Zytux™

Package leaflet: Information for the patient
Zytux™ 100 mg/ 10 ml concentrate for solution for infusion
Zytux™ 500 mg/ 50 ml concentrate for solution for infusion
Rituximab

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 Zytux™ is and what it is used for

Zytux™ contains the active substance called Rituximab, which is a monoclonal antibody (a protein) and anti-neoplastic (anti-cancer) agent. Zytux™ binds specifically to the CD20 antigen located on pre-B and mature B lymphocytes (a type of white blood cells). CD20 is present on more than 90% of B-cell non-Hodgkin's lymphomas (NHL), a cancer that starts in the lymphocytes. By doing so, it causes the malignant cells to die.

Zytux™ is used for:

Non-Hodgkin's lymphoma (NHL):

NHL is a disease of the lymph tissue (part of the immune system) that affects B-Lymphocytes.
Zytux™ is indicated for the treatment of CD20-positive non-Hodgkin lymphomas (NHL) including:

- Follicular lymphoma (stage III-IV), as initial treatment in combination with other chemotherapy agents in patients who were previously untreated.
- As maintenance therapy in patients with follicular lymphoma (stage III-IV) who have responded to initial therapy.
- As single-agent therapy in patients with follicular lymphoma (stage III-IV) who experienced recurrence of the disease or who did not respond to the initial treatment.
- Diffuse large B-cell NHL, in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy.

Chronic lymphocytic leukemia (CLL):

CLL is a type of cancer in which the bone marrow makes too many abnormal lymphocytes which accumulate mainly in the bone marrow and blood. CLL is one of the most common types of leukemia in adults.
Zytux™ is indicated for the treatment of CD20-positive chronic lymphocytic leukemia (CLL) (in combination with fludarabine and cyclophosphamide).

Rheumatoid Arthritis (RA):

RA is an inflammatory disease of joints. Zytux™ is indicated for the treatment of moderately to severely active RA in adults. If you did not respond well to other medicines specific for treatment of RA, such as disease-modifying anti-rheumatic drugs (DMARD) and tumor necrosis factor (TNF) inhibitor, you will be given Zytux™ in combination with Methotrexate.
As measured by X-ray, Rituximab has been shown to reduce joint damage progression rate, improve physical function and ability to perform normal daily activities, when given in combination with methotrexate.

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA):

GPA and MPA are two forms of inflammation of the blood vessels mainly affecting lungs and kidneys, but other organs could also be affected. B lymphocytes are involved in the cause of these conditions. Zytux™, in combination with glucocorticoids, is indicated for induction of remission in adult patients with severe, active GPA (Wegener's) and MPA.

2. What you need to know before you use Zytux™?

Do not use Zytux™:

- If you have ever had an allergic reaction to Rituximab, murine proteins or any of the other ingredients of this medicine (Listed in section 6).
- If you have a severe active infection.
- If you have a weakened immune system.
- If you have severe heart failure or severe uncontrolled heart disease (this point is when Zytux™ is used for the treatment of rheumatoid arthritis, granulomatosis with polyangiitis or microscopic polyangiitis).

Warnings and Precautions:

Talk to your doctor pharmacist or nurse before using Zytux™

- If you experience new or worsening neurological symptoms or signs such as vision loss, mental deterioration, speech disturbance, inability to coordinate movements; tell your doctor immediately, you should be monitored closely by a neurologist. You must be evaluated for a rare, serious brain infection called Progressive Multifocal Leukoencephalopathy (PML).
- If you experience infusion related reactions (severe shortness of breath accompanied by bronchospasm and hypoxia, low blood pressure, swelling of your skin (angioedema), fever, chills and hive) contact your physician immediately. The majority of these severe events usually occur within 30-120 minutes of the infusion. Such symptoms may point to the existence of potentially life-threatening conditions. If these symptoms occur, you should be evaluated and carefully monitored until complete resolution of signs and symptoms.
- Tell your doctor if you have a history of heart disease (such as angina, palpitations or heart failure) or chemotherapy toxic to heart, because you should be monitored closely.
- If you notice low neutrophil and low platelet counts in your regular full blood counts consult with your doctor.
- If you have active, severe infection inform your doctor. Because infections can happen during treatment with Zytux™. Also, if you have ever had a hepatitis B infection, you must be carefully checked by your doctor for signs of this infection. Rare cases of Hepatitis B reactivation have been reported in patients receiving Rituximab.
- If you have recently received or you are planning to inject a vaccination tell your doctor. While taking Zytux™ or in the months after you stop Zytux™, vaccination with live vaccines is not recommended.
- If you experience severe skin reactions contact your physician immediately. In case of certain severe skin reactions; your treatment should be permanently discontinued.

