AryoTrust™ (Trastuzumab)

Health Care Professional Information

Manufactured by:
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Warnings: cardiomyopathy, infusion reactions, embryo-fetal toxicity, and pulmonary toxicity

cardiomyopathy

Trastuzumab administration can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving Trastuzumab with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with AryoTrust™. Discontinue AryoTrust™ treatment in patients receiving adjuvant therapy and withhold AryoTrust™ in patients with metastatic disease for clinically significant decrease in left ventricular function.

infusion reactions; pulmonary toxicity

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

embryo fetal toxicity

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

1. Indications and usage

1.1 adjuvant breast cancer

AryoTrust™ 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.

1.2 metastatic breast cancer

AryoTrust™ 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.

1.3 metastatic gastric cancer

AryoTrust™ 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.

2. Dosage and administration

2.1 recommended doses and schedules

Do not administer as an intravenous push or bolus. Do not mix AryoTrust™ with other drugs.

Do not substitute AryoTrust™(Trastuzumab) 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 AryoTrust™ 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 AryoTrust™™, administer AryoTrust™ at 6 mg/kg as an intravenous infusion over 30–90 minutes every three weeks.

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

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

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

Extending adjuvant treatment beyond one year is not recommended.

Metastatic treatment, breast cancer:

Administer AryoTrust™, 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 AryoTrust™ 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.

2.2 important dosing considerations

if the patient has missed a dose of AryoTrust™by one week or less, then the usual maintenance dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered as soon as possible. do not wait until the next planned cycle. subsequent AryoTrust™ maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

if the patient has missed a dose of AryoTrust™ by more than one week, a re-loading dose of AryoTrust™ should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) as soon as possible. subsequent AryoTrust™ 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.

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 AryoTrust™ for severe or life-threatening infusion reactions.

Cardiomyopathy

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

≥ 16% absolute decrease in IVEF from pre-treatment values

IVEF below institutional limits of normal and ≥ 10% absolute decrease in IVEF from pretreatment values.

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

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

2.3 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 AryoTrust™ (Trastuzumab) and not ado-Trastuzumab emtansine.

Reconstitution

Reconstitute each 150 mg vial of AryoTrust™ with 7.2 ml of sterile water for injection (SWFI). Reconstitute each 440 mg vial of AryoTrust™ with 20 ml of bacteriostatic water for injection (BWFI), usp, containing 1.1% benzyl alcohol as a preservative to yield a multi-dose solution containing 21 mg/ml Trastuzumab. In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 ml of 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 AryoTrust™. 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 AryoTrust™ at 2–8° c; discard unused AryoTrust™ after 20 days. If AryoTrust™ is reconstituted with SWFI without preservative, use immediately and discard any unused portion.

Dilution

Determine the dose (mg) of AryoTrust™. Calculate the volume of the 21 mg/ml reconstituted AryoTrust™ 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.

3. Dosage forms and strengths

150 mg lyophilized powder per single-use vial and 440 mg lyophilized powder per multi-use vial.

4. Contraindications

None.

5. Warnings and precautions

5.1 cardiomyopathy

AryoTrust™ can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death .AryoTrust™ can also cause asymptomatic decline in left ventricular ejection fraction (IVEF).

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

Withhold AryoTrust™ for ≥ 16% absolute decrease in IVEF from pre-treatment values or an IVEF value below institutional limits of normal and ≥ 10% absolute decrease in IVEF from pretreatment values .the safety of

continuation or resumption of AryoTrust™ in patients with Trastuzumab-induced left ventricular cardiac dysfunction has not been studied.

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

Cardiac monitoring

Conduct thorough cardiac assessment, including history, physical examination, and determination of IVEF by echocardiogram or muga scan. The following schedule is recommended:

Baseline IVEF measurement immediately prior to initiation of AryoTrust™.

IVEF measurements every 3 months during and upon completion of AryoTrust™.

Repeat IVEF measurement at 4 week intervals if AryoTrust™ is withheld for significant left ventricular cardiac dysfunction.

IVEF measurements every 6 months for at least 2 years following completion of AryoTrust™ as a component of adjuvant therapy.

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.

