<td>5 (0.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ventricular Dysfunction</td>
<td>4 (0.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Respiratory Thoracic Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>81 (5%)</td>
<td>34 (2%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>70 (4%)</td>
<td>9 (0.5%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>57 (3%)</td>
<td>26 (2%)</td>
</tr>
<tr>
<td>URI</td>
<td>46 (3%)</td>
<td>20 (1%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>36 (2%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
<td>32 (2%)</td>
<td>8 (0.5%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>26 (2%)</td>
<td>5 (0.3%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>25 (2%)</td>
<td>1 (0.06%)</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>4 (0.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Intercostal Pneumonitis</td>
<td>4 (0.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>123 (7%)</td>
<td>16 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>108 (6%)</td>
<td>19 (1%)</td>
</tr>
</tbody>
</table>

Adverse Reaction One Year Trastuzumab (n = 1678) vs Observation (n = 1708)

- Median follow-up duration of 12.6 months in the one-year trastuzumab treatment arm.
- The incidence of Grade 3 or higher adverse reactions was < 1% in both arms for each listed term.
- Higher level grouping term.

In Study 3, a comparison of 3-weekly trastuzumab treatment for two years versus one year was also performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year trastuzumab treatment arm (8.1% versus 4.6% in the one-year trastuzumab treatment arm). More patients experienced at least one adverse reaction of Grade 3 or higher in the 2-year trastuzumab treatment arm (20.4%) compared with the one-year trastuzumab treatment arm (16.3%).

The safety data from Studies 1 and 2 were obtained from 3655 patients, of whom 2000 received trastuzumab; the median treatment duration was 51 weeks. The median age was 49 years (range: 24–80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian.

In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving trastuzumab plus chemotherapy as compared to chemotherapy alone: fatigue (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flashes (17.1% vs. 15.0%), anemia (12.3% vs. 6.7%), dyspnea (11.8% vs. 4.6%), rash/desquamation (10.9% vs. 7.6%), leukopenia (10.5% vs. 8.4%), neutropenia (6.4% vs. 4.3%), headache (6.2% vs. 3.8%), pain (3.5% vs. 3.0%), edema (4.7% vs. 2.7%), and insomnia (4.5% vs. 1.5%). The majority of these events were Grade 2 in severity.

In Study 2, data collection was limited to the following investigator-attributed treatment-related adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgia, nail changes, motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during chemotherapy and/or trastuzumab treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients receiving trastuzumab plus chemotherapy as compared to chemotherapy alone: arthralgia (12.2% vs. 9.1%), nail changes (11.5% vs. 8.9%), dyspnea (2.2% vs. 0.8%), and diarrhea (2.2% vs. 0%). The majority of these events were Grade 2 in severity.

Safety data from Study 4 reflect exposure to trastuzumab as part of an adjuvant treatment regimen from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TOH: n = 1056]. The overall median treatment duration was 54 weeks in both the AC-TH and TOH arms.

The median number of infusions was 26 in the AC-TH arm and 30 in the TOH arm, including weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy period. Among these patients, the median age was 49 years.
The data below reflect exposure to trastuzumab in one randomized, open-label study, Study 1, 2, and 3 with the exception of a low incidence of CHF in the TCH arm. The data below are based on the exposure of 294 patients to trastuzumab in combination with a fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the trastuzumab plus chemotherapy arm, the initial dose of trastuzumab 8 mg/kg was administered on Day 1 (prior to chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was administered at 80 mg/m² on Day 1 and the fluoropyrimidine was administered as either capecitabine 1000 mg/m² orally twice a day on Days 1-14 or 5-fluorouracil 800 mg/m²/day as a continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21 day cycles. Median duration of trastuzumab treatment was 21 weeks; median number of trastuzumab infusions administered was eight.