When treated for Rheumatoid arthritis, granulomatosis with polyangiitis or microscopic polyangiitis tell your doctor:

- If you develop a new infection, even a mild one, or you have suffered from a severe infection in past. Before receiving a subsequent course of Zytux™ treatment, you should be re-evaluated for any potential risk of infections and you should wait until the infection has resolved completely.
- If you plan to receive vaccine during your therapy consult with your doctor. While taking Zytux™ or in the months after you stop Zytux™, vaccination with live vaccines is not recommended.

Children and Adolescents:

The safety and effectiveness of Rituximab has not been studied completely in patients under 18 years of age and there is not enough information.

Other medicines and Zytux™:

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, even those not prescribed by your doctor such as herbal medicines and over-the-counter drugs.
Tell your doctor about medicines you are taking for high blood pressure. You may experience drop in blood pressure during Zytux™ infusion. Your doctor may ask you not to use antihypertensive drugs 12 hours prior to Zytux™ administration.
Tell your doctor if you had previously received chemotherapy or immunosuppressant therapy.

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 or pharmacist for advice before taking this medicine You should be advised to use effective birth control methods during treatment with Zytux™ and for 12 months after treatment has concluded. Rituximab can cross the placental barrier and should be avoided during pregnancy unless the potential benefit for the mother outweighs the potential risk to the fetus.

Women using Zytux™ should not breast-feed during treatment and for 12 months after treatment has ended, since Rituximab may pass into human breast milk.

Effects on ability to drive or use machines:

There are not sufficient studies done to show the effect of Rituximab on driving or using machinery.

Excipients Warning:

This medicinal product contains 2.3 mmol (52.6 mg) Sodium per 10 ml vial and 11.5 mmol (263.2 mg) Sodium per 50 ml vial. Take this into account if you are on a low-Sodium diet.

3. How to use Zytux™?

Zytux™ is available on prescription only, and will be administered to you by an experienced healthcare professional in hospital setting. You will be observed directly by a doctor or nurse while it is being given.

Non-Hodgkin's lymphoma (NHL):

Monotherapy:

The recommended dose of Zytux™ is 375 mg/m^2 body surface area once weekly for 4 weeks. Repeated treatment courses with Zytux™ are possible.

Combination with chemotherapy:

The recommended dose of Zytux™ is 375 mg/m^2 body surface area per cycle on day 1 of each chemotherapy cycle, up to 8 cycles.

Maintenance therapy:

If you respond well to treatment the recommended dose is 375 mg/m^2 body surface area every 2 months (for untreated patients) or 3 months (for patients with disease recurrence) for a maximum period of two years (8 administrations in total).

Chronic lymphocytic leukemia (CLL):

The recommended dose of Zytux™ in combination with chemotherapy is 375 mg/m^2 body surface area on day 0 of the first treatment cycle followed by 500 mg/m^2 body surface area on day 1 of each subsequent cycle for 6 cycles in total.

Rheumatoid arthritis:

The recommended dose of Zytux™ is 1000 mg on days 1 and 15 in combination with methotrexate. Repeated courses of Zytux™ depends on your treatment evaluation.

Granulomatosis with polyangiitis or microscopic polyangiitis:

The recommended dose of Zytux™ is 375 mg/m^2 body surface area once weekly for 4 weeks.

Route and method of administration:

The diluted solution of Zytux™ should be administered as an intravenous infusion (drip).
Due to possible side effects of Zytux™, premedication with antipyretic, antihistamine and in some cases corticosteroids will usually be given by injection before starting Zytux™ administration.
The total number of infusions that you will be given depends on the indication which you have been treated for and how you respond to Zytux™. In Rheumatoid arthritis available data suggest that clinical response is usually achieved within 16 - 24 weeks of an initial treatment course.

If you forget to use Zytux™:

Always try to remember the schedule of your injections. If you ever forget to go to hospital for your infusion, consult with your physician as soon as possible for rescheduling the next appointment.

If you stop using Zytux™:

Never stop using your medicine before consulting your physician. In order to take the complete benefit from your medicine, always complete the treatment courses recommended by your doctor.
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.

Serious side effects

The below mentioned side effects may not happen commonly but if they do, they can be life-threatening. If you ever experience any of the following, contact your doctor immediately.