In post-marketing 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 AryoTrust™ 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.

5.3 embryo-fetal toxicity

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

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

5.4 pulmonary toxicity

AryoTrust™ 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.

5.5 HER2 testing

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for AryoTrust™ 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 technology 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.

Several FDA-approved commercial assays are available to aid in the selection of breast cancer and metastatic gastric cancer patients for AryoTrust™ therapy. Users should refer to the package inserts of specific assay kits for information on the intended use, and the validation and performance of each assay.

Limitations in assay precision make it inadvisable to rely on a single method to rule out potential AryoTrust™ benefit.

6. Adverse reactions

Note: percentages reported with single-agent therapy.

>10%:

Cardiovascular: decreased left ventricular ejection fraction (4% to 22%)

Central nervous system: pain (47%), chills (5% to 32%), headache (10% to 26%), insomnia (14%), dizziness (4% to 13%)

Dermatologic: skin rash (4% to 18%)

Gastrointestinal: nausea (6% to 33%), diarrhea (7% to 25%), vomiting (4% to 23%), Abdominal pain (2% to 22%), anorexia (14%)

Infection: infection (20%)

Neuromuscular & skeletal: weakness (4% to 42%), back pain (5% to 22%)

Respiratory: cough (5% to 26%), dyspnea (3% to 22%), rhinitis (2% to 14%), pharyngitis (12%)

Miscellaneous: infusion related reaction (21% to 40%, chills and fever most common; severe: 1%), fever (6% to 36%)

1% to 10%:

Cardiovascular: peripheral edema (5% to 10%), edema (8%), cardiac failure (2% to 7%; Severe: <1%), tachycardia (5%), hypertension (4%), arrhythmia (3%), palpitations (3%)

Central nervous system: paresthesia (2% to 9%), depression (6%), peripheral neuritis (2%), Neuropathy (1%)

Dermatologic: acne vulgaris (2%), nail disease (2%), pruritus (2%)

Gastrointestinal: constipation (2%), dyspepsia (2%)

Genitourinary: urinary tract infection (3% to 5%)

Hematologic & oncologic: anemia (4%; grade 3: <1%), leukopenia (3%)

Hypersensitivity: hypersensitivity reaction (3%)

Infection: influenza (4%), herpes simplex infection (2%)

Neuromuscular & skeletal: arthralgia (6% to 8%), ostealgia (3% to 7%), myalgia (4%), and muscle spasm (3%)

Respiratory: flu-like symptoms (2% to 10%), sinusitis (2% to 9%), nasopharyngitis (8%), Upper respiratory tract infection (3%), epistaxis (2%), pharyngolaryngeal pain (2%)

Miscellaneous: accidental injury (6%)

<1% (limited to important or life-threatening; as a single-agent or with combination Chemotherapy): adult respiratory distress syndrome, amblyopia, anaphylaxis, apnea, ascites, Asthma, ataxia, blood coagulation disorder, bronchitis, cardiogenic shock, cardiomyopathy,

cellulitis, cerebrovascular accident, colitis, coma, confusion, deafness, dermal ulcer, erysipelas, esophageal ulcer, febrile neutropenia, gastroenteritis, glomerulopathy, hematemesis, hemorrhage, hemorrhagic cystitis, hepatic failure, hepatitis, herpes zoster, hydrocephalus, hydronephrosis, hypercalcemia, hypotension, hypothyroidism, hypoxia, intestinal obstruction, interstitial pneumonitis, leukemia (acute), lymphangitis, madarosis, mania, meningitis, myopathy, neutropenia, neutropenic sepsis, oligohydramnios, onychoclasis, osteonecrosis, pancreatitis, pancytopenia, paresis, paroxysmal nocturnal dyspnea, pathological fracture, pericardial effusion, pleural effusion, pneumonitis, pneumothorax, pulmonary edema (noncardiogenic), pulmonary fibrosis, pulmonary hypertension, pyelonephritis, radiation injury, renal failure, respiratory failure, seizure, sepsis, syncope, stomatitis, thyroiditis (autoimmune), ventricular dysfunction

7. Drug interactions

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

8. use in specific populations

8.1 pregnancy

Risk summary

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. Apprise the patient of the potential risks to a fetus. There are clinical considerations if AryoTrust™ is used in a pregnant woman or if a patient becomes pregnant within 7 months following the last dose of AryoTrust™.