Table 5: Study 7: Per Patient Incidence of Adverse Reactions of All Grades (Incidence ≥ 5% between Arms) or Grade 3/4 (Incidence > 1% between Arms) and Higher Incidence in Trastuzumab Arm

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Trastuzumab + FC (N = 294)</th>
<th>FC (N = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grades 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Investigations</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>230 (78)</td>
<td>101 (34)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>83 (28)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Anemia</td>
<td>81 (28)</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>47 (16)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>109 (37)</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>72 (24)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>19 (6)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>102 (35)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Fever</td>
<td>54 (18)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Mucosal Inflammation</td>
<td>37 (13)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Chills</td>
<td>23 (8)</td>
<td>1 (&lt; 1)</td>
</tr>
</tbody>
</table>

The following subsections provide additional detail regarding adverse reactions observed in clinical trials of adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer, or post-marketing experience.

Cardiomyopathy
Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up...
was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year trastuzumab arm); and in Studies 1 and 2, 7.9 years in the AC-T arm, 8.3 years in the AC-TH arm. In Studies 1 and 2, 6% of all randomized patients with post-AC LVEF evaluation were not permitted to initiate trastuzumab following completion of AC chemotherapy due to cardiac dysfunction (LVEF < LLN or ≥ 16 point decline in LVEF from baseline to end of AC). Following initiation of trastuzumab therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving trastuzumab and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients receiving one-year trastuzumab monotherapy as compared to observation in Study 3 (see Table 6, Figures 1 and 2). The per-patient incidence of new-onset cardiac dysfunction, as measured by LVEF, remained similar when compared to the analysis performed at a median follow-up of 2.0 years in the AC-TH arm. This analysis also showed evidence of reversibility of left ventricular dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC-TH group being asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

**Table 6a:** Par-patient Incidence of New Onset Myocardial Dysfunction (by LVEF)

<table>
<thead>
<tr>
<th>Study</th>
<th>LVEF &lt; 50% and Absolute Decrease from Baseline</th>
<th>Absolute LVEF Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LVEF &lt; 50%</td>
<td>≥ 10% decrease</td>
</tr>
<tr>
<td><strong>Studies 1 &amp; 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC-TH (n = 1656)</td>
<td>23.1% (428)</td>
<td>18.5% (344)</td>
</tr>
<tr>
<td>AC-T (n = 1170)</td>
<td>11.7% (137)</td>
<td>7.0% (82)</td>
</tr>
<tr>
<td><strong>Study 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab (n = 1679)</td>
<td>8.6% (144)</td>
<td>7.0% (118)</td>
</tr>
<tr>
<td>Observation (n = 1708)</td>
<td>2.7% (46)</td>
<td>2.0% (35)</td>
</tr>
<tr>
<td><strong>Study 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCH (n = 1656)</td>
<td>8.5% (90)</td>
<td>5.9% (62)</td>
</tr>
<tr>
<td>AC-TH (n = 1068)</td>
<td>17.0% (182)</td>
<td>13.3% (142)</td>
</tr>
<tr>
<td>AC-T (n = 1050)</td>
<td>9.5% (100)</td>
<td>6.6% (69)</td>
</tr>
</tbody>
</table>

* For Studies 1, 2 and 3, events are counted from the beginning of trastuzumab treatment. For Study 4, events are counted from the date of randomization.
* Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC-T) or paclitaxel plus trastuzumab (AC-TH). Study 3: median follow-up of 8.3 years in the AC-TH arm.
* Median follow-up duration of 12.6 months in the one-year trastuzumab treatment arm. Study 4: doxorubicin and cyclophosphamide followed by docetaxel (AC-T) or docetaxel plus trastuzumab (AC-TH); docetaxel and carboplatin plus trastuzumab (TCH).

**Figure 1:** Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event

**Figure 2:** Study 3: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event

**Figure 3:** Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event

In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]), of selected NCI-CTC Grade 2–5 neutropenia (12.2% vs. 4.7% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone. Following the administration of trastuzumab as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was < 1%. In Study 7 (metastatic gastric cancer), on the trastuzumab containing arm as compared to the chemotherapy alone arm, the overall incidence of anemia was 28% compared to 21% and of NCI-CTC Grade 3/4 anemia was 12.2% compared to 10.3%.