Infusion reactions

Infusion reactions may occur during the first two hours of first infusion. Rituximab may cause some common infusion reaction symptoms such as fever, chills and shivering. Tell your doctor or nurse straight away if you have headache, vomiting, flushing or

palpitations, pain at the infusion site, blisters, itching, sickness, tiredness, breathing difficulties, tongue or throat swelling, itchy or runny nose. Tell your doctor or nurse if you have low platelet count in your blood or history of heart disease such as angina, because Rituximab may worsen these conditions. In this situation your doctor may decide to slow down the infusion rate or stop the infusion and may give you medications such as antihistamines or Paracetamol. When these symptoms go away or improve, the infusion can be continued. The incidence of infusion related symptoms generally decrease with subsequent infusions.

Infections

The probability of developing a very rare, serious and fatal brain infection PML (Progressive Multifocal Leukoencephalopathy) may increase by taking Rituximab. Tell your doctor immediately if you experience memory loss, trouble in thinking, difficulty walking and inability to coordinate movements, vision loss and speech disturbances.
Tell your doctor immediately if you have fever, cough, sore throat, chills, painful urination, which may be signs of infection. Rituximab may increase risk of colds, pneumonia and urinary tract infections.

Skin Reactions

Very rare, life-threatening and serious skin reaction can occur during treatment with Rituximab. Check with your doctor right away if you have blistering, peeling, red skin lesions, severe acne or skin rash, fever or chills, sores on the skin or on mucous membranes such as inside the mouth, genital areas or eyelids while you are using this medicine.

The following additional side effects have been observed and are listed in groups with decreasing frequency.

a) If you are being treated for non-Hodgkin's Lymphoma or chronic lymphocytic leukemia

Very common side effects (may affect more than 1 in 10 people)

- Bacterial or viral infections, bronchitis
- Decrease in Neutrophils (with or without fever), and platelets counts
- Nausea
- Itching, rash, hair loss
- Fever, chills, headache, weakness or lack of energy
- Decrease in immunoglobulin (IgG) and immunity

Common side effects (may affect up to 1 in 10 people)

- Blood infection (sepsis), pneumonia, cold, herpes zoster, respiratory tract infection, fungal infections, infection of unknown origin, hepatitis B, sinus and bronchial inflammation
- Decrease in red blood cells and all blood cells
- Allergic reactions
- Increase in blood sugar level, weight loss, swelling in the face and body, high levels of the enzyme LDH in the blood, low calcium levels in the blood
- Abnormal sensation of skin, typically tingling, pricking and numbness
- Agitation, dizziness, anxiety, vasodilation and sleeplessness
- Excessive secretion of tears and inflamed eye (conjunctivitis)
- Ringing sound in the ears, ear pain
- Cardiac disorder – such as heart attack, uneven or fast heart rate
- High or low blood pressure, orthostatic hypotension (drop in blood pressure while standing after sitting for a while)
- Bronchospasm, respiratory disease, chest pain, shortness of breath, cough and runny nose
- Vomiting, diarrhea, constipation, abdominal pain, difficulty or discomfort in swallowing, irritation or ulcers in the throat and mouth, indigestion, lack or loss of appetite
- Hives, increased sweating, night sweats
- Muscle problems such as tight muscles, joint or muscle pain, back and neck pain
- Shivering, weakness, fatigue, signs of flu and multiple-organ failure

Uncommon side effects (may affect up to 1 in 100 people)

- Blood clotting problems, decrease of red blood cell production and increase of red blood cell destruction (aplastic and haemolytic anemia), swollen or enlarged lymph nodes
- Depression, feeling nervous
- Decrease in taste sensitivity
- Asthma, airway obstruction and inflammation, lower than normal concentration of oxygen in blood
- Heart problems, angina, uneven heart rate
- Swelling of the stomach
- Infusion site pain

Rare side effects (may affect up to 1 in 1,000 people)

- Serious viral infection
- Severe life-threatening allergic reaction
- Severe cardiac disorder
- Lung disease affecting tissue and space around the air sacs of the lungs

Very rare side effects (may affect up to 1 in 10,000 people)

- Brain infection (Progressive Multifocal Leukoencephalopathy)
- Short term increase in the amount of some types of antibodies in blood (IgM)
- Chemical disturbances in the blood caused by breakdown of dying cancer cells
- Nerve damage in arms and legs, paralysed face
- Blindness
- Heart failure
- Inflammation of blood vessels including those leading to skin symptoms
- Respiratory failure
- Damage to the intestinal wall (perforation)
- Severe life-threatening skin problems causing fever, blisters, redness on the skin or on mucous membranes
- Kidney failure

Not known (frequency cannot be estimated from the available data)

