

Package leaflet: Information for the patient

AryoTrust 150 mg powder for concentrate for solution for infusion

AryoTrust 440 mg powder and solvent for concentrate for solution for infusion

Trastuzumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

1. What AryoTrust is and what it is used for
2. What you need to know before you take AryoTrust
3. How to use AryoTrust
4. Possible side effects
5. How to store AryoTrust
6. Contents of the pack and other information

1- What AryoTrust is and what it is used for

AryoTrust contains the active substance called Trastuzumab, which is a monoclonal antibody and antineoplastic agent. Monoclonal antibodies bind selectively to a target proteins or antigens. Breast and stomach cancer cells sometimes have large amounts of a protein (antigen) called human epidermal growth factor 2 (HER2) on their surface. When HER2 is activated, it helps cancer cells grow. AryoTrust is an antibody against the HER2 protein and binds to these proteins and stops them from becoming active and cause cancer cells to die.

- HER2 over expressing early breast cancer:

AryoTrust is indicated for adjuvant treatment in adults with early breast cancer with high levels of HER2.

- HER2 over expressing metastatic breast cancer: (cancer cells that have spread beyond the original tumors):

AryoTrust may be prescribed in combination with Paclitaxel or Docetaxel as first line treatment.

AryoTrust is indicated as single-agent therapy in adults who have received unsuccessful chemotherapy regimens in past.

It is also prescribed in combination with aromatase inhibitors in patients with high level of HER2 and hormone-receptor positive in metastatic breast cancer.

- HER2 over expressing metastatic gastric cancer:

AryoTrust may be prescribed in combination with Cisplatin, Capecitabine or 5-Fluorouracil in metastatic gastric cancer with high levels of HER2.

2- What you need to know before you take AryoTrust?

Do not use AryoTrust:

- If you are allergic to Trastuzumab or any of the other ingredients of this medicine (listed in section 6) and if you had anaphylactic reactions to murine proteins.
- If you have serious breathing problems such as shortness of breath at rest due to complications of your cancer or need oxygen therapy.

Appropriate precautions for use; special warnings

Talk to your doctor, pharmacist or nurse before using AryoTrust:

- If you have ever had any other treatment of cancer.

Treatment with AryoTrust can cause cardiac heart failure. The highest absolute incidence occurs when AryoTrust is administered with an anthracycline (Doxorubicin, Epirubicin ...) or taxane. (two other cancer chemotherapies) Tell your doctor immediately, you should be monitored closely.

- If you had pre-existing cardiovascular disease including heart failure, hypertension, coronary artery disease or cardiac valvular dysfunction. Your cardiologist should check your heart function immediately prior to initiation of AryoTrust, every 3 months during and upon completion (at least 2 years following) of AryoTrust.

- If you had infusion related reactions (dyspnea, hypotension, angioedema, and hive). The majority of these events occur during or within 2.5 hours of the first infusion. Although the possibility of such a late onset have been reported too. Contact your physician immediately if these symptoms occur, you should be evaluated and carefully monitored until complete resolution of signs and symptoms.

- If you had any breathing problems seek medical advice immediately. Such symptoms may point to the existence of potentially life-threatening conditions, especially if you had respiratory disorders or being treated concomitantly with taxanes in past.

Use in children and adolescents

The safety and effectiveness of AryoTrust in children and adolescents patients has not been established and it is not recommended.

Other medicines and AryoTrust

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines within 7 months after completion of the treatment with AryoTrust. (At least 7 month is required for AryoTrust to be removed from the body.)

Pregnancy and breast-feeding

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to be pregnant ask your doctor, pharmacist or nurse for advice before taking this medicine.

- You should be advised to use effective contraception during treatment with AryoTrust and for at least 7 months after treatment has concluded. AryoTrust can cause fetal harm when administered to a pregnant woman. AryoTrust should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

- Women using AryoTrust should not breast-feed during treatment and for at least 7 months after treatment has ended, since AryoTrust passes into human breast milk.

Effects on ability to drive and use machines

AryoTrust has no or negligible influence on the ability to drive or use machines. However, patients experiencing chills or fever should be advised not to drive and use machines until symptoms abate.

3-How to take AryoTrust

Method of administration

Detection of HER2 high levels in cancer cells is necessary for selection of treatment with AryoTrust, due to its benefit which has been report.

AryoTrust is available on prescription only, and will be given to you by a doctor or nurse in a hospital or clinic. You will be observed by a doctor or nurse while it is being given and at least 6 hours following the first dose and 2 hours following the next doses, in case you have any side effects.