**Neutropenia**

In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI CTC Grade 4–5 neutropenia (1.7% vs. 0.8% [Study 2]) and of selected Grade 2–5 neutropenia (6.4% vs. 4.3% [Study 1]) were increased in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to trastuzumab in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7 (metastatic gastric cancer) on the trastuzumab containing arm as compared to the chemotherapy alone arm, the incidence of NCI-CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile neutropenia 5.1% compared to 2.8%.
Post-Marketing Experience

The following adverse reactions have been identified during post-approval 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 drug exposure.

- **Infusion reaction** [see Warnings and Precautions (5.2)]
- **Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death** [see Warnings and Precautions (5.3)]
- **Gomerulopathy** [see Adverse Reactions (6.1)]
- **Immune thrombocytopenia**
- **Tumor lysis syndrome (TLS):** Cases of possible TLS have been reported in patients treated with trastuzumab. Patients with significant tumor burden (e.g. bulky metastases) may be at a higher risk. Patients could present with hyperuricemia, hyperphosphatemia, and acute renal failure which may represent possible TLS. Providers should consider additional monitoring and/or treatment as clinically indicated.

7 **DRUG INTERACTIONS**

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 [see Clinical Pharmacology (12.3)]. 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.

8 **USE IN SPECIFIC POPULATIONS**

8.1 **Pregnancy**

Risk Summary

Trastuzumab products 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 [see Data]. Apprise the patient of the potential risks to a fetus. There are clinical considerations if a trastuzumab product is used in a pregnant woman or if a patient becomes pregnant within 7 months following the last dose of a trastuzumab product [see Clinical Considerations]. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 5% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received trastuzumab during pregnancy or within 7 months prior to conception for oligohydramnios. Oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Human Data

In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting in the fetus 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 treatment was resumed after amniotic index improved and oligohydramnios resolved.

Animal Data

In studies where trastuzumab was administered to pregnant Cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the recommended weekly human dose of 2 mg/kg), trastuzumab corrected the placental barrier failure in some dams. Trastuzumab was present in the milk of lactating Cynomolgus monkeys but not associated with neonatal toxicity [see Data]. Consider the developmental and health benefits of breastfeeding along with the mother’s clinical need for HERZUMA treatment and any potential adverse effects. Apprise the patient of the potential risks to the breastfed infant fromHERZUMA or from the underlying maternal condition. This consideration should also take into account the trastuzumab product wash out period of 7 months [see Clinical Pharmacology (12.3)].

Data

In lactating Cynomolgus monkeys, trastuzumab was present in breast milk at about 2% of maternal serum concentrations after pre (beginning Gestation Day 120) and post-partum (through Post-partum Day 28) doses of 25 mg/kg administered twice weekly (25 times the recommended weekly human dose of 2 mg/kg of trastuzumab products). Infant monkeys with detectable serum levels of trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of age.

8.2 **Lactation**

Risk Summary

There is no information regarding the presence of trastuzumab products 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 gut or enter in substantial amounts in milk. Trastuzumab was present in the milk of lactating Cynomolgus monkeys but not associated with neonatal toxicity [see Data]. Consider the developmental and health benefits of breastfeeding along with the mother’s clinical need for HERZUMA treatment and any potential adverse effects of the breastfed infant from HERZUMA or from the underlying maternal condition. This consideration should also take into account the trastuzumab product wash out period of 7 months [see Clinical Pharmacology (12.3)].

Data

In lactating Cynomolgus monkeys, trastuzumab was present in breast milk at about 2% of maternal serum concentrations after pre (beginning Gestation Day 120) and post-partum (through Post-partum Day 28) doses of 25 mg/kg administered twice weekly (25 times the recommended weekly human dose of 2 mg/kg of trastuzumab products). Infant monkeys with detectable serum levels of trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of age.
8.4 Pediatric Use

The safety and effectiveness of trastuzumab products in pediatric patients have not been established.

