

SELECTED SAFETY INFORMATION

CARDIOMYOPATHY

- Administration of trastuzumab products can result in subclinical and clinical cardiac failure. The incidence and severity was highest in patients receiving a trastuzumab product with anthracycline-containing chemotherapy regimens. In a pivotal adjuvant breast cancer trial, one patient who developed congestive heart failure (CHF) died of cardiomyopathy.
- Evaluate left ventricular function in all patients prior to and during treatment with ONTRUZANT. Discontinue ONTRUZANT treatment in patients receiving adjuvant therapy and withhold ONTRUZANT in patients with metastatic disease for clinically significant decrease in left ventricular function.

INFUSION REACTIONS; PULMONARY TOXICITY

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

EMBRYO-FETAL TOXICITY

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

WARNINGS AND PRECAUTIONS

CARDIOMYOPATHY

Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. Trastuzumab products can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

There is a 4- to 6-fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving trastuzumab products as a single agent or in combination therapy compared with those not receiving trastuzumab products. The highest absolute incidence occurs when a trastuzumab product is administered with an anthracycline.

Withhold ONTRUZANT for $\geq 16\%$ absolute decrease in LVEF from pretreatment 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 ONTRUZANT in patients with trastuzumab-product-induced left ventricular cardiac dysfunction has not been studied.

Patients who receive anthracycline after stopping ONTRUZANT may also be at increased risk of cardiac dysfunction.

Cardiac Monitoring: Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

- Baseline LVEF measurement immediately prior to initiation of ONTRUZANT
- LVEF measurements every 3 months during and upon completion of ONTRUZANT
- Repeat LVEF measurement at 4-week intervals if ONTRUZANT is withheld for significant left ventricular cardiac dysfunction.
- LVEF measurements every 6 months for at least 2 years following completion of ONTRUZANT 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 ONTRUZANT 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 products after experiencing a severe infusion reaction. Prior to resumption of trastuzumab infusion, the majority of patients who experienced a severe infusion reaction were premedicated with antihistamines and/or corticosteroids. While some patients tolerated trastuzumab infusions, others had recurrent severe infusion reactions despite premedications.

EMBRYO-FETAL TOXICITY

Trastuzumab products can cause fetal harm when administered to a pregnant woman. In postmarketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Verify the pregnancy status of females of reproductive potential prior to the initiation of ONTRUZANT. Advise pregnant women and females of reproductive potential that exposure to ONTRUZANT 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 ONTRUZANT.

PULMONARY TOXICITY

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

EXACERBATION OF CHEMOTHERAPY-INDUCED NEUTROPENIA

In randomized, controlled clinical trials, the per-patient incidences of NCI-CTC Grade 3 to 4 neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not.

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. 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.

ADVERSE REACTIONS

The most common adverse reactions in patients receiving trastuzumab products in the adjuvant and metastatic breast cancer setting are fever, chills, 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.

In the metastatic gastric cancer setting, the most common adverse reactions ($\geq 10\%$) that were increased

(≥5% difference) in the 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.

USE IN SPECIFIC POPULATIONS

LACTATION

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 and infant circulation in substantial amounts. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for ONTRUZANT treatment and any potential adverse effects on the breastfed child from ONTRUZANT or from the underlying maternal condition. This consideration should also take into account the trastuzumab product washout period of 7 months.

PEDIATRIC USE

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

GERIATRIC USE

Trastuzumab has been studied in patients who were 65 years of age or over in the adjuvant and 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 or adjuvant therapy.

Before prescribing ONTRUZANT, please read the accompanying [Prescribing Information](#), including the Boxed Warning about cardiomyopathy, infusion reactions (pulmonary toxicity), and embryo-fetal toxicity.

HER2, human epidermal growth factor receptor 2; ER/PR, estrogen receptor/progesterone receptor; FDA, US Food and Drug Administration; MUGA, multigated acquisition; NCI-CTC, National Cancer Institute - Common Terminology Criteria; PK, pharmacokinetics; IgG, Immunoglobulin G.

If you have any questions about ONTRUZANT, please contact your Merck Account Executive.