Your doctor will calculate dose of AryoTrust depends on your body weight. It is given by a drip into a vein (intravenous

infusion). AryoTrust may be administrated as a weekly (one loading dose and maintenance doses repeated weekly) or three-weekly schedule (one loading dose and maintenance doses repeated every 3 weeks).

The first infusion will be given to you over 90 minutes, if it is well tolerated the infusion on your next visit may be given over 30-90 minutes depends on your treatment schedule.

Use in children and adolescents

AryoTrust is not recommended for anyone under the age of 18.

Duration of treatment

The total number of infusions that you will be given depends on how you respond to the treatment.

If you experience any side effects, depending on its important your doctor will decide to continue, delay or stop your treatment.

If you forget to take AryoTrust

If you has missed a dose of AryoTrust by one week or less, then the usual maintenance dose (depend on the treatment regimen) should be administered as soon as possible. Do not wait until the next appointment. 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, as soon as possible. Subsequent AryoTrust maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If you stop taking AryoTrust

Do not stop treatment without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4- Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Cardiomyopathy

AryoTrust can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death. The incidence and severity was highest in patients receiving AryoTrust with anthracycline-containing chemotherapy regimens. Contact your doctor right away if you experience any chest pain, fast, slow, or uneven heartbeat, trouble breathing specially a sudden difficulty with breathing at night, increased coughing or abnormal swelling in your ankles or legs and rapid weight gain. These could be symptoms of serious heart problems.

Severe infusion reactions:

AryoTrust may cause some common infusion reaction such as fever, chills and flu like symptoms. Besides, other serious infusion reaction can be life threatening and requires immediate medical attention. Tell your doctor or nurse straight away if you have nausea, vomiting, shaking, dizziness, headache, trouble with breathing, high or low blood pressure, irregular heartbeat, swelling of the face and lips and hives while you receive the medicine or after the infusion.

Pulmonary toxicity:

AryoTrust may cause lung disease or breathing problems. Tell your doctor right away if you are having shortness of breath, chest tightness, or any type of breathing problem while receiving this medicine.

Exacerbation of chemotherapy-induced neutropenia:

AryoTrust can temporarily lower the number of white blood cells in your blood, which increases the chance of getting an infection. Avoid contact people with infections. Check with your doctor right away if you get a fever or chills, a cough or sore throat, body aches and have painful or difficult urination.

At least 7 months after the treatment have been finished with AryoTrust, if you notice any of the above symptoms, immediately inform your doctor.
The known side effects of AryoTrust include the following in groups of decreasing frequency:

- Very common: (may affect more than 1 in 10 people)
 - Infections
 - Diarrhea, constipation
 - Dyspepsia
 - Weakness
 - Skin rashes
 - Chest pain, abdominal pain
 - Joint pain, muscle pain
 - Low counts of red blood cells, white blood cells and platelet
 - Watery eyes, runny nose
 - Nose bleeds
 - Conjunctivitis
 - Hair loss
 - Tremor
 - Hot flush
 - Dizziness
 - Nail disorders
 - Weight loss, loss of appetite
 - Insomnia
 - Numbness or tingling of hands or feet
 - Pain, swelling, redness or tingling of hands or feet
 - Vomiting and nausea
 - Headache
 - Cough
- Common: (may affect up to 1 in 10 people)
 - Allergic reactions, itchy rash
 - Throat, bladder, skin and lungs infections
 - Inflammation of the breast, pancreas or liver
 - Kidney disorders
 - Sleepiness
 - Hemorrhoids
 - Dry mouth, skin, eyes
 - Sweating
 - Feeling weak and unwell
 - Anxiety, depression
 - Asthma, lung disorders
 - Back, neck and bone pain
 - Acne
 - Leg cramps
- Uncommon: (may affect up to 1 in 100 people)
 - Deafness
 - Bumpy rash
 - Blood infection
- Rare: (may affect up to 1 in 1,000 people)
 - Weakness
 - Jaundice
 - Inflammation of the lungs
- Not known: (frequency cannot be estimated from the available data)
 - Abnormal or impaired blood clotting
 - Anaphylactic reactions
 - High potassium levels
 - Swelling of the brain
 - Swelling or bleeding at the back of the eyes
 - Shock
 - Slow heart rate, abnormal heart rhythm
 - Respiratory distress, respiratory failure
 - Acute accumulation of fluid in the lungs
 - Acute narrowing of the airways
 - Abnormally low oxygen levels in the blood
 - Liver and kidney damage
 - Swelling of the face, lips and throat
 - Abnormally low levels of fluid around baby in womb

Failure of lungs to develop in the womb
Abnormal kidney development in the womb

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system fda.gov.ir or +98-21-22382641. By reporting side effects, you can help provide more information on the safety of this medicine.