8.5 Geriatric Use

Trastuzumab has been administered to 386 patients who were 65 years of age or over in the adjuvant treatment and 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 Studies 5 and 6, or adjuvant therapy in Studies 1 and 2. Limitations in data collection and differences in study design of the 4 studies of trastuzumab in adjuvant treatment of breast cancer provided some determination of whether the toxicity profile of trastuzumab in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of trastuzumab treatment in older patients is different from that observed in patients < 65 years of age for metastatic disease and adjuvant treatment.

In Study 7 (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.

10 OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 8 mg/kg have not been tested.

11 DESCRIPTION

Trastuzumab-pkrb 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-pkrb is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture. HERZUMA (trastuzumab-pkrb) for injection is a sterile, white to pale yellow, preservative-free lyophilized powder with a cake-like appearance, for intravenous administration.

Each multiple-dose vial of HERZUMA delivers 420 mg trastuzumab-pkrb, 839 mg α,α-trehalose dihydrate, 9.5 mg L-histidine HCl, 6.1 mg L-histidine, and 1.7 mg polyborate 20. Reconstitution with 20 mL of the appropriate diluent (BWF1 or SWFI) yields a solution containing 21 mg/mL trastuzumab-pkrb that delivers 20 mL (420 mg) of trastuzumab-pkrb, at a pH of approximately 6. If HERZUMA is reconstituted with SWFI without preservative, the reconstituted solution is considered single-dose.

Each single-dose vial of HERZUMA delivers 150 mg trastuzumab-pkrb, 299.6 mg α,α-trehalose dihydrate, 3.4 mg L-histidine HCl, 2.2 mg L-histidine, and 0.8 mg polyborate 20. Reconstitution with 7.4 mL of sterile water for injection (SWFI) yields a solution containing 21 mg/mL trastuzumab-pkrb that delivers 7.15 mL (150 mg trastuzumab-pkrb), at a pH of approximately 6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The HER2 (or c-erbB-2) protein, which encodes a transmembrane receptor protein of 185 kDa, 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.

12.2 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 were no apparent relationships between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors.

12.3 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 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 7 and 8, respectively.

Population PK based - sparse-multiplications 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 [see Warnings and Precautions (8.1) and Use in Specific Populations (8.1, 8.2)].

### Table 7: Population Predicted Cycle 1 PK Exposures (Median with 5th – 95th Percentiles) In Breast Cancer and MGC Patients

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Primary tumor type</th>
<th>N</th>
<th>Cmax,ssb (µg/mL)</th>
<th>AUC0-21 days (µg day/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg/kg + 6 mg/kg q3w</td>
<td>Breast cancer</td>
<td>1195</td>
<td>29.4 (5.8 to 59.5)</td>
<td>178 (117 to 291)</td>
</tr>
<tr>
<td></td>
<td>MGC</td>
<td>274</td>
<td>23.1 (6.1 to 50.3)</td>
<td>132 (84.2 to 225)</td>
</tr>
<tr>
<td>4 mg/kg + 2 mg/kg qw</td>
<td>Breast cancer</td>
<td>1195</td>
<td>37.7 (12.3 to 70.9)</td>
<td>88.3 (56 - 144)</td>
</tr>
</tbody>
</table>

### Table 8: Population Predicted Steady State PK Exposures (Median with 5th – 95th Percentiles) In Breast Cancer and MGC Patients

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Primary tumor type</th>
<th>N</th>
<th>Cmax,ssb (µg/mL)</th>
<th>AUC0-21 days (µg day/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg/kg + 6 mg/kg q3w</td>
<td>Breast cancer</td>
<td>1195</td>
<td>47.4 (5 to 115)</td>
<td>179 (107 to 309)</td>
</tr>
<tr>
<td></td>
<td>MGC</td>
<td>274</td>
<td>32.9 (6.1 to 88.9)</td>
<td>131 (72.5 to 261)</td>
</tr>
<tr>
<td>4 mg/kg + 2 mg/kg qw</td>
<td>Breast cancer</td>
<td>1195</td>
<td>66.1 (14.9 to 142)</td>
<td>109 (51.0 to 209)</td>
</tr>
</tbody>
</table>

8. Steady-state trough serum concentration of trastuzumab

9. Maximum steady-state serum concentration of trastuzumab

Specific Populations

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.