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 4% and 15% to 20%, respectively.

Clinical considerations

Fetal/neonatal adverse reactions

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

DATA

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 therapy resumed after amniotic index improved, and oligohydramnios recurred.

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 crossed the placental barrier during the early (gestation days 20 to 50) and late (gestation days 120 to 150) phases of gestation. The resulting concentrations of Trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

8.2 lactation

Risk summary

There is no information regarding the presence of Trastuzumab in human milk, the effects on the breastfed infant, or the effects on milk production. Published data suggest human igg is present in human milk but does not enter the neonatal and infant circulation in substantial amounts.

Trastuzumab was present in the milk of lactating cynomolgus monkeys but not associated with neonatal toxicity .consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Trastuzumab treatment and any potential adverse effects on the breastfed child from Trastuzumab or from the underlying maternal condition. This consideration should also take into account the Trastuzumab wash out period of 7 months.

Data

In lactating cynomolgus monkeys, Trastuzumab was present in breast milk at about 0.3% 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). 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.

8.3 females and males of reproductive potential

Pregnancy testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of AryoTrust™.

Contraception

Females

AryoTrust™ can cause embryo-fetal harm when administered during pregnancy.

Advise females of reproductive potential to use effective contraception during treatment with AryoTrust™ and for 7 months following the last dose of AryoTrust™.

8.4 pediatric use

The safety and effectiveness of AryoTrust™ in pediatric patients have not been established.

8.5 geriatric use

The brand study:

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 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 preclude a 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 Herceptin, 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.

9. Over dosage

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

10. Description

AryoTrust™ (Trastuzumab) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab is produced by recombinant DNA technology in a mammalian cell (Chinese hamster ovary) culture containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

AryoTrust™ is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous administration. Each single-use vial of AryoTrust™ contains 150 mg Trastuzumab, 400 mg α, α-trehalose dihydrate, 9.9 mg l-histidine HCL, 6.4 mg l-histidine, and 1.8 mg polysorbate 20, usp. Each multi-use vial of AryoTrust™ contains 440 mg Trastuzumab, 400 mg α, α-trehalose dihydrate, and 9.9 mg l-histidine HCL, 6.4 mg l-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution the 440 mg vial with 20 ml of the appropriate diluent (BWFI or SWFI) yields a solution containing 21 mg/ml Trastuzumab at a ph. of approximately 6.

11. Clinical pharmacology

11.1 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.

AryoTrust™ 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.

11.2 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 was no apparent relationship between serum Trastuzumab concentrations and change in qtcf interval duration in patients with HER2 positive solid tumors.

12. Nonclinical toxicology

12.1 carcinogenesis, mutagenesis, impairment of fertility

AryoTrust™ 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 of Trastuzumab.

A fertility study was conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg of Trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.

13. How supplied/storage and handling

13.1 how supplied

AryoTrust™ is supplied in single-use vials containing 150 mg Trastuzumab and multi-use vial containing 440 mg Trastuzumab as lyophilized sterile powder, under vacuum. Each carton of 440 mg contains one vial AryoTrust™ and one vial (20 ml) of bacteriostatic water for injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.

13.2 stability and storage

Vials of AryoTrust™ are stable at 2–8°c (36–46°f) prior to reconstitution.

Do not use beyond the expiration date stamped on the vial. A vial of 440 mg AryoTrust™ reconstituted with BWFI, as supplied, is stable for 20 days after reconstitution when stored refrigerated at 2–8°c (36–46°f). Discard any remaining multi-dose reconstituted solution after 20 days. A vial of AryoTrust™ reconstituted with unpreserved SWFI (not supplied) should be used immediately and any unused portion discarded. Do not freeze AryoTrust™ following reconstitution or dilution.

the solution of AryoTrust™ for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% sodium chloride injection, usp, should be stored at 2–8°c for no more than 24 hours prior to use.

Patients can be advised to get in touch with OrchidPharmed Patient Support Center for any question or report any Adverse Drug event.

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