5- How to store AryoTrust

Storage conditions

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and outer carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 - 8 °C). Do Not Freeze AryoTrust following reconstitution or dilution.

Keep the vial in outer carton to protect from light.

AryoTrust 150 mg powder for concentrate for solution for infusion

The reconstituted solution of AryoTrust with unpreserved Sterile Water for Injection (SWFI) (not supplied) should be used immediately. The product is not intended to be stored after reconstitution and dilution.

AryoTrust 440 mg powder and solvent for concentrate for solution for infusion

A vial of AryoTrust reconstituted with Bacteriostatic Water for Injection (BWFI) (supplied), containing benzyl alcohol as a preservative, is stable for 28 days after reconstitution when stored refrigerated at 2 - 8 °C. Discard any remaining multi-dose reconstituted solution after 28 days.

Do not use this medicine if you notice any particulate matter or discoloration before infusion.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6- Contents of the pack and other information

What AryoTrust contains

The active substance is Trastuzumab.

AryoTrust 150 mg powder for concentrate for solution for infusion

Each single use vial contains 150 mg of Trastuzumab that has to be dissolved in 7.2 ml of SWFI.

AryoTrust 440 mg powder and solvent for concentrate for solution for infusion

Each multiple use vial contains 440 mg of Trastuzumab that has to be dissolved in 20 ml of Bacteriostatic Water for Injection (BWFI).

The other ingredients are L-histidine hydrochloride/ L-histidine/ α, α-trehalose dihydrate/ polysorbate 20

What AryoTrust looks like and contents of the pack

AryoTrust is a white to pale yellow powder for concentrate for solution for intravenous infusion in a glass vial.

AryoTrust 150 mg powder for concentrate for solution for infusion

Each carton contains 1 vial of powder and a patient leaflet information.

AryoTrust 440 mg powder and solvent for concentrate for solution for infusion

Each carton contains 1 vial of powder, one vial (20 ml) of Bacteriostatic Water for Injection (BWFI) and a patient leaflet information.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

The following information is intended for medical or healthcare professionals only

Instructions for reconstitution, dilution and infusion of AryoTrust

Vials of AryoTrust should be stored in refrigerator (2 - 8 °C) in their closed original pack.

AryoTrust is intended for use under the guidance and supervision of a physician. The reconstituted and dilution infusion solution should be prepared by a trained medical professional using aseptic technique. Parental drug products should be inspected visually for particulate matter and discoloration prior to administration.

Step 1: Calculate the volume of reconstituted AryoTrust solution

• Base on loading dose of 4 mg/kg and maintenance dose of 2 mg/kg weekly regimen

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (4mg/kg for loading or 2mg/kg for maintenance)}}{21(\text{mg/mL, concentration of reconstituted solution})}$$

• Base on loading dose of 8 mg/kg and maintenance dose of 6 mg/kg three-weekly regimen

$$\text{Volume (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (8mg/kg for loading or 6mg/kg for maintenance)}}{21(\text{mg/mL, concentration of reconstituted solution})}$$

Step 2: Reconstitution

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A vial of AryoTrust reconstitute with 7.2 ml Sterile Water for Injection (not supplied). The resultant concentration is approximately 21 mg/ml.

A vial of AryoTrust reconstituted with unpreserved SWFI should be used immediately and unused portion discarded.

AryoTrust 440 mg powder and solvent for concentrate for solution for infusion

A vial of AryoTrust reconstitute with 20 ml Bacteriostatic Water for Injection (supplied). The resultant concentration is approximately 21 mg/ml. A vial of AryoTrust reconstituted with BWFI is stable for 28 days in refrigerator (2 - 8 °C).

If the patient has known hypersensitivity to benzyl alcohol, AryoTrust must be reconstituted with SWFI and must be used immediately and any unused portion discarded.

Gently swirl the solution by rotating the vial to dissolve the powder. Avoid prolonged or vigorous agitation. Do not shake. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colourless to light yellow. Do not use if the lyophilized cake has not fully dissolved or if discoloration or other foreign particles are present.

Step 3: Dilution

The calculated volume of reconstituted AryoTrust solution should be added to 250 ml of 0.9% sodium chloride solution in polyvinylchloride, polyethylene or polypropylene infusion bag. Gently invert the bag to mix the solution.

Do not use with glucose containing solutions. Do not mix or dilute with other drugs.

Step 4: Administration

AryoTrust loading dose should be administered by intravenous (IV) infusion over 90 minutes. Patients should be observed for fever and chills or other infusion associated symptoms. If prior infusions are well tolerated, subsequent weekly doses may be administered over 30-90 minutes.

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