Drug Interaction Studies

There have been no formal drug interaction studies performed with trastuzumab products in humans. Clinically significant interactions between trastuzumab and concomitant medications used in clinical trials have not been observed.

14 CLINICAL STUDIES

14.1 Adjuvant Breast Cancer

The safety and efficacy of trastuzumab in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women at definitive Disease-Free Survival analysis for one-year trastuzumab treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4). Studies 1 and 2.

In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a local laboratory (Study 1). Patients had a history of metastatic disease based on symptoms, abnormal electrocardiographic, radiologic, or left ventricular ejection fraction findings or uncontrolled hypertension (diastolic > 100 mm Hg or systolic > 200 mm Hg) were not eligible.
HERZUMA® (trastuzumab-pkrb) for injection

DESCRIPTION

HERZUMA® (trastuzumab-pkrb) for injection is a humanized monoclonal antibody indicated for the treatment of:

- HER2-positive metastatic breast cancer in combination with paclitaxel
- HER2-positive metastatic breast cancer in combination with chemotherapy
- HER2-positive locally advanced or metastatic breast cancer in combination with capecitabine
- HER2-positive locally advanced or metastatic breast cancer in combination with capecitabine and another HER2 inhibitor
- HER2-positive locally advanced or metastatic breast cancer in combination with trastuzumab (TCH)

INDICATIONS AND USAGE

HERZUMA® (trastuzumab-pkrb) for injection is indicated for the treatment of:

1. HER2-positive metastatic breast cancer in combination with paclitaxel
2. HER2-positive metastatic breast cancer in combination with chemotherapy
3. HER2-positive locally advanced or metastatic breast cancer in combination with capecitabine
4. HER2-positive locally advanced or metastatic breast cancer in combination with capecitabine and another HER2 inhibitor
5. HER2-positive locally advanced or metastatic breast cancer in combination with trastuzumab (TCH)

CONTRAINDICATIONS

HERZUMA® (trastuzumab-pkrb) for injection is contraindicated in patients with a known hypersensitivity to trastuzumab or any of the ingredients of HERZUMA® (trastuzumab-pkrb) for injection.

WARNINGS

1. Hypersensitivity Reactions

2. Tumor Lysis Syndrome

3. Cardiac Function

4. Pulmonary Embolism

5. Skin, Soft Tissue, and Bone Tumor

6. Meningoencephalitis

7. Primary and Secondary Neoplasms

8. Developmental Defects and Birth Defects

9. Administration

10. Drug Interactions

11. Pregnancy

12. Breastfeeding

13. Pediatric Use

14. Carcinogenesis, Mutagenesis, Impairment of Fertility

15. Ovarian and Testicular Function

16. Pediatric Use

17. Carcinogenesis, Mutagenesis, Impairment of Fertility

18. Ovarian and Testicular Function

19. Pregnancy

20. Breastfeeding

21. Pediatric Use

ADMINISTRATION

1. HER2-positive metastatic breast cancer:
   - HER2-positive metastatic breast cancer in combination with paclitaxel
   - HER2-positive metastatic breast cancer in combination with chemotherapy
   - HER2-positive locally advanced or metastatic breast cancer in combination with capecitabine
   - HER2-positive locally advanced or metastatic breast cancer in combination with capecitabine and another HER2 inhibitor
   - HER2-positive locally advanced or metastatic breast cancer in combination with trastuzumab (TCH)

2. HERZUMA® (trastuzumab-pkrb) for injection is administered at a dose of 4 mg/kg on the day of initiation of paclitaxel and then at a dose of 2 mg/kg weekly for a total of 52 weeks. Trastuzumab treatment was permanently discontinued in patients who developed congestive heart failure, or persistent/recurrent LVEF decline [see Dosage and Administration (2.3)]. Radiation therapy, if administered, was initiated after the completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-Free Survival (DFS) was the main outcome measure. Among the 2222 patients randomized, the median age was 49 (range 22 to 74 years; 6% 65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to randomization, all patients underwent primary surgery for breast cancer.