- Late-onset reduction in white blood cells
- Reduced platelets number that can be reversed,but can be fatal in rare cases
- Nerve damage and loss of other senses
- Hearing loss
- Abnormal substance accumulation in the lungs (Lung infiltration)

b) If you are being treated for rheumatoid arthritis

Very common side effects (may affect more than 1 in 10 people)

- Allergic reactions that occurs during an infusion or up to 24-hours after the infusion with symptoms of changes in blood pressure, nausea, rash, hives, itching, fever, blocked nose, shaking, rapid heartbeat, and fatigue
- Upper respiratory tract infection
- Urinary tract infections
- Headache
- Decrease in the amount of some types of anti-bodies in the blood (IgM)

Common side effects (may affect up to 1 in 10 people)

- Bronchitis, sinusitis
- Inflammation of the stomach causing vomiting and diarrhea
- Fungal foot infection
- Decrease in Neutrophils
- High cholesterol levels in the blood
- Abnormal sensations of the skin such as numbness or tingling
- Pain affecting the back and/or hip
- Dizziness
- Hair loss
- Anxiety, depression
- Indigestion, diarrhea, acid reflux, ulceration of the mouth, abdominal pain
- Pain in muscles or joints
- Decrease in the amount of some types of anti-bodies in the blood (IgG)

Uncommon side effects (may affect up to 1 in 100 people)

- Infusion related reactions, edema and fluid retention in the face and body
- Inflammation of the lungs and throat
- Allergic reactions including wheezing or shortness of breath

Rare side effects (may affect up to 1 in 1,000 people)

- Late-onset reduction in neutrophils
- Heart failure, myocardial infarction

Very rare side effects (may affect up to 1 in 10,000 people)

- Brain infection (Progressive Multifocal Leukoencephalopathy)
- Reactivation of Hepatitis B
- Severe life-threatening skin problems causing fever, blisters, redness on the skin or on mucous membranes
- Hypersensitivity reactions and Immune complex deposits that cause itching, arthritis, swollen lymph glands, fever and other systemic symptoms

c) If you are being treated for granulomatosis with polyangiitis or microscopic polyangiitis

Very common side effects (may affect more than 1 in 10 people)

- Infections such as chest infections, urinary tract infections colds and herpes
- Allergic reactions which usually occurs during infusion but may happen 24 hours after the infusion
- Diarrhea
- Cough or shortness of breath
- Nose bleeds
- High blood pressure
- Pain and inflammation of joint and muscle, back pain
- Tremor
- Dizziness
- Difficulty in sleeping
- Swelling and edema of the hands or ankles

Common side effects (may affect up to 1 in 10 people)

- Indigestion
- Constipation
- Acne
- Flushing or redness of the skin
- Blocked nose
- Pain in the muscles or in the hands or feet
- Muscle weakness
- Decrease in platelets
- Increase in the amount of potassium in the blood and changes the normal rhythm of heart

Very rare side effects (may affect up to 1 in 10, 000 people)

- Severe life-threatening skin problems causing fever, blisters, redness on the skin or on mucous membranes
- Recurrence of a previous Hepatitis B infection

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**. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Zytux™?

- 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.
- Keep the vial in the outer carton in order to protect from light.
- The prepared infusion solution of Zytux™ is chemically and physically stable for 24 hours at 2-8°C and subsequently 12 hours at 15-25°C.
- From the microbiological point of view, the prepared infusion solution of Zytux™ should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.
- Do not use Zytux™ if you notice any particulate matter or discoloration prior to administration.
- 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 to protect the environment.

6. Contents of the pack and other information

What Zytux™ contains

The active substance is Rituximab.
Each single use vial of Zytux™ contains 10 mg/ml Rituximab.
The 10 ml vial contains 100 mg Rituximab.
The 50 ml vial contains 500 mg Rituximab.
Other ingredients are Sodium chloride, Polysorbate 80, Sodium citrate dihydrate and Water for Injections.

What Zytux™ looks like and contents of the pack

Zytux™ supplied as a vial containing a clear, colorless concentrate for solution for infusion.
Each small box of Zytux™ 100 mg (10 ml) contains two vials and a patient information leaflet.
Each small box of Zytux™ 500 mg (50 ml) contains one vial and a patient information leaflet.

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ARYOGEN آریـــوژن فارمـد

Manufactured by AryoGen Pharmed
Alborz, Iran.
Zip code: 3164819711
Tel.: +98 26 36106480-4
Fax: +98 26 36104644
Email: contact@aryogen.com

HP.152580590-1.xxxxxx B.xxxxxxx EPL-03-1218-01 250 x 280