3. The results for DFS for the integrated analysis of Studies 1, 2, and 3, and Study 4 are presented in Table 9. For Studies 1 and 2, the DFS hazard ratio for a median follow-up of 2.0 years in the AC-TH arm is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the AC-TH arm is presented in Figure 5. The duration of DFS for Study 4 is presented in Figure 6. Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall population: patients with low tumor grade, patients within specific ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients > 65 years of age. For Studies 1 and 2, the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median follow-up, the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81). In patients > 50 years of age (n = 1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive) (n = 2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and PR-negative) (n = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size < 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

4. The study results for the primary mixed population (n = 6660) are presented in Table 9. For DFS, the DFS hazard ratio for a median follow-up of 2.0 years in the AC-TH arm is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the AC-TH arm is presented in Figure 5. The duration of DFS for Study 4 is presented in Figure 6. Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall population: patients with low tumor grade, patients within specific ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients > 65 years of age. For Studies 1 and 2, the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median follow-up, the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81). In patients > 50 years of age (n = 1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive) (n = 2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and PR-negative) (n = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size < 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

5. Table 9: Efficacy Results from Adjunctive Treatment of Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

<table>
<thead>
<tr>
<th>Study</th>
<th>DFS events</th>
<th>DFS Hazard ratio (95% CI) p-value</th>
<th>Deaths (OS events)</th>
<th>OS Hazard ratio p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>133</td>
<td>0.48 (0.39, 0.59) p &lt; 0.0001</td>
<td>289</td>
<td>0.64 (0.55, 0.74) p &lt; 0.0001</td>
</tr>
<tr>
<td>Study 2</td>
<td>261</td>
<td>0.54 (0.44, 0.67) p &lt; 0.0001</td>
<td>418</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>127</td>
<td>0.60 (0.48, 0.76) p &lt; 0.0001</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>134</td>
<td>0.47 (0.38, 0.56) p &lt; 0.0001</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>AC-TH (n = 2031b)</td>
<td>180</td>
<td>0.60 (0.48 – 0.76) p &lt; 0.0001</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>AC-T (n = 2032)</td>
<td>180</td>
<td>0.60 (0.48 – 0.76) p &lt; 0.0001</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval

a Efficacy evaluable population, for the primary DFS analysis, following a median follow-up of 2.0 years in the AC-TH arm.

b Efficacy evaluable population, for the final OS analysis, following 707 deaths (8.3 years of median follow-up in the AC-TH arm).

c Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

d Stratified log-rank test.

Table 9: Efficacy Results from Adjunctive Treatment of Breast Cancer (Studies 1 + 2, Study 3, and Study 4)
Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available. The results are shown in Table 10. The number of events in Study 2 was small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH+/IHC unknown subgroups.

Table 10: Treatment Outcomes in Studies 2 and 3 as a Function of HER2 Overexpression or Amplification

<table>
<thead>
<tr>
<th>HER2 Assay Result</th>
<th>Study 2</th>
<th>Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients</td>
<td>Hazard Ratio DFS (95% CI)</td>
</tr>
<tr>
<td>IHC 3+ FISH (+)</td>
<td>1170</td>
<td>0.42 (0.27, 0.64)</td>
</tr>
<tr>
<td>IHC 3+ FISH (-)</td>
<td>51</td>
<td>0.71 (0.04, 11.79)</td>
</tr>
<tr>
<td>IHC &lt; 3+ FISH (+)</td>
<td>174</td>
<td>1.01 (0.18, 5.55)</td>
</tr>
<tr>
<td>IHC unknown / FISH (+)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

a IHC by HercepTest, FISH by PathVysion (HER2/CEP17 ratio ≥ 2.0) as performed at a central laboratory.
b All cases in this category in Study 3 were IHC 2+.
c Median follow-up duration of 12.6 months in the one-year trastuzumab treatment arm.

14.4 Metastatic Breast Cancer

The safety and efficacy of trastuzumab in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label, single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

Previously Untreated Metastatic Breast Cancer (Study 5)

Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or in combination with trastuzumab given intravenously as a 4 mg/kg loading dose followed by weekly doses of trastuzumab at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m² over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m² or epirubicin 75 mg/m² plus 600 mg/m² cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to receive chemotherapy alone in this study received trastuzumab at the time of disease progression as part of a separate extension study.

Based upon the determination by an independent response evaluation committee, the patients randomized to trastuzumab and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), and a longer median duration of response, as compared with patients randomized to chemotherapy alone. Patients randomized to trastuzumab and chemotherapy also had a longer median survival (see Table 11). These treatment effects were observed both in patients who received trastuzumab plus paclitaxel and in those who received trastuzumab plus AC, however, the magnitude of the effects was greater in the paclitaxel subgroup.

Table 11: Study 5: Efficacy Results in First-Line Treatment for Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Combined Results</th>
<th>Paclitaxel Subgroup</th>
<th>AC Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + All Chemotherapy (n = 235)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Chemotherapy (n = 234)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab + Paclitaxel (n = 92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (n = 96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab + AC (n = 143)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC (n = 138)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary Endpoint

<table>
<thead>
<tr>
<th>Median Response</th>
<th>Trastuzumab + All Chemotherapy (n = 235)</th>
<th>Trastuzumab + Paclitaxel (n = 92)</th>
<th>Paclitaxel (n = 96)</th>
<th>Trastuzumab + AC (n = 143)</th>
<th>AC (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP (mos)</td>
<td>7.2</td>
<td>4.5</td>
<td>6.7</td>
<td>2.5</td>
<td>7.6</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary Endpoints

<table>
<thead>
<tr>
<th>Overall Response Rate</th>
<th>Trastuzumab + All Chemotherapy (n = 235)</th>
<th>Trastuzumab + Paclitaxel (n = 92)</th>
<th>Paclitaxel (n = 96)</th>
<th>Trastuzumab + AC (n = 143)</th>
<th>AC (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP (mos)</td>
<td>45</td>
<td>29</td>
<td>38</td>
<td>50</td>
<td>38</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median Response Duration (mos)

<table>
<thead>
<tr>
<th>Trastuzumab + All Chemotherapy (n = 235)</th>
<th>Trastuzumab + Paclitaxel (n = 92)</th>
<th>Paclitaxel (n = 96)</th>
<th>Trastuzumab + AC (n = 143)</th>
<th>AC (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP (mos)</td>
<td>8.3</td>
<td>5.8</td>
<td>8.3</td>
<td>4.3</td>
</tr>
</tbody>
</table>
HERZUMA® (trastuzumab-pkrb) for injection

had received prior radiotherapy.

Table 12: Treatment Effects in Study 5 as a Function of HER2 Overexpression or Amplification

<table>
<thead>
<tr>
<th>HER2 Assay Result</th>
<th>Number of Patients (N)</th>
<th>Relative Risk for Time to Disease Progression (95% CI)</th>
<th>Relative Risk for Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA 2+ or 3+</td>
<td>469</td>
<td>0.59 (0.40, 0.81)</td>
<td>0.70 (0.53, 0.91)</td>
</tr>
<tr>
<td>FISH (+)</td>
<td>325</td>
<td>0.69 (0.55, 0.87)</td>
<td>0.70 (0.53, 0.91)</td>
</tr>
<tr>
<td>FISH (−)</td>
<td>126</td>
<td>0.69 (0.55, 0.87)</td>
<td>0.70 (0.53, 0.91)</td>
</tr>
<tr>
<td>CTA 2+</td>
<td>120</td>
<td>0.76 (0.61, 1.00)</td>
<td>0.90 (0.70, 1.15)</td>
</tr>
<tr>
<td>FISH (+)</td>
<td>32</td>
<td>0.34 (0.22, 0.54)</td>
<td>0.90 (0.70, 1.15)</td>
</tr>
<tr>
<td>FISH (−)</td>
<td>82</td>
<td>0.43 (0.28, 0.65)</td>
<td>0.90 (0.70, 1.15)</td>
</tr>
<tr>
<td>CTA 3+</td>
<td>349</td>
<td>0.33 (0.22, 0.50)</td>
<td>0.90 (0.70, 1.15)</td>
</tr>
<tr>
<td>FISH (+)</td>
<td>293</td>
<td>0.42 (0.30, 0.55)</td>
<td>0.90 (0.70, 1.15)</td>
</tr>
<tr>
<td>FISH (−)</td>
<td>43</td>
<td>0.43 (0.30, 0.60)</td>
<td>0.90 (0.70, 1.15)</td>
</tr>
</tbody>
</table>

\[a\] FISH testing results were available for 451 of the 469 patients enrolled on study.

\[b\] The relative risk represents the risk of progression or death in the trastuzumab plus chemotherapy arm versus the chemotherapy arm.

Previously Treated Metastatic Breast Cancer (Study 6)

Trastuzumab was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior hormone ablative treatment with hormonal contraceptive. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of trastuzumab at 2 mg/kg IV.

The ORR (complete response + partial response) as determined by an Independent Response Evaluation Committee was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to skin and lymph nodes. The overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

14.3 Metastatic Gastric Cancer

The safety and efficacy of trastuzumab in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 594 patients were randomized 1:1 to trastuzumab in combination with cisplatin and a fluoropyrimidine (FC-H) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0, 1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil).

All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%).

On the trastuzumab-containing arm, trastuzumab was administered as an IV infusion at an initial dose of 6 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms, cisplatin was administered at a dose of 80 mg/m² Day 1 every 3 weeks for 6 cycles as a 2 hour IV infusion. On both study arms, capecitabine was administered at 1000 mg/m²/day from Day 1 to Day 5 every 3 weeks for 6 cycles.

The median age of the study population was 60 years (range: 21-83); 76% were male; 53% were Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1; 62% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these patients, 25% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant therapy, and 2% had received prior radiotherapy.

An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 14.

Table 14: Exploratory Analyses by HER2 Status Using Updated Overall Survival Results

<table>
<thead>
<tr>
<th>FC (N = 296)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Deaths / n (%)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
</tr>
</tbody>
</table>

\[a\] Two patients on the FC arm who were FISH+ but IHC status unknown were excluded from the exploratory subgroup analyses.

\[b\] Five patients on the trastuzumab-containing arm who were FISH+, but IHC status unknown were excluded from the exploratory subgroup analyses.

\[c\] Includes 6 patients on chemotherapy arm, 10 patients on trastuzumab arm with FISH− / IHC3+ and 8 patients on chemotherapy arm, 8 patients on trastuzumab arm with FISH status unknown, IHC 3+.
HERZUMA® (trastuzumab-pkrb) for injection

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
420 mg Multiple-dose vial NDC 63459-305-47
HERZUMA (trastuzumab-pkrb) for Injection 420 mg/vial is supplied in a multiple-dose vial as a white to pale yellow lyophilized sterile powder, under vacuum. Each carton contains one multiple-dose vial (420 mg/vial) of HERZUMA and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.

150 mg Single-dose vial NDC 63459-303-43
HERZUMA (trastuzumab-pkrb) for Injection 150 mg/vial is supplied in a single-dose vial as a white to pale yellow lyophilized sterile powder, under vacuum. Each carton contains one single-dose vial (150 mg/vial) of HERZUMA.

16.2 Storage
Store HERZUMA vials in the refrigerator at 2°C to 8°C (36°F to 46°F) until time of reconstitution.

17 PATIENT COUNSELING INFORMATION
Cardiomyopathy
• Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [see Boxed Warning: Cardiomyopathy].

Embryo-Fetal Toxicity
• Advise pregnant women and females of reproductive potential that HERZUMA exposure during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy [see Use in Specific Populations (8.1)].
• Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of HERZUMA [see Use in Specific Populations (8.3)].

HERZUMA® (trastuzumab-pkrb)
Manufactured by:
CELLTRION, Inc.
23, Academy-ro,
Yeon-su-gu, Incheon
22014, Republic of Korea
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Marketed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

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